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ALTERNATIVE THERAPIES

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ALTERNATIVE THERAPIES

All things considered, a significant amount of progress has been made since alert clinicians first described the outbreak of *Pneumocystis carinii* pneumonia and Kaposi's sarcoma in 1981. Since then the full spectrum of AIDS-related disease has been defined and prognostic markers have been identified. The causative retrovirus was recognized as the etiologic agent in 1984. Since then, it has been named, renamed, sequenced, cloned, and has generated more basic science investigations and manuscript publications than any other organism in recent history. Two years after isolation of the human immunodeficiency virus, an effective anti-retroviral therapy had been tested, approved and licensed. With the addition of prophylactic therapies for *Pneumocystis carinii* pneumonia, the average life span of the newly diagnosed person with AIDS is now twice what it was just eight years ago. For most, however, this life span continues to be measured in months rather than years.

Despite this remarkable progress, many, particularly those infected with HIV or at risk, have felt a sense of frustration at the pace of conquest. Born into the generation when smallpox and polio had been conquered with vaccines and the mysteries of Legionnaire's disease and toxic shock syndrome had been rapidly unravelled, many of the young adults threatened by HIV were surprised that more could not be done more quickly. Perhaps the most vocal critics have been representatives from the United States' highest incidence group for HIV infection, the male homosexual community.

The acceptance of the homosexual lifestyle as a viable alternative had made great strides in the mid-decades of this century. Emerging from the repression and clandestine closets of the forties and fifties, the gay lifestyle was advanced by the sexual revolution of the sixties and seventies and thrust into the public view, closer to the collective consciousness of American society. Elaborate networks and well-organized campaigns kept the gay rights movement progressing smoothly forward during the 1970's. Effective communication systems, including a sophisticated and professional gay press, kept the community informed of potential threats to continued advances, civil liberties and human rights. It was into this well-oiled machinery that the monkey-wrench of HIV infection unexpectedly appeared as the 1980's opened. A community previously occupied with fighting for their rights was now faced with the challenge of fighting for their lives.

In addition to belonging to a politically disenfranchised population, the gay male in the 30 to 40 year old age bracket was also a newcomer to the medical care industry. For the most part, the majority of individuals at risk for HIV infection had not previously made significant use of the health care delivery system. The lack of consumer savvy coupled with more than an insignificant amount of mistrust for the predominantly heterosexual white male medical establishment combined to create a general sense of suspicion, particularly towards the research and regulatory organizations, but in some cases towards the primary care provider as well.

For the first few years of the AIDS epidemic, cases were scant and the impact on the population was limited. An occasional acquaintance of a friend's friend may have been diagnosed with the unusual cancer or the severe pneumonia but most

gay men considered the disease a rare occurrence and nothing that could effect their lives. By 1983, it became more evident despite the absence of an etiologic agent, that the disease was likely viral in origin and sexually transmitted. The gay male community was asked to make significant adjustments to their lifestyle and adapt restrictive practices to assure safer sexual encounters. Increased numbers of cases diagnosed brought the epidemic to within striking distance of most people's circle of friends. Increased screening for laboratory evidence of the immune deficiency demonstrated that a much larger number of people were affected than just those who were ill with life-threatening AIDS. Surely, it was hoped, if only the causative agent could be discovered, a cure would be forthcoming.

By 1984, human immunodeficiency virus had been isolated from specimens of patients with AIDS and AIDS-related conditions. The face of the enemy was known. Expectations ran high that a cure, or at the least a vaccine, would be available in no time. A society which had put men on the moon certainly should have no trouble devising the technology to combat a minute retrovirus.

Disappointment and distrust began to emerge by 1985. HIV had now been recognized for a year. Effective therapy had been found for Legionnaire's disease and toxic shock syndrome in much less time. Substantial progress had been made in dissecting the structure and function of the viral genome. Why was no progress being made in discovering an effective anti-viral agent? Why was it taking so long to investigate the agents that had demonstrated some *in vitro* activity against the retrovirus? Why were the clinical trials that were opening limited to so few patients and especially limited only to patients with end-stage disease as opposed

to those earlier in the infection whose immune systems could potentially be preserved by an early intervention?

A Movement Begins

Vitamin C, long reported to have broad anti-viral activity, also demonstrated in *vitro* activity against a human retrovirus.⁽¹⁾ In close proximity to Linus Pauling and his research institute, the AIDS at-risk population in San Francisco began self-treatment with ascorbic acid. High doses, up to 50 grams a day orally, or intravenous infusion were recommended. Anecdotal reports of prolonged survival in patients self-medicating with these regimens were circulated through the gay community grapevine and reported in the gay press. An orthopedic surgeon who championed the cause made the rounds of the lecture circuit at gay community gatherings offering testimonials to the benefits of vitamin C while himself attached to a liter of ascorbate solution via intravenous tubing. Interested patients received infusions in the homes of the proponents of this therapy who offered their residences as make-shift intravenous vitamin C clinics. Patients choosing instead to dose themselves orally were advised to escalate their vitamin C intake to "bowel tolerance", ingesting as much oral ascorbate as possible without developing completely intolerable diarrhea. Attempts were made to coordinate the investigation of potential benefits of high dose vitamin C through a prospective placebo-controlled clinical trial that was submitted to a number of funding agencies but was not approved. Subsequently, many of the advocates of ascorbate therapy expired secondary to the progression of their AIDS-related illnesses. Enthusiasm for further pursuit of this line of investigation then waned.

In addition to offering their own possible AIDS remedies, the community also devised ways to obtain agents that were being investigated by the medical establishment for their potential immunomodulating or anti-retroviral activity. In 1985, clinical trials of isoprinosine and ribavirin were underway in a number of medical centers in high impact HIV infection areas.^(2,3) It soon became known to the community that these same agents, not available in the United States, were widely sold in Mexican pharmacies. Individuals crossed the border to obtain their own supply of drugs from nearby pharmacies. Soon it became clear that a potential for profit existed. Responding to the increased demand for isoprinosine and ribavirin, and a devalued peso, prices in Tijuana pharmacies tripled within a year. Members of the gay community banded together in groups to make large scale deeply discounted purchases, effectively abolishing the price increase. Interested buyers, however, still had to pick up their purchases in Mexican border towns. An anonymous individual, writing under the pseudonym "Tooth Fairy" began supplying packets of information describing the purchase, use and importation of isoprinosine and ribavirin. However, this publicity eventually also resulted in an official FDA policy permitting such importations on a personal use basis. Numerous encounters between border agents and infected importers with their contraband of hope were reported in the media; a story highly reminiscent of the Laetrile and the cancer saga of years past.

Another throwback to days gone by was the community-initiated evaluation of dinitro-chloro-benzene (DNCB) as a potential AIDS therapy. DNCB had been used as a topical sensitizer and for testing anergy prior to the availability of currently used antigens. A small body of investigation suggested that topical application of

the sensitizing agent had efficacy in dermatologic conditions such as alopecia areata and common warts.^(4,5) Postulating a similar etiologic mechanism between warts and the lesions of Kaposi's sarcoma, a community dermatologist in San Francisco began applying DNCB in a 1% concentration dissolved in acetone to his patients' Kaposi's sarcoma lesions. He noted occasional responses but was more impressed by an apparent increase in helper lymphocyte number in patients repeatedly painted with sensitizing quantities of DNCB on clear skin.⁽⁶⁾ The treatment produced a characteristic temporary circular skin irritation which clearly "tattooed" participants in this underground treatment program.

DNCB was a widely available chemical purchased in kilogram quantities from photographic supply houses by a group that called itself the "Kamakazis". A solution was professionally mixed by the Kamakazis and distributed free of charge to individuals interested in trying the substance for its possible immune augmenting or anti-Kaposi's sarcoma effects. A nation-wide network of Kamakazis arose. When the dermatologist published the short article describing results of the T4 lymphocyte values in patients he was treating, the DNCB underground achieved some media exposure. At the suggestion of a television reporter, "Kamakazis" was dropped as too esoteric an illusion and the network of the DNCB distributors was henceforth dubbed the "Guerrilla Clinics". An infrastructure for drug distribution of alternative treatments on a national level had evolved. By 1987, it was reported that 14 guerilla clinics across the country were distributing drug and it was estimated that 5000 individuals were painting themselves with the sensitizer.⁽⁷⁾

With the availability of a distribution infrastructure and an increasing number of alternative therapies which were becoming available, a need for information dissemination arose. The ability to inform potential consumers of the availability of numerous agents quickly surpassed the capabilities and primary goals of the gay press. Organizations and publications devoted primarily to the spread of up-to-date knowledge on available underground treatments began to appear. Project Inform, a community-based group of AIDS activists in San Francisco, was created, in part, to provide such information. Using a twenty-four hour hotline and a monthly newsletter, Project Inform quickly developed into a major clearing house for the alternative treatment movement.⁽⁸⁾ The first issue of AIDS Treatment News, a bi-weekly update, first appeared in January 1987. The statement of purpose of this subscription newsletter is to report "on experimental and alternative treatments, especially those available now. It collects information from medical journals and from interviews with scientists, physicians and other health practitioners and persons with AIDS or ARC. Long time survivors have usually tried many different treatments and found combinations which work for them. AIDS Treatment News does not recommend particular therapies but seeks to increase the options available."⁽⁹⁾ Treatment Issues, the Gay Men's Health Crises (GMHC) Newsletter of Experimental AIDS Therapies, began publication as a "newsletter devoted to experimental AIDS therapies" in 1987. It also cautioned subscribers that "describing an experimental therapy should not be construed as recommending it. All new treatment should be done under a physician's care."⁽¹⁰⁾ Ironically, with the availability of these sophisticated publications aimed predominantly at the consumer population, the providing physicians were frequently ignorant of the particular new agent about which their patient was inquiring as a

potential therapeutic intervention.

Since the inception of the movement, zidovudine has been approved and licensed as the only therapy for HIV infection. The acceptance of zidovudine by advocates of the alternative therapy movement is mixed. Some hail it as a true lifesaver; others avoid it at all costs, dreading its toxicities. Realizing that the ultimate decision regarding whether or not any eligible individual will be treated with zidovudine is left to the patient and his/her provider, it was felt that the use of other agents need not necessarily be considered as strictly alternative. Instead, momentum developed to change the name of community investigated agents from "alternative" to "complementary" therapies. Thus, an individual could be taking zidovudine and "complementing" its activity with self-administered medications.

Alternative Access to Therapies

Recently there has been increased blurring between those treatments that are being evaluated by the established medical machinery and those which are undergoing widespread distribution in the affected community. In addition to alternative therapies, alternative means of obtaining investigational treatments have emerged. As with the ribavirin and isoprinosine importation in 1985, most of these alternative means of acquisition have involved transport of agents from foreign countries. Dextran sulfate, for example, was a drug that began to be considered as a potential anti-retroviral agent on the basis of its *in vitro* activity in mid-1986, even before the zidovudine placebo controlled Phase II trial had been terminated.⁽¹¹⁾ The actual Phase I dextran sulfate protocol was written in early 1987. It was recommended that the scientists who had demonstrated the *in vitro* activity publish

in the medical literature to increase enthusiasm for participation in clinical trials of the agent. Coincident with the publication, knowledge of dextran sulfate's easy availability from pharmacies in Japan became widespread. As the first patients were beginning the FDA approved Phase I clinical trial, others established networks for importation and sale of oral dextran sulfate purchased in Japan. Increasing availability of "street" dextran sulfate threatened to hamper the interpretation of data from patients participating in the Phase I trial.⁽¹²⁾ Rumor had it that a patient who was receiving the lowest dosage in the official dose escalation study supplemented his protocol dose with "street" obtained dextran sulfate to achieve the dose he believed would have anti-viral efficacy.

Becoming aware of the increased demand for dextran sulfate from their pharmacies, the Japanese authorities effected a shut down of exportation. Accusations and allegations flew. Threats of embassy demonstrations were made. In an effort to moderate this problem, the Food and Drug Administration soon announced that importation of drugs from foreign countries for personal use would be acceptable. This enabled individuals to bring in up to a three months' supply of a particular agent. So once again, as a large Phase I/II trial was initiated through the National Institute of Allergy and Infectious Disease AIDS Clinical Trials Group mechanism, easy availability of imported dextran sulfate returned.

Other alternative and creative means of obtaining drugs came to light during the dextran sulfate study. The Principal Investigator received an anonymous letter signed only "name withheld". The letter read:

"I buy my dextran sulfate from one of the participants in your study. He does not take the dextran, and his lab values show it. He stays in your study to get the dextran to sell and to have free lab tests

regularly. On the other hand, I do take the dextran. I take 1500 mg in three doses of 600 mg, 600 mg, and 300 mg at bed time. I have been since April 1988. My T-cells have gone from 289 to 884, gradually, as a result. I understand from my friend in your study that several participants are not taking the doses you think they are. I am writing because I know personally that dextran is a valuable anti-viral medication. I am hoping your test results will in some way reflect this erroneous input. Would a lie detector test be helpful?"

Dextran sulfate taken orally causes some gastrointestinal problems, but for the most part it is well-tolerated. Further studies have questioned whether the oral agent is even absorbed from the gastrointestinal tract.⁽¹³⁾ In general, most of the alternative or complementary treatments that have been championed by the movement have been similarly non-toxic. There almost appears to have been tacit assumption that "non-toxic" was equal to "efficacious" in the domain of self-administered HIV related medications. Additionally, those in the treatment movement felt that toxic drugs could not be safely handled. Thus, the ability to do significant harm through the complementary therapies program had been quite limited.

More recently, however, the stakes have increased as alternative distribution of a substance undergoing orthodox evaluation has produced possible untoward effects in the recipients. GLQ223 is a purified extract from the root tuber of a Chinese cucumber (*Trichosanthes kirilowii*). *In vitro* studies have demonstrated that this purified protein extract is capable of killing HIV infected macrophages and blocking replication of the virus in T-helper cells.⁽¹⁴⁾ In China, the root itself has been used for centuries as an abortifacient and, more recently, to treat choriocarcinomas. As Phase I safety trials of Compound Q were gearing up at a recognized AIDS treatment center, treatment activists were obtaining a similar compound from a

manufacturer in Shanghai, despite ongoing political turmoil in China.⁽¹⁵⁾ Sufficient quantities of Compound Q were exported to establish a treatment network in four United States cities. Patients were given vials of the substance to bring to the collaborating physicians. They asked their provider to inject them with the substance, thereby foregoing the need for the physician to obtain regulatory approval to participate in this "treatment experience". Extensive data was collected by the collaborating physicians along the lines of a traditional clinical study. The community network treated thirty-five patients with a fixed dose while the Phase I trial had completed evaluation of only the first four patients receiving one-twentieth of the community regimen dosage.

News of this underground network delivering "Community Q" to interested patients broke in the national media with the death of one of the patient participants. Additional reports of a number of patients possibly sustaining significant adverse side effects accompanied the reported fatality. Rather than expressing any compunction, organizers of this program of distribution and treatment with the unauthorized substance felt they had clearly demonstrated the need for major reforms in the system. Again, citing the lack of speed in the development and testing of drugs for HIV infection, the treatment activists maintain that they have challenged academic medicine, government programs and the Food and Drug Administration. At the same time, others felt that perhaps the alternative therapies movement had gone a step too far.

Currently Used Therapies

Despite rapid turnover of popular alternatives in the network, leading to the perception of a "Drug of the Month Club", a number of complementary therapies have persisted in their use by the HIV-infected community for sometime. A recent informal survey of 50 hospitalized AIDS patients in Chicago revealed that seven were using "unapproved medications".⁽¹⁶⁾ These were usually obtained from "non-physician practitioners, many of whom worked in community-organized alternative care clinics". When acupuncture, imagery and massage therapy were included as "alternative therapies", 36% of the AIDS patients in this study, compared to 2 of 30 cancer patients and 3 of 64 general medical patients were employing these modalities. Physicians caring for patients who might have access to some of these agents should be aware of their rationale for use, the existence of available efficacy data and the potential toxicities of these self-administered treatments. Some of the widely administered agents are reviewed below.

AL 721

AL 721 is a mixture including 70% neutral lipids, 20% phosphatidylcholine and 10 % phosphatidyl-diethanolamine.⁽¹⁷⁾ The components are all extracted from egg yolks and undergo an acetone extraction, felt by the developer to be the key to their activity. In Israel, AL 721 has been demonstrated to possibly increase immunologic function in the elderly.⁽¹⁸⁾ A report from Gallo's laboratory at the National Cancer Institute published in the New England Journal of Medicine in 1985 suggested *in vitro* efficacy of AL 721 in preventing the AIDS retrovirus from infecting susceptible target lymphocytes.⁽¹⁹⁾ It was postulated that through changes in the cholesterol of both the lymphocyte membrane and the virus envelope that the critical receptor binding would not occur, thus aborting the infection.

AL 721 was licensed to a sponsoring pharmaceutical company. It was unclear as to whether the substance was actually a drug or a food product. The license holder was more interested in developing it as a pharmaceutical agent. In the effort to speed availability of AL 721, health food companies and non-profit organizations arose to distribute an egg-based work-alike. The People With AIDS (PWA) Health Group which originally started in conjunction with the PWA Coalition in New York City became independent because the PWA Coalition charter did not allow for the sale of nutritional supplements. In San Francisco, the Healing Alternative Buyer's Club initially began distributing orders for AL 721 work-alikes that they bought through New York City associates. Subsequently, they also became independent. Reports of people using the substance claimed more energy, reduced night sweats, clearing of skin problems and an improved sense of well-being.⁽²⁰⁾

Individuals who were creating their own AL 721 work-alikes were advised that too much lecithin in the recipe could produce nausea, diarrhea, depression and anorexia. The formula required constant refrigeration. Individuals were also cautioned that there was a suggestion that a "rebound effect" might occur with increased viral production following the abrupt cessation of AL 721 therapy.

An early trial of AL 721 at St. Lukes-Roosevelt Hospital in New York City, evaluated 10 gm BID following fat-free meals.⁽²¹⁾ Eight patients with lymphadenopathy or ARC were treated. Five of seven patients showed decreased ability to culture virus from their peripheral blood. A decreased p24 antigen level was seen in one of five patients treated. HIV reappeared three months after cessation of therapy. One patient developed AIDS ten weeks following the study.

Long term follow-up in the eight patients showed four to have developed full-blown AIDS and two advanced ARC. It was the potential for benefit against HIV, however, became well-known. In the absence of any further formally organized trials at academic medical centers or through government sponsored mechanisms, individuals began to prepare home formulas of AL 721 that were disseminated in the alternative treatment newsletters. Following a recipe that required five tablespoons of lecithin combined with twelve tablespoons of water, subsequently whipped together with melted butter, individuals began to produce their own AL 721 "work-alikes".^{20}

The activist community became quite distressed that further trials of AL 721 within the mainstream medical establishment still were not planned. The frustration was summarized in the April 24, 1987 issue of AIDS Treatment News. "For this potential treatment, like a number of others, has fallen victim to a public policy nightmare of bureaucratic and commercial red tape. All but lost to institutional medicine, AL 721 has joined an underground, grass-roots circuit of national AIDS/ARC treatments, well supported by all existing evidence but largely ignored by the official research system for institutional (not scientific or medical) reasons".

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An open label, multiple dose ranging trial of AL 721 in patients with persistent generalized lymphadenopathy and AIDS-related complex was initiated through the National Institute of Allergy and Infectious Disease AIDS Clinical Treatment Group process as Protocol 022.^{22} The protocol began to enroll patients in December 1987. Forty-two patients were accrued; however, the trial was interrupted in April

1988 because of a reportedly limited drug supply. Ten patients received AL 721 20 gm PO BID. Patients were enrolled in cohorts of 10 to successively higher dosage levels in increments of 10 gms BID. Although the maximally tolerated dose was not reached in this study, 50 gm twice daily was the maximum dose evaluated. Patients were evaluated for toxicity and disease progression as well as immunologic and virologic markers. Serum lipid profiles were also monitored. Toxicities were predominantly confined to the gastrointestinal tract with 70% of the patients experiencing mild or moderate diarrhea. Mild to moderate nausea and abdominal pain occurred in 40-50%. In this eight week trial, AL 721 was concluded to be well tolerated even at higher dosages. A modest weight gain and a significant increase in serum cholesterol levels was observed. No indication of antiviral or immunorestorative effect was noted. Enrollment of additional HIV p24 antigen positive patients will be sought to finally assess the potential anti-retroviral efficacy of this substance. At this time, enthusiasm for egg lipid substances in the alternative treatment community also appears to be waning.

Naltrexone

Naltrexone is a narcotic antagonist which increases serum endorphin levels. Endorphins are felt to be a link in the communication between the brain and the immune system by advocates of psychoneuroimmunology. Reportedly, cells of the immune system have opiate receptors that respond to endorphins. Low dose naltrexone is felt to increase the number and the sensitivity of these opiate receptors. Initial evaluation of naltrexone in patients with HIV infection were conducted by a New York psychiatrist.⁽²³⁾ In a placebo-controlled trial begun in 1985, it was noted that AIDS patients on extremely low dosages of naltrexone at

bedtime appeared to be protected from the development of opportunistic infections. The patients who had received naltrexone were also noted to have a significant drop in their endogenous levels of serum alpha interferon. In patients treated on the placebo arm of this trial, five of sixteen developed opportunistic infections. No opportunistic infections developed in the twenty-two patients on naltrexone. After these observations, the study was unblinded and all patients were treated with the agent. When patients were switched from placebo to naltrexone, a similar drop in alpha interferon levels to physiological antiviral levels was seen. Patients who did not demonstrate this decline in alpha interferon levels all died within eight months. In patients sustaining the fall in their serum alpha interferon levels, a 40% 39 month survival was noted. Only one of the ten surviving AIDS patients suffered another opportunistic infection in the course of the trial. The other nine are all working full-time and are symptom-free 4 years following their AIDS diagnosis and thirty-nine months after starting naltrexone. Responders reportedly show stabilization of their T4 lymphocyte count as well as an increase in lymphocyte proliferative responses. The data from this trial has yet to be submitted for publication in a refereed journal.

Naltrexone tablets are available in 50 mg dosages. The recommended regimen in persons with HIV infection is an extremely low dose, 1.75 mg at bedtime. Individuals self-medicating with this program have obtained this substance from cooperating pharmacists who concoct a dilute solution. The daily cost of the regimen is only fifteen cents. The drug causes no side effects and has been suggested to be a "gentle treatment which mobilizes the person's own healing power". ^{24}

Dextran Sulfate

As mentioned above, dextran sulfate was initially evaluated following *in vitro* studies demonstrating its ability to block HIV infection of susceptible cells, including macrophages as well as lymphocytes. The anti-viral activity of dextran sulfate *in vitro* extended to other enveloped viruses, including HIV 2 and members of the herpes family.^(25,26) The accessibility and entrance of dextran sulfate into the underground alternative therapy market has been reviewed.

Although recent reports of questionable oral bioavailability and lack of efficacy of dextran sulfate have caused a decrease in its status as a popular self-administered agent, some individuals do continue to ingest oral dextran sulfate, frequently in combination with zidovudine. It is important to be aware that the side effects of these two compounds can be similar, especially with regard to laboratory parameters. Dextran sulfate increases hepatic transaminases. Zidovudine is metabolized by the liver and there may be complications of additive toxicities if the two are taken together in an unmonitored fashion.⁽²⁷⁾ Similarly, another laboratory side effect seen in the controlled trials was granulocytopenia which may also be a complication of the zidovudine treatment.⁽²⁸⁾

The subjective side effects most commonly reported by patients on oral dextran sulfate include abdominal bloating, often severe, with cramping and diarrhea. Reports of bloody diarrhea have also occurred. A recent study in which oral dextran sulfate was fed to mice demonstrated that the gastrointestinal flora of test animals changed and damage to the mucosa was seen.⁽²⁹⁾ This may also be the source of some of the gastrointestinal side effects reported in patients taking oral

dextran sulfate. A central nervous system dysphoric effect has also been described in patients on oral dextran sulfate. Some patients developed frank confusion. Headaches have also been reported.

Antabuse

In 1985 trials commenced in France to evaluate diethyldithiocarbamate (DTC), a chelating agent, as a potential immune potentiator. The agent had shown some efficacy in patients with malignant disease.⁽³⁰⁾ Early reports of the DTC trials demonstrated a potential immune augmenting effect.⁽³¹⁾ Demands for increased testing of the agent led to the initiation of trials in the United States as well. However, the number of clinical centers participating in the US trials and the speed with which the trials were started was frustrating to many who hoped that this agent would show promise. The alternative treatment networks discovered that raw DTC could be purchased or produced. Although the do-it-yourself compound was more likely to produce an offensive garbage-like smell, individuals began to take rectally administered DTC in an enema form or in suppositories. Absorption was presumed by the development of a chemical taste and smell in the patient after the DTC had presumably reached the blood stream. Others developed techniques to produce enteric coated capsules so that the homemade DTC could be taken orally, avoiding destruction by gastric acidity.

Antabuse (disulfiram) is metabolized in part to diethyldithiocarbamate. The exact percentage of Antabuse that converts to DTC in the bloodstream is uncertain. Activists claim that pharmaceutical literature supports the fact that the majority of Antabuse is broken down to DTC, whereas the French pharmaceutical

manufacturer states that the conversion is minuscule and the area under the curve is inadequate when oral disulfiram is administered as compared to the once weekly dose of oral DTC. Nonetheless, this information plus anecdotal reports of alcoholics with HIV infection on Antabuse having retained normal numbers of CD4+ lymphocytes led to the initiation of underground acceptance of Antabuse as an alternative treatment regimen. Advocates recommended that individuals take 500 mg of Antabuse orally twice a week. It was hoped that necessary blood levels could be achieved with this regimen. The main toxicity is the Antabuse-alcohol reaction. A metallic or garlic-like taste has been a frequently reported side effect. Otherwise patients have had little difficulty with this agent. Physicians should be aware that disulfiram decreases the rate at which certain other drugs are metabolized and therefore may increase the blood levels and possible clinical toxicity of certain substances. In the meantime, reports of controlled clinical trials performed in Europe continue to suggest possible immune enhancement from DTC therapy.⁽³²⁾ Results of the multicenter placebo-controlled trial which began in the US in January 1987 are currently being evaluated.

Hypericin

Hypericin, derived from Saint John's wort, a common plant used in herbal medicine, has been shown to strongly inhibit retroviral infection in laboratory and animal tests.⁽³³⁾ The agent has been used by herbalists, especially in Germany and the Soviet Union, as an anti-depressant for some time. Mice have been protected from infection by Friend leukemia virus when pretreated with hypericin. The authors of the Proceedings of the National Academy of Sciences manuscript which describe these animal studies extrapolate and claim that "preliminary *in vitro* studies with

pseudohypericin indicate that it can reduce the spread of human immunodeficiency virus." The major toxicity of hypericin has been photosensitivity. Increased liver function tests may be associated with medicinal use of the herbal tea. Reports of the herb itself poisoning grazing livestock have prompted caution in the use of St. John's wort tea as a potential anti-retroviral agent. However, enthusiasm to further investigate the agent which might cost as little as five dollars a month in its natural form as an alternative treatment is supported by AIDS Treatment News. "The fact that the drug can be given by mouth, has already been used in humans, and is found in a widely available plant continuously used as a medicinal herb and sold at little cost suggest that this treatment possibility might also be developed through the herbal and alternative treatment traditions, avoiding the years of delay built into mainstream pharmaceutical development".⁽³⁴⁾

Potential Benefits of Alternative Therapies

Despite the significant progress made in a short period of time, as yet there is no cure for HIV infection. People infected with the virus continue to undergo decimation of the cellular immune system and ultimately develop life-threatening opportunistic infections or malignancies. Numerous potential anti-retroviral, immunomodulatory and antibiotic regimens are under study through the National Institute of Allergy and Infectious Disease AIDS Clinical Trials Group mechanism. Other agents are being tested as pilot studies at academic medical centers and AIDS treatment clinics nationwide and throughout the world. The alternative therapies movement also provides the opportunity for testing increased numbers of potentially useful AIDS therapeutics. Certainly, even in the absence of careful monitoring and protocol analysis, should one of the alternatives turn out to be the

"magic bullet", it is likely that this would be recognized. In addition, it must be appreciated that all individuals with HIV infection are not able at this time to participate in established clinical trials. This may be due to geographic constraints or eligibility limitations of specific protocols. Others may continue to harbor some innate distrust of the medical establishment. Self-medicating with alternative or complementary therapies allows individuals with HIV infection to gain a sense of empowerment. Patients feel that they are taking their health and well-being into their hands, creating their own treatment regimen, instead of merely being dependent on the rules and regulations of the bureaucratic medical machinery. To many, this may provide a significant amount of hope which, at least compared to anxiety, could have a beneficial effect on the host response.

Potential Risks of Alternative Therapies

Just as hope may be a beneficial outgrowth of participating in alternative therapies programs, false hope can be detrimental. HIV infected individuals may find themselves investing not only their expectations but their finances into treatments which have very little possibility of positive effects. This was alluded to in AIDS Treatment News issue describing the formation of a task force to investigate AIDS consumer fraud and quackery established by the California State Attorney General's Office. "With so much unknown about AIDS, and with existing treatments so unsatisfactory, it will be hard to find consensus on how to distinguish legitimate, unproven and unconventional treatment attempts from unconscionable schemes to exploit people's desperation".⁽³⁵⁾

It is accepted that HIV prefers to infect cells of the immune system that are stimulated. In view of the unknown effect of many of the alternative treatments on the underlying immune system status, care must be taken that agents not activate lymphocytes, thus making them more susceptible to HIV infection. Similarly, substances that may suppress the cellular or other aspects of the immune system may prove detrimental to patients with HIV infection. It is for these reasons that individuals are cautioned against taking underground complementary therapies without physician monitoring.

Many patients feel that they cannot honestly report their use of alternative treatment regimens to their providers. They feel that use of such substances would be regarded as rebellious and non-compliant with the physician's wishes. Many patients would rather hide their self-medication histories than confess to the use of the various compounds that they may be ingesting. It is difficult for the provider to evaluate a patient's symptoms or the potential toxicities of drugs that are being prescribed without knowing that the patient may also be taking additional substances which could produce symptomatology or lead to drug-drug interactions. This complex patient-provider interaction can also be threatened by activist groups which foster the misconception of an "us vs. them" mentality rather than encouraging the perception of all of us working together against the common enemy - the human immunodeficiency virus. In the extreme, activism of this sort threatens to drive a wedge between the patient and the provider, compromising the therapeutic alliance. In the words of Galen, "He cures the most successfully in whom the people have the most confidence."

Finally, it has already been described above how the use of alternative regimens by patients participating in standard treatment evaluation protocols can serve to neutralize the possibility of obtaining any meaningful results. Patients who are not reporting other complementary therapies while participating in a Phase I trial of a new substance may obscure the true toxicities of the agent. Similarly in efficacy trials, if an individual is self-medicating with additional agents other than the one being clinically monitored, it becomes unclear as to what, in fact, may be producing the beneficial effect.

Recommendations

The alternative therapy movement in HIV treatment may serve to alter some of the traditional models of health care provision. Although there may be other diseases where the provider may be meticulously informed about latest advances in treatment by their knowledgeable patients, they are few. Physicians and other health care providers need to keep themselves informed as to the information that their patient population may be learning with regard to experimental treatment protocols. In addition to the community-based publications mentioned, the American Foundation for AIDS Research, with technical assistance from the National Institute of Allergy and Infectious Diseases and the Pharmaceutical Manufacturers Association, publishes a quarterly AIDS/HIV Experimental Treatment Directory.⁽³⁶⁾ This provides patients and providers with summaries of ongoing trials of the vast majority of potential HIV therapeutics occurring nationwide. To capture some of the information generated by patients self-administering alternative medications, physicians could join together to collect a standardized database of patient information. The HIV Alternative Treatment Database which has been

initiated by the County Community Consortium of Bay Area HIV Health Care Providers in the San Francisco region hopes to generate an observational database.⁽³⁷⁾ If enough patients are taking similar alternative regimens, some data may become available to elucidate potentially useful or possibly harmful treatment schemes. Although such observational databases are no substitution for carefully controlled prospective clinical trials, trends suggesting efficacy of a regimen could then be confirmed by a more classical clinical trial. In this way valuable data that otherwise would simply evaporate may be turned into pilot support for conducting a more orthodox evaluation.

The ability to question patients with regard to their use of alternative regimens in a non-judgmental and informed manner will greatly expedite the physician's access to this important historical information. Once the knowledge of use of alternative therapies has been obtained, physicians might be more cognizant of appropriate requirements for monitoring the clinical status of the particular patient. The patient-physician interaction may be encouraged to yield increased trust from both directions. With the growth of such understanding, an increased sense of partnership in the patient-provider relationship would likely result. Clinical investigators might also consider protocol designs which are more realistic regarding the use of concomittant medications. Current restrictions only serve to foster a "lie or die" choice for the patient study participant.

Regardless of an individual's attitude towards the use of alternative therapies by the HIV infected or other patient populations, physicians can no longer bury their heads and ignore the existence of such practices. Patients must be questioned

regarding the use of any non-prescribed medications. By informing themselves of the nature of these alternative therapies, their potential rationale for use, their most frequent toxicities, and by adopting a compassionate understanding for the forces which drive patients to seek such regimens, the health care provider can nurture the confidence and trust that may itself provide a significant therapeutic benefit for the patient with HIV infection.

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REFERENCES

1. Blakeslee JR, Yamamoto N, Hinuma Y. Human T-cell leukemia virus I induction by 5-iodo-2'-deoxyuridine and N-methyl-N'-nitro-N-nitrosoguanidine: Inhibition by retinoids, L-ascorbic acid, and DL- α -tocopherol. *Cancer Res* 1985; 45: 3471-3476.
2. Tsang PH, Tangnavarad S, Solomon S and Bekesi JG. Modulation of T- and B-lymphocyte functions by isoprinosine in homosexual subjects with prodomata and patients with acquired immune deficiency syndrome (AIDS), *J. Clin. Immunology* 1984; 4: 469.
3. McCormick JB, Getchell JP, Mitchell SW, et al. Ribavirin suppresses replication of lymphadenopathy-associated virus in cultures of human adult T-lymphocytes. *Lancet* 1984; 2: 1367 -1369.
4. Eriksen, Knud. Treatment of the common wart by induced allergic inflammation. *Dermatologica* 1980; 160: 161 -166.
5. Happle R. Antigenic competition as a therapeutic concept for alopecia areata. *Archives of Dermatology Res* 1980; 267: 109-114.
6. Mills BL. Stimulation of T-cellular immunity by cutaneous application of dinitrochlorobenzene. *J Am Acad Dermatol* 1986; VI: 1089-1090.
7. James JS. *AIDS Treatment News* 1987; 38, August 14.

8. P.I. Perspective. (Quarterly) Project Inform. National Hotline: 1-800-822-7422.
California Hotline: 1-800-334-7422.
9. AIDS Treatment News, James JS, P.O. Box 411256, San Francisco, CA 94141.
Published biweekly. 415-255-0588.
10. Treatment Issues: The GMHC Newsletter of Experimental AIDS Therapies. GMHC,
Department of Medical Information, 129 West 20th Street, New York, NY 10011.
Published ten times a year.
11. Ueno R, Kuno S. Dextran sulfate, a potent anti-HIV agent *in vitro* having synergism
with zidovudine [Letter]. Lancet 1987; ii: 1379.
12. Abrams D, Kuno S, Wong R, et al. Oral dextran sulfate (UA001) in the treatment of
the acquired immunodeficiency syndrome (AIDS) and AIDS-Related complex. Ann Inter
Med 1989; 110: 183-188.
13. Lorentsen K, Hendrix C, Collins J, et al. Dextran sulfate is poorly absorbed after oral
administration. Abstract T.B.P. 295 Vth International Conference on AIDS, Montreal
1989.
14. McGrath MS, Hwang KM, Caldwell SE. GLQ 223: An inhibitor of human
immunodeficiency virus replication in acutely and chronically infected cells of
lymphocyte and mononuclear phagocyte lineage. Proc Natl Acad Sci 1989; 86: 2844-
2848.

15. James JS. AIDS Treatment News 1989; 81: June 16.
16. Hand R. Alternative therapies used by patients with AIDS. N Eng J Med 1989; 320: 672-673.
17. Lytem M, Shinitzky M. A special lipid mixture for membrane fluidization. Biochim Biophys Acta 1985; 812: 133-138.
18. Shinitzky M, Lyte M, Heron DS, Samuel D. Intervention in membrane aging - the development and application of active lipid. In: Regelson W, Sinex FM eds. Intervention in the aging process: basic research and preclinical screening. Vol 3B, New York: Alan R. Liss 1983; 175-186.
19. Sarin PS, Gallo RC, Scheer DI, et al. Effects of a novel compound (AL 721) on HTLV-III infectivity in vitro. N Eng J Med 1985; 313: 1289-1290.
20. James JS. AIDS Treatment News 1987; 30: April 24
21. Grieco MH et al. Open study of AL 721 in HIV infected subjects with generalized lymphadenopathy syndrome (LAS). Abstract TP 223. III International Conference on AIDS, Washington, DC, 1987.
22. Mildvan D, Armstrong D, Antoniskis et al. An open label dose-ranging trial of AL 721 in PGL and ARC. Abstract W.B.P. 312, Vth International Conference on AIDS, Montreal, 1989

23. Bihari B, Drury F, Ragone V, et al. Low-Dose naltrexone in the treatment of AIDS: Long term follow-up results. Abstract M.C.P. 62, Vth International Conference on AIDS, Montreal, 1989.
24. James JS. AIDS Treatment News 1986; 16: October 24.
25. De Somer P, De Clerq E, Billiau A, et al. Anti-viral activity of polyacrylic acid and polymethacrylic acid. J. Virol. 1968; 2:886-93.
26. Mitsuya H, Looney DJ, Kuno S, et al. Dextran sulfate suppression of viruses in the HIV family: inhibition of virion binding to CD4+ cells. Science. 1988; 240: 646-9.
27. Good SS, Durack DT, de Miranda P. Biotransformation in various species and in humans of 3'-azido-3'-deoxythymidine, a potential agent for the treatment of AIDS. Fed Proc 1986; 45:444.
28. Richman DD, Fischl MA, Grieco MH, et al. The toxicity of Azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex: a double-blind placebo-controlled trial. N Eng J Med 1987; 317: 192-7.
29. Wells CL, Erlandsen SL, Rhame FS. Effect of oral dextran sulfate on the mouse intestine. Abstract W.B.P. 289 - Vth International Conference on AIDS, Montreal, 1989.