

To the Graduate Council:

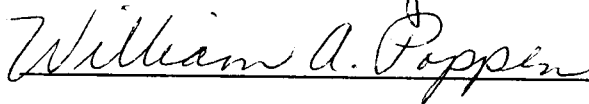
I am submitting herewith a dissertation written by John D. Parkinson entitled "Variables in HIV-Positive Patients that Serve to Predict Response to Whole-Body Hyperthermia." I have examined the final copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Education, with a major in Health Education.


James J. Neutens, Major Professor

We have read this dissertation
and recommend its acceptance:







Accepted for the Council:


Associate Vice Chancellor
and Dean of The Graduate School

VARIABLES IN HIV-POSITIVE PATIENTS THAT
SERVE TO PREDICT RESPONSE TO
WHOLE-BODY HYPERTHERMIA

A Dissertation
Presented for the
Doctor of Education
Degree
The University of Tennessee, Knoxville

John D. Parkinson

December 1991

ACKNOWLEDGMENTS

A very personal thanks goes to the following for making this possible.

My Committee for their cooperation, recommendations, and personal tolerance in leading me through this. The Committee consisted of:

Dr. James Neutens, Chairman

Dr. Charles Hamilton

Dr. Gene Hayes

Dr. Bill Poppen

Dr. Kenneth Alonso, Director of Laboratory Atlanta, for his personal warmth and courtesy extended to me. His willingness to patiently educate me in the area of my topic and his unselfishness in sharing data will never be forgotten.

I am very grateful to Anne Upchurch for her personal effort in arranging the material in the final acceptable format and making sure all necessary copies and forms were completed and on time.

The many things that secretaries do to make things workable on an ongoing basis are too numerous to mention. I would like to thank all of them and particularly Pat Wrinkle of the Department of Health, Leisure and Safety and Janet Bradford of the University Hospital's Department of OB-GYN.

ABSTRACT

This study utilized a small population of HIV-positive, symptomatic patients who were being treated with whole-body hyperthermia for Kaposi's sarcoma. An effort was made to identify any trends in the properties of the patients that might aid in the prediction of the HIV response to hyperthermia. This would allow for better patient selection for future treatments.

The group consisted of ten HIV-positive, Caucasian young adult males with confirmed Kaposi's sarcoma. All the subjects had been on the usual AIDS therapies but were no longer responding. They were each administered one hyperthermic session in which their body's temperature was elevated to 42°C and maintained for one hour.

Pre-treatment and one month post-treatment p24 antigen levels (a marker of HIV activity) and CD4 cell counts (a marker of the status of the immune system) were obtained.

The sample size did not lend itself to statistical procedures. However, the following trends and observations were noted.

1. Hyperthermia did not cause HIV replication, a fear that has blocked HIV-positive patients from access to hyperthermia.

2. Hyperthermia appeared to be a safe procedure, even in patients whose immune system was severely compromised.

3. The desired (decrease) effect on the p24 antigen level and the desired (increase) effect on the CD4 cell count appeared to be the greatest in patients whose immune system had not yet become severely depleted, suggesting early intervention with hyperthermia would be most beneficial.

Certainly, care must be used in any attempt to generalize from this small population. However, the observations do suggest certain promising trends that should be investigated further before conclusions as to their significance can be determined.

TABLE OF CONTENTS

Chapter	Page
1. INTRODUCTION	1
Problem Statement	2
Research Statements	3
Justification	3
Limitations	7
Delimitations	8
Assumptions	8
Definition of Terms	8
2. REVIEW OF THE LITERATURE	10
Introduction	10
AIDS Prevalence	11
Cost of AIDS	12
The AIDS Virus	14
Progression of the Disease from Infection to AIDS	15
Present Treatment of AIDS	17
Hyperthermia and Its Recorded Use on AIDS Patients in 1990	20
NIH's Response to Hyperthermic Treatment of Patients	22
Theory Supported Use of Hyperthermia in HIV Infections	24
Characteristics of Hyperthermia as a Treatment Modality	27
AIDS and Education	31
Summary	34

Chapter	Page
3. METHODOLOGY	36
Study Population	36
Treatment Procedure	36
Laboratory	37
Data Recording	37
Variables	37
Data Collection and Analysis	38
Case Study Analysis	38
Explored trends	
Significance of the trends	
Summary	40
4. RESULTS OF THE STUDY	41
Introduction	41
Subjects	41
Treatment Administered	41
Data Table	42
Summary	44
5. SUMMARY	46
BIBLIOGRAPHY	49
APPENDIX	63
VITA	65

CHAPTER 1

INTRODUCTION

The first reported case of AIDS in the United States was in 1981 by Gottlieb in a patient with pneumocystis. By the end of March, 1990, there were 124,536 cases reported (WHO, 1990c). In 1990, there were approximately 56,000 new cases in the United States. In 1993 there will be an estimated 104,000 new cases. Cost for the care of AIDS patients is estimated at \$4.3 billion for 1990 and \$7.8 billion for 1993 (Kerley, 1990; Hellinger, 1990).

AIDS/HIV-seropositive persons still remain without a curative treatment. The chemotherapies available for treatment, although powerful viricidal drugs, have been unable to eradicate the virus from the body.

Hyperthermia as a treatment tool is a controlled method of elevating the body's temperature for a therapeutic effect. It was theorized that hyperthermia, by helping break down the protective envelope of the virus, could be useful in treating patients infected with retroviruses such as HIV-1, the causative virus of AIDS (Yatvin, 1988; Marcial-Vega, 1990). Other theories suggest hyperthermia could be beneficial in the management of HIV infections by effectively stimulating the immune system of the host. This bolstered system would then be able to defend itself from the virus (Shidnia, 1990; Katner, 1990).

In 1990, whole-body hyperthermia (WBH) was used on two AIDS human subjects in the United States. The results were remission of their Kaposi's sarcoma, improvement in their p24 antigen levels, and improvement in their general overall physical symptomatology (Logan, 1990a). These findings were later questioned by the National Institute of Health (NIH) which has led to continued controversy between the NIH and researchers in hyperthermia.

As whole-body hyperthermia (WBH) is researched world wide, it becomes imperative to identify the variables of HIV infected persons that will aid in predicting the response to this treatment. A focus of education then becomes the incorporation of this information into all AIDS programs. This intent would be to increase the general awareness of health care providers and the public to appropriate patient criteria for selected and specific treatments. The result would be earlier treatment of an identified target segment of the infected population.

Problem Statement

The problem of this study was to identify variables in HIV-positive patients that would serve as predictors of response to whole-body hyperthermia treatment.

Research Statements

1. Which of the following variables appeared to be useful in predicting how an HIV-positive patient will respond to whole-body hyperthermia?
 - A. Level of p24 antigens prior to treatment
 - B. Level of CD4+ cell count prior to treatment
2. Did hyperthermia appear to affect the level of CD4+ cells?
3. Did hyperthermia appear to result in HIV replication as reflected by an increase in the p24 antigen level?
4. Did hyperthermia appear to be a safe treatment?

Justification

It is estimated that AIDS spreads at the rate of 4 to 12 persons per every infected person (Gordon, 1989). The World Health Organization (WHO) estimates that presently there are as many as 1.3 million cases of AIDS world-wide. This does not include the asymptomatic HIV infected persons of which there are an estimated 1 million just in the United States (WHO, 1991).

Treatment for AIDS or HIV-seropositive patients has, to this point, lacked permanency. It has consisted mainly of zidovudine (AZT), a powerful anti-retroviral agent which delays the deterioration of the host's immune system. It is indicated for use in the early, asymptomatic stage of the

infection (Kess et al., 1991; Staff, 1990a). Recently AZT has come under attack for not being nearly as effective as indicated by the initial figures provided by its parent company, Burroughs Wellcome (Cotton, 1991).

Present studies are encouraging for other agents such as 2',3'- dideoxyinosine (ddI) and dideoxyeytidine (ddC). These two drugs appear to delay the progression of the disease in those patients who no longer are responding to AZT (Cotton, 1991). Again, it produces a delay in the progression, not a cure. A vaccine from MicroGeneSys, Inc. is being tested as an immunotherapeutic agent. This vaccine, VaxSyn HIV-1 (p24), is intended for use in persons who are HIV positive but whose immune system is still well intact as indicated by a CD4 cell count above 500 per cubic millimeter. The initial human trials of this vaccine were started in the fall of 1990 at the National Institute of Allergy and Infectious Diseases Clinical Center (Goldsmith, 1991).

Another approach that is being studied is the effect of hyperthermia on the HIV. It is an accepted medical fact that viruses can be killed with heat. This includes the retroviruses, the family of the AIDS causative virus (Marcial-Vega, 1990). Hyperthermia has been used as an adjunctive treatment in the management of neoplasms for approximately 10 years. It has been found to be a safe and well tolerated treatment (Shidnia, 1990; Bicher, 1990).

Since the virus can be killed by heat and hyperthermia is an available treatment modality, researching the effects of hyperthermia on this particular virus seemed a logical step.

Using CD4 cells as a marker, the likelihood of developing AIDS within 18 months can be predicted. For example, a person with a CD4 cell count of 100 stands a 58% chance of developing AIDS within 18 months. A person with a level of 500 cells stands a 4% chance of developing AIDS within the same time limit (Fahey et al., 1986). These CD4 levels can be used as markers for response to treatment. A good response to AZT is defined as a 100/mm³ increase in the CD4 cells (Cotton, 1991).

Other treatment modalities, such as aerosolized pentamidine for the prophylactic treatment of pneumocystis pneumonia, are aimed at symptomatic relief or prevention and management of the opportunistic diseases (Miller-Catchpole & Rapoza, 1990). However, there are still no agents available or under study that are curative or even effective at all stages of infection.

It seemed logical that many patient variables would influence the effectiveness of any specific treatment. Presently there is growing evidence that sex and ethnic differences affect the response to AZT (Hamilton et al., 1989). However, there are no studies in the literature that focus on specific variables of HIV-positive patients and how these variables affect, or are affected by, whole-

body hyperthermia. Collecting and analyzing data from the records of patients who have undergone WBH will aid in the appropriate patient selection process. It also could provide a basis for modifying a treatment protocol for application to a broader patient group.

Hyperthermia appears to have the potential of converting thousands of HIV-positive persons, some symptomatic and others asymptomatic, into healthy, productive members of society. This would eliminate unmeasurable physical, social, and psychological pain while releasing some of the billions of health care dollars presently destined for the care of the growing number of chronically ill AIDS patients (\$6.5 billion for 1992) into other areas of health care (Hellinger, 1990).

Evidence suggestive of the effectiveness of hyperthermia is reflected in the following case report of the first known AIDS patient to undergo whole-body hyperthermia:

In February, 1990, a 33 year old, white, male, AIDS patient with progressive Kaposi's sarcoma (KS) was treated with extracorporeal whole-body hyperthermia. He had previously been treated with the conventional chemotherapies but continued deteriorating. Following the hyperthermia treatment, his repeated HIV cultures were reported negative and his p24 antigens were reported negative. His general physical symptomatology was remarkably improved. The

Kaposi's lesions showed clearing or marked regression. The procedure was tolerated well and the patient showed no later complications to the treatment (Logan, 1990a, Alonso, 1990a). Since January, 1991, the patient's CD4+ cell count showed a decrease but the patient's good general health symptomatology was maintained. He is on no viricidal. He has requested another whole-body hyperthermia treatment. This request was denied because of the government's refusal to allow further use of hyperthermia as a treatment for AIDS (Logan, 1990a).

As variables are identified as affecting the response to treatment, the process of increasing the awareness of health care providers and the public to these variables will be a major educational task. As variables are recognized as more specific to expected treatment response, educators will be able to develop programs appropriate for different segments of the HIV infected population. The end results will be a better informed general population and identification of infected persons into appropriate treatment groups. The matching of the groups with the appropriate treatment protocol should lead to the most effective treatment strategy.

Limitations

The cooperation in the sharing of data by the physician/director of The Laboratory Atlanta Foundation for

Cancer Research and Treatment, Inc. (coordinator of data collection/interpretation in the study) was necessary.

Delimitations

Due to the time frame, data only on those patients treated by September, 1991 and whose data are available prior to the fall of 1991 through Laboratory Atlanta Foundation for Cancer Research and Treatment were used in this study.

Assumptions

1. All relevant treatment data were accessible.
2. HIV-positive patients reported honestly in those items of self-reporting.

Definition of Terms

1. p24 antigen--One of the protein antigens of the virus which gives rise to antibody formation by the host. It serves as the basis for one of the more commonly used screening test for sero-positivity. Its level also correlates directly with the severity of the disease progression.

2. HIV-1--The retrovirus which is responsible for most of the AIDS cases. HIV-2 is also thought to be a causative agent for the disease. It does not appear to be as virulent or as wide spread as HIV-1.

3. AIDS--Acquired Immune Deficiency Syndrome.
4. HIV-positive--Indicates infection with the HIV virus. It does not imply the person is symptomatic.
5. Whole-body hyperthermia (WBH)--A controlled method of elevating the entire body's temperature for therapeutic purposes.
6. CD4 cells--These are the type of cells which are attacked and used by the virus in its maturation process leading to depletion of the cells and suppression of the immune system. These cells also are used to titrate the severity of the compromise of the immune system. In that capacity, they serve as an indicator for the initiation of chemotherapy. When the CD4 cell count drops below 500, the patient is usually placed on AZT. A CD4 count of 200 or less will justify the diagnosis of AIDS even in the absence of any other findings or symptoms of a disease or process.
7. AZT (zidovudine)--This is a potent viricidal agent and is the most commonly used chemotherapy in HIV-infected persons. Zidovudine is an analogue of thymidine and is more accurately referred to as ZDV. Most of the public still refers to the medication as AZT.
8. Extracorporeal hyperthermia--This is a method of inducing hyperthermia by shunting the blood out of the body, through a heat exchanger, and back into the body for a therapeutic purpose. The case described previously underwent extracorporeal hyperthermia.

CHAPTER 2

REVIEW OF THE LITERATURE

Introduction

AIDS, unheard of until ten years ago, has resulted in the most severe strain on the health care system that has faced society in modern times. This chapter includes a review of the disease including its prevalence, individual and societal cost, unique characteristics of the AIDS virus and the disease progression. It then recognizes some political, religious, and ethical situations specific to this disease. Preventive measures, including education, and available treatment programs are briefly reviewed.

The chapter then discusses whole-body hyperthermia as a theory supported treatment modality to be used in the fight against the HIV virus. The physiological stress produced by whole-body hyperthermia and resultant safety of the procedure are reviewed.

Although studies attempting to identify variables which could serve as predictors of treatment response in HIV-positive patients are lacking in the literature, there are reports that certain characteristics of an individual, such as genetics, may play a role in the progression of the AIDS disease (Gorman, 1990). However, studies focusing on patient variables that determine or influence treatment

outcomes are just now beginning to appear in the literature.

AIDS Prevalence

The number of AIDS cases is growing at an alarming rate. There were, as of March 1990, 124,536 cases reported in the United States. Three months prior to that time, there were only 82,764 reported cases (Kerley, 1990).

By February 1, 1991, WHO had received confirmation of 323,378 cases world wide. This included cases reported from 158 countries that report to WHO. This figure was an increase of 9,000 compared to the January figure (WHO, 1991). WHO also estimated that while only 323,378 cases had been reported, 1.3 million cases probably existed. In addition, in the United States it was estimated that approximately 1 million persons were infected with the HIV virus and of this number approximately 60% would have a CD4+ cell count of less than 500/mm³ (CDC, 1990b).

The first decade of AIDS saw approximately 500,000 cases in women and children world wide. It was estimated that by the year 2000, there would be approximately 10 million children infected with AIDS. During the 1990s approximately 3 million women and children world wide are expected to die from AIDS (WHO, 1991; CDC, 1991).

In the cities of the Americas, Western Europe, and sub-Saharan Africa, AIDS was the number one killer of women ages 20-40. Additionally, in the major cities of these areas,

30% of the infant and child mortality rate was attributed to AIDS (WHO, 1990b).

In 1986, it was reported that heterosexual transmission was responsible for approximately 70% of AIDS cases reported in Haiti (Johnson and Pape, 1989). In 1991, in this country, the rate of infection in women exceeded that of men by 27% to 18% respectively (WHO, 1991).

Aids spreads at an estimated 4 to 12 persons becoming infected per every infected person. In order to contain the epidemic, this rate should be cut to approximately 1 to 1 (Gordon, 1989). In the absence of curative antiviral chemotherapies, AIDS, as a major health problem will continue to increase into the future years even if the transmission of the disease were to stop today (Rutherford & Werdegarr, 1989).

Cost of AIDS

The lifetime medical cost per AIDS patient was estimated to be \$85,000. This was higher than the earlier estimates of \$40,000 to \$75,000 (Hellinger, 1991). This cost was based on a 15 month survival period. When based on the projected number of cases, this amounts to approximately \$3.3 billion in 1989, \$5.8 billion in 1991, 6.5 billion in 1992, 7.8 billion for 1993 and was projected to reach 10.4 billion by 1994 (Kerley, 1990; Hellinger, 1990). There is a tendency to look to broad-based community services as an

effort to contain cost. However, if the experience with the long term care of the elderly is an indication, this will only increase the total overall cost of care (Benjamin, 1988). Internationally, the United States government in 1989 designated 69 million dollars to programs through various agencies. The primary agency was the WHO and its Global Programme on AIDS (Aultman et al., 1989). All these costs have placed a strain on the nation's entire health economy.

Other areas of indirect monetary cost included the increased employee safety precautions implemented in the workplace, particularly at health delivery sites. This necessitated broad based and on-going employee educational programs and increased the usage of various protective supplies such as gloves, masks, and gowns. Another indirect cost was the loss of tax revenues secondary to the patient leaving the labor market. Frequently other tax generating persons, the caretakers, also have had to quit work (Kess et al., 1991).

While the indirect costs are difficult to estimate, the psychosocial cost are impossible to estimate. The emotional drain, the retaliation of a frightened society, all contribute to imposing a cost to the victim and family that has not been witnessed in this century. The HIV infected person is subjected to discrimination in housing, employment and even health care. An infected person fears losing or

being unable to obtain insurance coverage. New employment always brings the associated anxiety of HIV screening. These are only a few of the recognized psychosocial costs (Kess et al., 1991). The psychosocial burden and pain are so great that counselling to both patients and health care providers should be integrated into any AIDS program (Blomberg & Flynn, 1989; Eakin & Taylor, 1990).

The AIDS Virus

The AIDS virus is a master of viruses. Its life cycle is extremely intricate and sophisticated. It passes through several complicated steps to reach maturity, including using the properties of the host cells to aid in its maturation. It is classed as a retrovirus but its genome is much more complex than that of other retroviruses. The virus' RNA (genetic material) uses virus supplied enzyme functions to reverse-transcribe its RNA template into a DNA copy which is then incorporated into the host cell's own genetic material permanently (Terwilliger et al., 1990)%. The RNA is surrounded by proteins including the P24 (basis for one of the testing methods). Surrounding these proteins is a membrane or envelope of glycoproteins. One of these, the gp120, is what binds to the CD4 molecule of the human immune cell. From this binding, the virus enters the cell and can remain there for long periods (latency time) before erupting to then infect other cells (Gorman, 1990). Now that these

properties are better understood, they serve as targets of investigators as points of intervention by chemicals or other treatment modalities (Buchbinder, 1990). This understanding of the virus has resulted also in the development of several potential vaccines (Lane, 1990).

Progression of the Disease from Infection to AIDS

When a person becomes contaminated or inoculated with the virus, he/she stands about a 50% chance of becoming infected. It appears that variables of the exposed person influence whether exposure leads to infection. The stage of the disease in the infected person as well as the route of contamination also influence whether infection occurs (Pinching, 1988). The WHO reported that 30% of infants born to infected mothers will test HIV-positive with four-fifths of this group dying before the age of five. It is not understood what variables determine which children become infected and why 70% of children of infected mothers escape infection (Editor, 1991b).

Once infection does occur, many factors collectively decide how the disease will progress. The individual may remain an asymptomatic carrier, become a symptomatic AIDS related complex (ARC) patient, or develop AIDS. What determines which way the disease progresses is not clear. It appears that infection, malnutrition, infancy, multiple

pregnancy, and drugs that have an immunosuppressive effect may contribute to a more rapid course of the disease from asymptomatic to the symptomatic stage (Pinching, 1988).

Gall and Montagnier, co-discoverers of HIV, are split on the role that other factors play in the progression of the disease. Montagnier feels strongly that coinfection with mycoplasma, especially mycoplasma pirum, may be a significant factor in the depletion of the CD4 cells that is characteristic of HIV progression. This mycoplasma attacks the T lymphocytes and is commonly found as a systemic infection in AIDS patients. He points out that this may be one reason anti-viral drugs alone do not cure the disease. He suggests treatment should be broader than just targeting the HIV. Gall, on the other hand, does not feel the presence of such cofactors is necessary for HIV progression (Cotton, 1990).

Genetics is another factor that appears to play a major role in the initial disease susceptibility (Pinching, 1988). The mechanics of how genetics affects the progression of the disease is not understood. African-Americans and Latinos have the highest representations in the HIV infected population. This is greater than can be explained on the basis of other known factors such as exposures (Gorman, 1990).

There is another recognized virus, HIV-2, that is associated with AIDS but is distinct from HIV-1. It is

beginning to get a lot more attention. It is more limited in its habitat, being seen more frequently in Africa. While it is felt it can cause AIDS, researchers at this time do not know how pathogenic it is compared to HIV-1 (Romieu et al., 1990). Tests for the detection of the AIDS virus are now available that can, with a high degree of sensitivity and specificity, distinguish between HIV-1 and HIV-2.

Present Treatment of AIDS

It has been suggested that a vaccination will be ready for clinical human trial in 2 to 3 years. How effective the expected vaccine will be is unknown. Several approaches have taken in an effort to develop a workable vaccine, including a cell line from the armyworm or caterpillar (Neil, 1990; Lane, 1990).

Even with an effective vaccine preventing new infections, those persons presently HIV positive will be requiring treatment for years to come. According to Hickey's estimate in 1988, the number would be approximately 2 million. The CDC's estimate in 1990 was reduced to approximately 1 million (CDC, 1990).

Infected persons are faced with a very limited arsenal of treatments. The most common antiretroviral drug in use is zidovudine (known commonly as AZT). AZT was released in 1987 and initially was used only after a person was diagnosed with AIDS. It now is used in asymptomatic HIV

patients (Staff, 1990b). This drug decreases the replication of the virus. It is not curative and can lead to extreme hematologic toxicity, including anemia or neutropenia (Volberding et al., 1990).

There are new drugs just entering the market but are usually reserved until toxicity from AZT occurs. Included are ddI (dideoxyinosine from Bristol-Myers Squibb Co.) and ddC (dideoxyeytidine from Hoffmann-LaRoche). These are used generally in patients who are no longer responding to or have developed a toxicity to AZT (Cotton, 1991). Various vaccines are being used as therapeutic agents. Among these are the Salk HIV immunogen that is intended to promote passive immunity in infected persons. The Becton Dickinson Corp is testing another form of immunotherapy of patients with AIDS-related complex. The National Institute of Allergy and Infectious Diseases (NIAID) is testing the VaxSyn HIV-1 (p24) as a treatment for asymptomatic sero-positive patients (Goldsmith, 1991). Another preparation, not on the market yet, which looks very promising is made from a compound found in the pokeweed. This pokeweed substrate has been shown to exhibit antiviral activity against similar viruses (Zarling, 1990).

Isoptinosine is a drug used in Sweden and Denmark. It is not a viricidal and is not considered a potential curative for the infection. This drug, used in a study of 831 HIV-positive patients, appears to aid the immune system

in preventing the progression of the infection to clinical AIDS. The drug, manufactured in the United States, shows promise but is viewed with skepticism by our FDA and is not in use in this country (Cotton, 1991).

Dementia is frequently associated with HIV infection. Its mechanism, however, is not understood. One possible clue was reported by Dreyer, 1990. He found a 300 fold increase in intracellular calcium of neurons when exposed to gp 120 (one of the coat proteins of the HIV virus). He also found that a calcium channel blocker, specifically nimodipine, would block this increase. While this may prove to be an aid in the management of AIDS dementia, it is not a curative for the infection.

The HIV produces a protease enzyme which in turn produces proteins required for the virus to replicate (Dreyer, 1990). According to Dreyer, Abbott Laboratories have developed a protease inhibitor which could be given to humans at a concentration sufficient to prevent replication at only 1/500 of the human toxic level. This certainly looks promising but it is not yet available.

Since the virus attaches to the CD4 receptors, one treatment approach was to administer solubilized CD4 receptors to infected persons. Hopefully the free-floating CD4 receptors would tie up the virus that would otherwise attach to the CD4 receptors of living immune cells (Gorman, 1990). One such study sponsored by the National Institute

of Allergy and Infectious Diseases' AIDS Clinical Trials Group found that recombinant soluble CD4 (rscd4) was well tolerated in the 25 male patients tested. There were no reports of any serious toxic symptoms secondary to the drug. Those patients demonstrated a decrease in their HIV-p24 antigen levels suggesting the compound did have antiviral activity (Gorman, 1990).

The hr5, a mutant of the adenovirus Ela, may well have an inhibitory effect on the replication of the HIV-1 virus. This is still in the early study stages and needs further research but looks promising.

In June of 1991 at the International Conference on AIDS held in Florence, Italy, many other variations of vaccines and drugs were introduced as hopefuls. Some were in the human phase of testing. It appeared more progress was being made in the area of treatment than in the area of preventive vaccines (Staff, 1990b).

Hyperthermia and Its Recorded Use on AIDS Patients in 1990

Although Yatvin had, in 1988, theorized a combination treatment approach (which included hyperthermia) in HIV-infected patients, hyperthermia had not been used in a patient known to be HIV-positive until February, 1990. At that time Alonso and Logan of Atlanta treated a patient with Kaposi's sarcoma (KS) using hyperthermia. There was a

significant improvement in his AIDS status as demonstrated by improvement of general physical symptoms, a marked increase in his t4 cells as well as regression of the KS lesions (Logan, 1990; Jenkins, 1990).

A second AIDS patient with KS was treated a few months after the first case. According to the treating physicians, this patient's referring physician had given the patient only 2-4 weeks to live prior to the treatment. Personal communication with the treating physicians several months post-treatment described the patient as having improved but remained in critical condition. The patient had returned to Chicago and continued under the care of his physician there.

A third patient was treated in Mexico during the summer of 1990. This patient was extremely ill prior to treatment according to his private physician who had referred him for the hyperthermia. This patient died several hours after the treatment. It is the opinion of the referring physician that he did die directly as a result of the hyperthermia treatment because his health had deteriorated to such a point he could not handle the physiological stress of the treatment. The Mexican government did not allow specimen review to determine the effect of the hyperthermia on the HIV (Alonso, 1990a).

NIH's Response to Hyperthermic Treatment of Patients

The first two AIDS patients treated with hyperthermia were actually treated for their Kaposi's sarcoma, not their HIV infection. Following the treatment, general physical improvement was noted suggesting to the doctors that the HIV infection, as well as the Kaposi's sarcoma, had benefitted (Logan, 1990a).

NIH did a field visit to the treatment site in Atlanta. In their summary, NIH left the impression that the initial diagnostic findings on the first two patients were erroneous. They concluded that further research in the use of hyperthermia as a treatment for AIDS was unwarranted (NIH, 1990). The summary report did not address any of the theory-based research being done at various centers throughout the United States at that time. NIH did not respond to inquiries concerning some errors in their data and their subsequent report (Alonso, 1990).

The NIH summary report brought a disturbed reaction from physicians across the country. Bernard Bihari, Medical Director for the Community Research Initiative (which is an AIDS research organization in New York) had seen the first patient treated and agreed with Alonso's diagnosis. Steinhart, an internist in Miami who treats AIDS patients, also agreed. Both physicians felt there was sufficient scientific background to warrant further research with

hyperthermia as an AIDS treatment. Steinhart supported the experiments being done independently without NIH's agreement (Editor A, 1990).

McLaren had reviewed the report and suggested it for publication in the Molecular Oncology and Tumor Journal. McLaren had been conducting hyperthermia for 10 years and felt the use of hyperthermia in HIV infections was theory supported (Editor, 1990a).

Dr. Robert Jenkins of Los Angeles made a site visit to Atlanta in June, 1990. He examined the first patient who had been treated. He agreed the patient had significantly improved. He supported continued research in the area and felt an efficacy study should be done promptly (Editor, 1990a).

At the 7th annual meeting of the American Society of Clinical Hyperthermic Oncology in Atlanta, November, 1990, one afternoon was designated for presentations concerning hyperthermia and AIDS. Although an invitation had been extended to the NIH, they did not send anyone to defend or support their negative comments regarding hyperthermia as a possible treatment for the AIDS virus.

The scientific presentations were unanimously in support for the continued research of hyperthermia as a treatment for the HIV. It was not a question of "does it work," but more of a question of when is the best time to

use it, how does it work, and should it be used with other modalities.

Theory Supported Use of Hyperthermia in HIV Infections

Spire of the Pasteur Institute in 1985 raised the possibility of heat being useful against the HIV. He found it was possible to get a 40% reduction of the virus by exposing them to 42°C for 30 minutes. Wong et al. (1989) at the conference on AIDS also supported the viricidal effect of heat on the HIV.

Yatvin, 1988, recognized the possibility of modifying the virus' protective envelope as a focal point for treatment. This envelope has a high lipid content and serves to protect the virus from what would otherwise be lethal agents. He suggested using compounds already available and known to have this property (including a low lipid diet and hyperthermia) to damage the membrane, thus making the virus vulnerable to a kill by the already available viricidal. In this theory, heat would not be used to kill the virus directly but would damage the virus' envelope, making it vulnerable to the viricidal agents.

Stanley, of the NIH's section on allergy and infectious diseases, in 1989 reported that findings from the laboratory supported the concern that heat would cause replications of the virus. This report served as the basis for the

nationally publicized negative response from NIH toward hyperthermia. In June of 1990, Dr. Fauci, the director of the allergy and infectious disease section at the time, appeared on national TV news and concluded that hyperthermia results in HIV replication. Dr. Fauci used the Stanley study to support his conclusion. He failed to present any review of other research in the literature pertinent to the effects of heat on the HIV (none of which supported the replication findings). At the 1990 November conference of ASCHO, general concern was expressed regarding the methodology of the Stanley study and the resultant generalizability of that report (Alonso, 1990b; Marcial-Vega, 1990).

Katner hypothesized that hyperthermia would lead to increased activity by the virus but also increased exposure of the virus. By being exposed, the virus could be killed by the patient's own immune system (which is also stimulated by the hyperthermia) and/or available viricidal. It was his feeling that as long as the virus was allowed to hide and remain inactive, it could not be eradicated. Hyperthermia, he felt, would serve as that necessary catalyst. Although he submitted this hypothesis to the NIH for consideration, he did not get a response from them (Katner, 1990).

Levin reported to the ASCHO in 1990 that heat had been found to increase the lethality of certain drugs. He felt that membrane modification seemed to be the key mechanism

with hyperthermia and that this modification occurred best at a temperature of 42°C. He stressed that the temperature might be able to be kept at a lower point if combined with chemotherapy.

Marcial-Vega found that there appeared to be a greater percent of a virus kill if the concentration of the virus was smaller. This could indicate the need for early intervention in the disease process if optimum results are to be achieved. Marcial-Vega, aware of the latency period of the virus, used 20 days as the cut off point in his laboratory experiment. If no virus was detectable after that time, the patient should, theoretically, be free. He used a HeLA CD4(+) monolayer culture to detect evidence of the virus.

Logan, of Atlanta and one of the two doctors who treated the first two patients, stated that while the core body temperature was 42°C, the blood's temperature, as it passed through the heat exchanger, was increased to 44°C. The body's total blood volume passed through the exchanger every three minutes. He suggested that maybe the killed viral particles could pass back into the system and serve as a type of vaccine (Logan, 1990a).

Characteristics of Hyperthermia as a Treatment Modality

Although not knowingly used in the past on HIV-positive patients, hyperthermia is a treatment that has gained acceptance as a therapeutic tool. It generally is used in conjunction with radiation or chemotherapy for various forms of neoplasms.

It was observed that some types of cancer cells appeared more sensitive to heat (41°C or greater) than normal cells (Robins et al., 1989). Levin, in 1990, reported to the ASCHO his experience with over 1200 patients. He felt that the cell kill does not all occur at the time of the initial hyperthermia but necrosis exists over a period of time following the treatment. During that time, chemotherapies and radiation appeared to be more effective on the already damaged cell. He also found that heat increases the lethality of certain drugs, suggesting some combinations (heat and drug) were better than others. He felt membrane modification seemed to be the key mechanism with hyperthermia and that this modification occurs best at a temperature of 42°C . It was his opinion that the temperature might be able to be kept at a lower point if combined with chemotherapy. The fact that hyperthermia enhances certain chemotherapies was supported by repeated clinical studies (Stewart & Bibbs, 1984; Li, 1984).

It appears that 42°C is the limitation of safe systemic hyperthermia (Bull, 1984). In the treatment of neoplasms, whole-body hyperthermia allows systemic or metastatic disease lesions or agents to be reached at one time as contrasted to regional or local hyperthermia (Li, 1984). Since HIV infection is systemic and not a localized disease, this could be another reason for considering whole-body hyperthermia treatment.

In treating neoplasms with hyperthermia, it was shown that the time it takes to achieve the desired temperatures was dependent on several factors. For example, the higher the degree of emaciation, the greater the amount of tumor mass, and the slower the metabolic state, the longer it will take to reach the desired temperature. This becomes a problem because of the increased cardiovascular load (Bull, 1984). This might suggest that patients with advanced opportunistic disease are not good candidates for WBH but treatment instead should be initiated at the earliest point of known infection. At that point, the body's physiological system could better withstand the stress of the treatment.

Whole-body hyperthermia, while stressful to the patient- particularly the cardiovascular system- appears to be well tolerated. Robins et al., in 1985 administered a total of 52 treatments to 12 patients as an aid in the management of neoplastic diseases. They did fluid and electrolyte replacement as needed throughout the treatments.

The patients tolerated the treatments well. The temperatures ranged from 39.5 C to 40.5 C for one group of patients and 41.55 C and 41.8 C for another group. This same investigative group also gave a group of patients treatments biweekly and reported them as being well tolerated (Robins, 1985).

It is interesting that, in mice, it is possible to develop a short-time thermotolerance. By subjecting the mouse to hyperthermia at a temperature lower than the desired target temperature and then subjecting it several hours later (maximum benefits were obtained 48 hours later) to the target temperature increased the survival rate significantly (Weshler et al., 1989). A similar study was done by Kapp, (1983) who also concluded it was possible to develop a thermal tolerance. Since most AIDS victims are physically weakened, this might be a consideration in attempting to decrease the physiological stress on the body's system.

In one study by Cronau et al., 1984, it was estimated that during a hyperthermia treatment the heart would increase its output by as much as 200% of its normal load and would increase its oxygen uptake by as much as 35%. That is a good argument for general anesthesia. Under general anesthesia, the doctor has better control of changes in the patients physiological system. Sweating alone can account for 10 cc of fluid loss/min/1 degree rise in

temperature. To raise a temperature to 42° C in 2 hours and maintain it for another 2 hours, the patient could lose as much as 5 liters of fluid through this process (Cronau et al., 1984).

This reflects the tremendous physiological stress the body undergoes in response to whole-body hyperthermia. It suggests the need for early intervention in HIV-positive patients rather than attempting to intervene in an advanced AIDS state. Caution therefore should be taken when evaluating any treatment. A treatment, such as whole-body hyperthermia, which produces such stress on the body's systems probably will have a greater mortality associated with it if patients with severely compromised physiological systems are not screened out through the patient selection criteria.

Shidnia reported that he favors the microwave method of delivering hyperthermia. He described it as both a safe and effective method. He has treated over 200 patients with microwave hyperthermia twice a week at temperatures of 40-41° C as an adjunctive treatment in the management of neoplasms. None of his patients have developed toxicity to the treatments. With microwave, no anesthesia is required. He plans to implement a protocol for AIDS patients in 1991 (Shidnea, 1990).

Dr. Bicher, of Los Angeles, found in his studies that using local hyperthermia along with low doses of

radiotherapy for Kaposi's sarcoma resulted in remarkable improvement. None of the patients' immune response system was compromised due to the treatments. He described the results as "the lesions seem to melt away" and added "hyperthermia works."

AIDS and Education

Advocating methods of and the need for prevention of AIDS certainly has been a top priority in the United States. This was evidenced by the Surgeon General Koop's efforts to mail AIDS information to the citizens. It is also evidenced by the priority given to education by the Preventive Task Force (U.S., 1990).

However, there is evidence that indicates the possession of knowledge alone will not alter sexual behavior sufficiently to control the disease. No sexually transmitted disease (STD) has been controlled through education without treatment. In the 1990 study by MacDonald et al. of college students' behavior, it was found that "neither fear of acquiring AIDS or any STD nor knowledge about HIV or STD appeared to significantly influence the decision to abstain from coital activity." Realistically, and from previous experience with sexually transmitted diseases, behavior change is not going to happen to the extent needed to control the disease (Wertheimer, 1990; Glasner & Kaslow, 1990).

The dissemination of information leading to behavior change tends to be less effective in certain populations in American society. The chronic mentally ill population is an example. From one study, it was estimated that as high as 17% of this population may be infected with the virus (Carmen & Brady, 1990). Migrant workers historically are in settings that experience high rates of sexually transmitted diseases and would be expected to have a high HIV infection rate (Hunt, 1989).

World wide, one out of every 250 women giving birth has tested positive for HIV. Women, in 1990, have shown an increase of 29% in cases of AIDS compared to an 18% increase of cases in men (WHO, 1991). Harkess, et al. found that persons with a positive serologic test for syphilis showed a 6.3% HIV positive test while the negative syphilis persons showed only a 0.8% positive for HIV. They also found that of those persons positive for syphilis who were between the ages of 20 to 39 years the rate for positive HIV increased to 17.6%.

Another barrier to control is the long incubation period during which time the infected person is a carrier. For years the infected person unknowingly may infect others. While it is not possible to say how long a person can have the infection without developing AIDS, mathematical models predict 100% of infected persons will develop AIDS at some point in time if left untreated (Hessol et al., 1989).

The rapid spread of AIDS throughout the underdeveloped countries is probably not going to be remedied through education. Many factors contribute to this, including a lack of basic knowledge and a general suspiciousness toward outside educators (Volberding, 1989).

Educators must sometimes work in environments in which this disease is being used as a political weapon for self-interest groups. It was reported to the National Conference on the Prevention of HIV infection and AIDS among Racial and Ethnic Minorities in the United States that the Nation of Islam had deliberately disseminated information to the Black communities that AIDS is a disease developed by the Whites to destroy the Black population (Thomas et al., 1991b).

The state of New York has so many cases of adolescent AIDS that the city's school chancellor supported an AIDS educational plan which would allow New York State's high school students to get condoms from the school without parental permission (American Medical News Staff, 1990b).

* In the study by Cloverdale et al. and reported to the Fifth International Conference on AIDS, physicians are failing to provide AIDS preventive education to their patients. In this study, while 92% of physicians felt it was their responsibility to educate their patients about AIDS, only 11% reported doing so. Approximately one third of the physicians admitted their discomfort in discussing

the sexual habits and life styles of their patients (Cloverdale et al., 1990).

Treatment, while not curative at this point, has improved in its effectiveness in countering the various specific opportunistic diseases and syndromes secondary to the infection and even in suppressing the replication of the virus. As treatment is changing, the view toward AIDS is changing.

While preventive education was initially the only available tool to combat the disease, the advances that have been made in treating or delaying the progression of the disease should now be included in all educational efforts.

Summary

Many patient factors appear to influence the infectability and progress of HIV. It stands to reason that identifiable patient factors will equally influence treatment response. The literature does not offer guidelines for selecting patients for whole-body hyperthermia based on patient identified variables.

This study attempted to identify those variables that might help in selecting appropriate HIV-infected candidates for treatment with whole-body hyperthermia. With knowledge of the selection criteria, persons may be more willing to actively seek testing and treatment.

With identified variables as predictors of response, educators will be able to reorganize their AIDS programs. Instead of just educating everyone with the safe-sex, no needles themes, education will expand to include methods of treatment. This treatment education will not only be in general concepts but also will focus on targeted segments of the infected population with specific treatment approaches. This will be a monumental educational task but a necessary one to assure the rapid and appropriate treatment of the infected population.

CHAPTER 3

METHODOLOGY

Study Population

The study consisted of adult HIV positive persons, all of whom had evidence of immune compromise as evidenced by a decrease in their CD4 cell count and the presence of Kaposi's sarcoma, an opportunistic disease.

Owing to the small number of patients in this study and the lack of any kind of random process in the method of patient selection, this population may not reflect the infected population at large and extreme caution should be used in attempting to generalize to a larger population.

Treatment Procedure

All the patients in the study underwent whole-body hyperthermia as a planned treatment for Kaposi's sarcoma. Percutaneous femoral catheters were used to shunt the patients' blood through a dialysis coil where it was heated to 47°C. The core temperatures of the patients were maintained at 42°C for 1 hour through a controlled heating method. Following treatment and a few hours of observation, if no complications were observed, the patients were allowed to leave the hospital.

Laboratory

All laboratory findings necessary to confirm the HIV-positivity, the diagnosis of Kaposi sarcoma, the CD4 cell count, and the p24 antigen level were available to the treating physician prior to the patient's selection for treatment.

The one-month post-treatment follow up level of CD4 cells and the p24 antigen level were utilized for comparison to the pre-treatment level.

Data Recording

The data collecting sheet contained information relevant to the research variables listed below. It also included an identification number for the record. No other personal history was retrieved from the records.

Variables

In this study population, the variables which were recorded and explored were the following:

1. Levels of CD4+ cells pre- and one month post-treatment
2. Levels of p24 antigen pre- and one month post-treatment
3. Treatment related mortality

Data Collection and Analysis

This study was done in Pavia, Italy, using the protocol of Laboratory Atlanta Foundation for Cancer Research and Treatment, Inc. Atlanta, Georgia. The protocol was submitted to and approved by a Human Ethics Committee meeting World Health Organization criteria.

Laboratory Atlanta maintained all data created from the study. With the permission of Laboratory Atlanta, data relevant to the above variables were collected.

Obviously this was not a random process but rather a convenient sample. While every effort was made to move in the direction to use statistical procedures, unfortunately the number of available patients receiving treatment did not lend itself to that end. Therefore, a case study analysis was submitted. Any observed trends or patterns observed from this study may then serve as the framework for the formation of other hypotheses and further investigative research into the area.

Case Study Analysis

Explored Trends

Using the case study analysis, an effort was made to demonstrate trends suggested by the limited available data.

Based on that data, the following trends were explored:

1. In this study, did hyperthermia appear to result in viral replication?

2. What influence, if any, did the patient's pre-treatment CD4 cell count have on the patient's response as reflected by the post-treatment CD4 cell count?

3. What influence, if any, did the patient's pre-treatment p24 antigen level have on the patient's response as reflected by the post-treatment p24 antigen levels?

4. Did hyperthermia appear to be a safe treatment, even for patients with severe immune system compromise?

Significance of the Trends

Each of the explored trends in this study allowed further data to be applied in a continuing effort to address the following pertinent concerns regarding hyperthermia and HIV.

1. HIV-infected persons are denied hyperthermia treatments for fear of causing replication of the virus. Did this study support that fear?

2. The CD4 cell count is accepted as a marker of the immune system's status. By observing any changes in the CD4 count following treatment, how did hyperthermia appear, in this study, to affect the immune system?

3. Did the magnitude of the effect of hyperthermia on the CD4 cell count appear to be influenced by the level of the CD4 cell count prior to the treatment?

4. The p24 antigen level is accepted as a marker of the HIV activity. By observing any changes in the p24 antigen level following treatment, how did hyperthermia

appear, in this study, to affect the level of viral activity?

5. Did the magnitude of the effect of hyperthermia on the p24 antigen level appear to be influenced by the p24 level prior to treatment?

6. From the changes in the CD4 counts and p24 level, when in the progression of the disease did hyperthermia appear to be most effective?

7. Was the morbidity/mortality rate acceptable?

Summary

This study was limited in the sample size and lacked randomization. Therefore it lacks generalizability. It did allow for the examining of observations in an effort to define trends which might lend themselves to better selection of patients for hyperthermia treatment.

CHAPTER 4

RESULTS OF THE STUDY

Introduction

This chapter discusses the subjects of the study population, the treatment administered and the findings of the study.

Subjects

Ten subjects, all male, young adult Caucasians, all diagnosed with AIDS, and all suffering from confirmed Kaposi's sarcoma were each administered one treatment session of whole-body hyperthermia.

The p24 antigen level, an accepted marker of HIV activity, was elevated in all subjects.

The CD4 cell count, an accepted marker of the immune system's compromise in HIV patients, were all decreased. Two of the ten had CD4 counts above 400 while the remaining eight had counts below 60.

Treatment Administered

With catheters placed percutaneously into the femoral artery of one leg and in the femoral vein of the other leg, the subjects, under general anesthesia, were connected to a dialysis coil allowing the blood to be shunted through the

coil and heated to 47°C before re-entering the body. The body's core temperature was monitored by rectal, intramuscular, and blood placed thermometers which had been calibrated to be accurate to 0.1°C. The process was maintained until the core temperature reached 42°C and maintained at that temperature for one hour. An intravenous line was open to allow fluid and electrolyte replacement. Unassisted cool-down was allowed.

Data Table

Table 1 shows the individual patient's pre-treatment and the one month post-treatment CD4 cell count and p24 antigen level.

The percentage of change noted above would be misleading without the associated numbers. However, the following observations and their apparent importance were noted.

1. The p24 antigen levels remained unchanged or was decreased in every patient. There was nothing noted to support the fear that hyperthermia would cause increased replication.

2. It appears that the more dramatic reductions of the p24 level are noted in those patients with a greater pre-treatment level of viral activity which might suggest there are fewer virus in the latent stage making them more vulnerable.

Table 1. Comparison of Pre-Treatment and One Month Post-Treatment Values

<u>p24 Antigen Level</u>					<u>CD4 Cell Count</u>			
Pt.	Pre	Post	Diff	%Diff	Pre	Post	Diff	%Diff
1	4	2	2	-50	32	45	13	+40
2	20	10	10	-50	8	40	32	+400
3	4	2	2	-50	55	112	57	+103
4	4	4	NC	NC	42	45	3	+7
5	4	4	NC	NC	23	23	0	NC
6	40	22	18	-45	21	24	3	+14
7	10	2	8	-80	12	12	NC	NC
8	840	410	430	-51	570	810	240	+42
9	900	550	350	-39	440	770	330	+75
10	4	2	2	-50	11	12	1	+9

4. The CD4 cell count remained unchanged or was increased in every patient.

5. The most impressive change seems to occur in patients whose immune system is more intact as reflected by a higher pre-treatment CD4 cell count. This would support using hyperthermia as an early treatment intervention prior to severe compromise of the immune system.

6. All of the ten patients treated survived with no reports of any major complications at the one month post-treatment follow up.

Summary

Ten adult, HIV-positive, Caucasian males underwent one session of hyperthermia treatment for HIV related Kaposi's sarcoma. The treatment involved extracorporeal heating of the blood to 47°C and recirculating the blood into the body until the monitored core temperature reached 42°C and was maintained at that temperature for one hour.

The subjects represented a wide range of immune system compromise as evidenced by the pre-treatment variation in the CD4 cell count. The highest CD4 count was 570 and the lowest was 8. There also was a wide range of viral activity as evidenced by the pre-treatment p24 antigen level. The highest p24 level was 900 and the lowest was 4 (five patients had a level of 4).

One month following hyperthermia, the CD4 cell count either was unchanged or increased. One month following hyperthermia, the p24 antigen level either was unchanged or decreased. The most obvious changes occurred in the patients with both high CD4 counts and high p24 levels.

No life threatening complications to the treatment were reported.

Briefly, these findings suggested that hyperthermia is a safe treatment, even in patients with severe immune system compromise. In this study, hyperthermia did not cause viral replication. The stage of the disease progression, as reflected by the patient's pre-treatment CD4 cell count and the p24 antigen level, appeared to be a major determinant in the patient's response to hyperthermia.

CHAPTER 5

SUMMARY

This study was an attempt to identify variables which might serve as predictors of HIV-positive patients' response to hyperthermia. The study did not lend itself to statistical procedures because of the size of the sample and the absence of randomization. The study population was a convenient population, comprised of all the patients of a clinical project who received one session of whole-body hyperthermia as treatment for Kaposi's sarcoma.

Data from this group of patients were evaluated in an effort to determine if the pre-treatment data compared to the one month post-treatment data suggested the presence of any trends or observations that might support or be contrary to previous ideas or suggest new ideas.

Fear of viral replication is an issue that has prevented HIV-positive patients from possibly benefiting from hyperthermia. None of the patients in this limited population showed any evidence of increased HIV activity as evidenced by the one month post-treatment p24 antigen levels compared to the pre-treatment levels. Instead, the trend suggested that viral activity was decreased.

The CD4 cell count, a marker of the status of the immune system, either showed improvement (an increase) or no change in comparing the pre-treatment levels with the one

month post-treatment levels. This trend would support those researchers who suggest that hyperthermia might serve as a direct stimulant to the immune system. None of the patients appeared to experience further suppression of their immune system following hyperthermia.

The most obvious changes in the CD4 count were noted in those patients whose pre-treatment CD4 levels were above 400. Those with severe compromise of their immune system experienced essentially no change. This suggested that hyperthermia should be considered as a treatment in the early stages of the infection before the immune system is too depleted to respond.

It was also interesting that the patients with the highest pre-treatment CD4 cell count also had the highest pre-treatment p24 antigen levels. Those patients showed the most impressive post-treatment reduction in their p24 levels. This supports those who advocate that hyperthermia serves as a viricidal in and of itself.

There were no reported serious complications or deaths in this study group. From this group, it would appear that hyperthermia is a safe treatment even on patients with a severely compromised immune system.

This study supports the need for further investigation of hyperthermia in HIV-positive patients and, perhaps, using the CD4 cell count and p24 antigen levels as an aid in selecting patients for future treatments.

Some possible areas of future investigation would include the following:

1. What would be the effect of repeated hyperthermic sessions on the CD4 count and the p24 level?
2. What degree of change in the CD4 count and p24 level would suggest a repeated hyperthermic session?
3. Would patient thermotolerance develop with repeated sessions and, if so, would this permit higher temperatures to be reached without increasing the morbidity/mortality?
4. At what level is the immune system to be considered too compromised to respond to hyperthermia?
5. Will children, women, pregnant women, and other racial groups follow the same trends as noted in this study?
6. What other markers in addition to the CD4 count and p24 antigen level will emerge as predictors of response to hyperthermia?
7. What would be the change in the CD4 cell count and p24 level over several months of post-treatment observation?

While the above are all worthy of immediate investigation, they are not likely to receive the attention they deserve until further studies like this one pressures the government to review its position on funding research in this area. Until this occurs, the reality is that hyperthermia treatment will not be accessible to the varied HIV patient populations in this country, even as a research tool.

BIBLIOGRAPHY

BIBLIOGRAPHY

- Ahia, R. (1991). Compliance with safer-sex guidelines among adolescent males: Application of the Health Belief Model and Protection Motivation Theory. Health Education, 22 (1), 49-52.
- Albert, J., Naucier, A., Bottiger, B., & Broliden, P. (1990). Replicative capacity of HIV-2, like HIV-1, correlates with severity of immunodeficiency. Acquired Immune Deficiency Syndrome, 4 (4), 291-295.(abstract)
- Alonso, K. (1990a). Personal Communication. Draft of unpublished material.
- Alonso, K. (1990b). Response to NIH's field study report (unpublished). Personal communication.
- American Medical News Staff, (1990a, February). Haitian blood donor ban dropped. American Medical News.
- American Medical News Staff, (1990b, February). School condom plan. American Medical News.
- American Medical News Staff, (1990c, February). HIV infection labeled as STD; board to clarify testing policy. American Medical News.
- American Medical News Staff, (1990d, February). Hospice fights discrimination to offer 'small place of dignity.' American Medical News.
- Anderson, M. & Christenson, G. (1991). Ethnic breakdown of AIDS related knowledge and attitudes from the National Adolescent Student Health Survey. Health Education, 22 (1), 30-34.
- Aultman, K., Harris, J., & Wells, J. (1989). The international AIDS activities of the United States government. Agency for International Development (A. I. D.). Reported at the International Conference on AIDS. (Abstract No. T.G.P.1). 5, 1004.
- Benitez, R. & Sotomayor, J. (1989). A comprehensive and cost-effective approach to the management of AIDS patients on an outpatient care facility: The results of a patient survey. International Conference on AIDS (Abstract), 5, 1055.

- Benjamin, A. (1988). Long term care and AIDS: Perspectives from experience with the elderly. Milbank Quarterly, 66 (3), 415-443.
- Bicher, H. (1990). Local hyperthermia therapy of Kaposi's sarcoma in the AIDS patients. Presented at the 7th annual meeting of the American Society of Clinical Hyperthermic Oncology.
- Bloch, A., Rieder, H., Kelly, G., & Cauthen, G. (1989). The epidemiology of tuberculosis in the United States. Seminar of Respiratory Infections, 4 (3), 157-170.
- Blomberg, P. & Flynn, N. (1989). Comprehensive HIV case management protocols for 26 Northern California counties. As reported at the International Conference on AIDS. Abs no. W.B.P.63,
- Braun, M., Heyward, W., & Curran, J. (1990). The global epidemiology of HIV infection and AIDS. Annual Review of Microbiology, 44, 555-557.
- Brinnel, H. (1986). Intracranial temperature during passive heat exposure in humans. Brain Research, 363 (1), 170-173.
- Buchbinder, A. (1990). Virology of the human immunodeficiency virus type 1. Ear, Nose, and Throat Journal, 69 (6), 376, 379-384.
- Bull, J. (1984). Whole-body hyperthermia session: summary of discussion. Cancer Research (suppl), 44, 4884s-4885s.
- Carmen, E. & Brady, S. (1990). Aids risk and prevention for the chronically mentally ill. Hospital Community Psychiatry, 41 (6), 652-657.
- Carpenter, P., Conant, M., Francis, D., Kizer, K., & Werdegarr, D. (1990). From the eye of the hurricane--a multi-disciplinary AIDS strategy for the 90s. Reported at the International Conference on AIDS (Abstract no. 4115). 6 (2), 482.
- Carretta, R. (1990). AIDS education practices among Massachusetts physicians. Journal of Community Health, 15 (3), 147-162.
- CDC, (1990a). AIDS in women-United States. Morbidity and Mortality Weekly Report, 39, 845-846.

- CDC, (1990b). HIV prevalence estimates and AIDS case projections for the United States: Report based on a workshop. Morbidity and Mortality, 16, 1-31.
- CDC, (1991). AIDS in women- United States. Journal of the American Medical Association, 265 (1), 23.
- Cotton, P. (1990). Cofactor questions divides codiscoverers of HIV. Journal of the American Medical Association, 264 (24), 3111-3112.
- Cotton, P. (1991). HIV surrogate markers weighed. Journal of the American Medical Association, 265 (11), 3111-3112.
- Cotton, P. (1990). Controversy continues as experts ponder zidovudine's role in early HIV intervention. Journal of the American Medical Association, 263, 1605.
- Cloverdale, J., Aruffo, J., Laux, L., Vallobona, C., & Thornby, J. (1990). Aids, minority patients, and doctors: What's the risk? Who's talking? Southern Medical Journal, 83 (12), 1380-1383.
- Cronau, L., Bourke, D., & Bull, J. (1984). General anesthesia for whole-body hyperthermia. Cancer Research (suppl), 44, 4873s-4877s.
- Dreyer, D. (1990). Calcium channel blocker believed to prevent AIDS-related dementia. The Psychiatric Times, 7 (10), (abstract)
- Eakin, J. & Taylor, K. (1990). The psychosocial impact of AIDS on health care providers: Critical analysis of the literature and implications for policy. Psychiatric Times 6 (3), 315.
- Edgar, H. & Rothman, D. (1990). New rules for new drugs: The challenge of AIDS to the regulatory process. Milbank Quarterly (suppl), 68s (1), 111s-142s. (Abstract).
- Editor (A), (1990, September). Physicians question government's finding on hyperthermia for AIDS. AIDS Alert.
- Editor (B), (1991). AIDS cases in women and children up dramatically. Psychiatric Times, 8 (1), 32.

- Ellerbrock, T. & Rogers, M. (1990). Epidemiology of human immunodeficiency virus infection in women in the United States. Obstetrical and Gynecological Clinics of North America, 17 (3), 523-524.
- Erickson, J. (1990). Protease inhibitor blocks HIV replication. Compound A-74704 (abstract), Science, 6 (2), 373.
- Erickson, R. (1990). International behavioral responses to a health hazard. Society of Science and Medicine, 31 (9), 951-962.
- Essex, M., Kanki, P., Marlink, R., Chou, M., & Lee, T. (1990). Antigenic characterization of the human immunodeficiency viruses. Journal of the American Academy of Dermatology, 22 (6 pt 2), 1206-1210.
- Fahey, J., Taylor, J., Korns, E. (1986). Diagnostic and prognostic factors in AIDS. Mt. Sinai Journal of Medicine, 53, 657-663.
- Fajar, K. (1984). Pathological effects of hyperthermia in normal tissues. Cancer Research (suppl), 44s, 4826s-4835s.
- Fennell, R. (1990). Knowledge, attitudes, and beliefs of students regarding AIDS: A review. Health Education, 21 (4), 20-25.
- Fennell, R. (1991). Evaluating the effectiveness of a credit semester course on AIDS among college students. Health Education, 22 (1), 35-42.
- Francis, D., Gorman, M., Anderson, R., & Fenstersheib, M. (1989). Targeting AIDS prevention and treatment toward HIV-1-infected persons. The concept of early intervention. Journal of the American Medical Association, 262 (18), 2572-2576.
- Freedman, B. & McGill/Boston Research Group, (1989). Non-validated therapies and HIV disease. Hastings Center Report, 19, 14-20.
- Glasner, P., Kaslow, R. (1990). The epidemiology of human immunodeficiency virus infection. Journal of Consulting Clinical Psychology, 58 (1), 13-21.
- Goldsmith, M. (1991). AIDS vaccines inch closer to useful existence. Journal of the American Medical Association, 265 (11), 1356-1357.

- Gordon, R. (1989). A critical review of the physics and statistics of condoms and their role in individual versus societal survival of the AIDS epidemic. Journal of Sex and Marital Therapy, 15 (1), 5-30.
- Gorman, J. (1990). Psychosocial aspects of AIDS. Presented at the 143rd annual meeting of the American Psychiatric Association. Peer to Peer, 2, 22-23.
- Gorna, R., Campbell, D., Eede, M., Harris, D., & Hazell, M. (1989). The development of community-based AIDS initiatives. Presented at the International Conference on AIDS, 5:937, (abstract no. E.810).
- Group, (1990). HIV infection, pregnant women and newborns. Journal of the American Medical Association, 264 (18), 2416-2420.
- Hall, E. & Roizin, T. (1984). Biological effects of heat. Cancer Research (suppl), 44s, 4708s-4713s.
- Hamilton, J., Compton, C., Weinhold, K., Simberkoff, M., Hartigan, P. (1989). Tissue Culture and p24 methods of HIV detection compared and correlated with demographic data in symptomatic ARC patients. Presented at the International Conference on AIDS, Abstract T.B.P. 118.
- Harkess, J., Kudlac, J., & Istre, G. (1990). Syphilis, human immunodeficiency virus infection, and targeting prevention. Southern Medical Journal, 83 (11), 1253-1255.
- Hay, J., Osmond, D., & Jacobson, M. (1988). Projecting the medical cost of AIDS and ARC in the United States. Acquired Immune Deficiency Syndrome, 1 (5), 466-485.
- Hellinger, F. (1990). Updated forecasts of the cost of medical care for persons with AIDS. Public Health Reports, 105 (1), 1-12.
- Herrick, C. & Smith, J. (1989). Ethical dilemmas and AIDS: nursing issues regarding rights and obligations. Nursing Forum, 24 (3-4), 35-46.
- Hessol, N., Lifson, A. & Rutherford, G. (1989). Natural history of human immunodeficiency virus infection and key predictors of HIV disease progression. In P. Volberding & M. Jacobson (Eds.). AIDS Clinical Review (pp. 69-93). New York: Marcel Dekker

- Hickey, M. & Weaver, K. (1988). Nutritional management of patients with ARC or AIDS. Gastroenterological Clinics of North America, 17 (3), 545-561.
- Holman, S. (1989). Epidemiology and transmission of HIV infection in women. Journal of Nurse Midwifery, 34 (5), 233-241.
- Holzer, T., Allen, R., Heymen, D., & Kennedy, M. (1990). Discrimination of HIV-2 infection from HIV-1 infection by western blot and radioimmunoprecipitation analysis. AIDS Research of Human Retroviruses, 6 (4), 515-524.(abstract)
- Hunt, C. (1989). Migrant labor and sexually transmitted disease: AIDS in Africa. Journal of Health and Social Behavior, 30 (4), 353-373.
- Jacobson, M., McGrath, M., Joseph, P., Molaghan, J., & et al, (1989). Zidovudine-induced fever. Journal of Acquired Immune Deficiency Syndrome, 2 (4), 382-388.
- Jenkins, R. (1990). Hyperthermia: A first hand report. Being Alive, July, 14,
- Johnson, W. & Pape, J. (1989). AIDS in Haiti. Immunology Series, 44, 65-78.
- Jones, H., Ellis, N., Tappe, M., & Lindsay, G. (1991). HIV related beliefs, knowledge, and behaviors of ninth and eleventh grade public school students. Health Education, 22 (1), 12-19.
- Jones, L. (1991). HIV off barred avisitor, immigrant list. American Medical News January 21, 15.
- Joseph, P., Marzouk, J., & Phelps, R. (1990). Oral clindamycin plus primaquine for pneumocystis carinii pneumonia. International Conference on AIDS, (Abstract no. 2078).
- Kannagi, M., Masuda, T., Hattori, T., Kanoh, T., & et al, (1990). Interference with human immunodeficiency virus (HIV) replication by CD8+ T cells in peripheral blood leukocytes of asymptomatic HIV carriers in vitro. Journal of Virology, 64 (7), 3399-3406.
- Kapp, D. & Lord, P. (1983). Thermal tolerance to whole body hyperthermia. International Journal of Radiation Oncology Biology Physics, 9 (6), 917-921.

- Karjalainen, J. & Vitasalo, M. (1986). Fever and cardiac rhythm. Archives of Internal Medicine, 146 (6), 1169-1171.
- Kaslow, R. & Francis, D. (1990). Epidemiology of AIDS: General considerations. Report by the National Institute of Allergy and Infectious Diseases.
- Katner, H. (1990, November). Potential indirect effects of hyperthermia on HIV mediated by the immune system; an alternative hypothesis. Presented at the 7th annual meeting of the American Society of Clinical Hyperthermic Oncology, (Abstract p.28), November.
- Kerley, L. (1990). The escalating health care cost of AIDS; who will pay? Nursing Forum, 25 (1), 5-14.
- Kess, S., Bresolin, L. & Henning, J. (1991). HIV Early Care: AMA Physician Guidelines. Chicago: American Medical Association.
- Lane, H. (1990). Virologic and immunologic aspects of acquired immunodeficiency syndrome. Surgery of Gynecology and Obstetrics, 171 (suppl).
- Lee, J., Branan, L., Watkins, L., Hoff, G., Bayer, W., & Tegtmeier, G. (1991). Voluntary human immunodeficiency virus testing. Southern Medical Journal, 84 (2), 198-199.
- Levin, R. (1990). Work in progress: Chemotherapy and hyperthermia at American International Hospital. Presented at the 7th Annual meeting of the American Society of Clinical Hyperthermic Oncology, November. Abstract, 28.
- Levy, J., Mitra, G., & Mozen, M. (1984). Recovery and inactivation of infectious retroviruses from factor VIII concentration. Lancet, 2 (8405), 722-723.
- Li, G. (1984). Thermal biology and physiology in clinical hyperthermia. Cancer Research, 44 (suppl), 4886s-4893s.
- Li, G., Meyer, J., Mak, J., & Hahn, G. (1983). Heat induced protection on mice against thermal death. Cancer Research (suppl), 43, 5758s-5760s.
- Lnage, R. & Frame, J. (1991). Assessment of Risk for HIV-1 infection for missionaries in Sub-Saharan Africa. Southern Medical Journal, 84 (2), 193-197.

- Logan, W. (1990a). Rationale and the use of extra-corporeal hyperthermia in the management of AIDS patients. Presented at the 7th annual meeting of the American Society of Clinical Hyperthermic Oncology (ASCHO). Abstract p. 30,
- Logan, W., Alonso, K. (1990b). Unpublished data.
- MacDonald, N., Wells, G., Fisher, W., & Warren, W. (1990). 1990 high-risk std/hiv behavior among college students. Journal of the American Medical Association, 263 (23), 3155-3159.
- Macy, D., Macy, C., Scott, R., Gillette, E., & Speer, J. (1985). Physiological studies of whole-body hyperthermia of dogs. Cancer Research, 45 (6), 2769-2773.
- Mann, J. (1991). Global AIDS: Status of the pandemic. Health Education, 22 (1), 6-8.
- Mann, J., Dam, M., & Kay, K. (1990). Global coordination of national public health strategies. Law and Medicine Health Care, 18 (1-2), 20-28.
- Marcial-Vega, V. (1990). In vitro heat sensitivity on the AIDS virus. Presented at the 7th annual meeting of the American Society of Clinical Hyperthermic Oncology. (Abstract) p. 26.
- Marshall, P., O'Keefe, J., Fisher, S., Caruso, A., & Surdukowski, J. (1990). Patient's fear of contracting the acquired immunodeficiency syndrome from physicians. Archives of Internal Medicine, 150 (7), 1501-1506.
- Meng, T., Fischl, M., & Raichman, D. (1990). Aids Clinical Trials Group: phase I/II study of combination 2', 3'-dideoxycytidine and zidovudine in patients with acquired immunodeficiency syndrome (AIDS) and advanced AIDS-related complex. American Journal of Medicine (Suppl), 88 (5B), 27s-30s.
- Meyer, R., Page, R., Thrall, D., Dewhirst, M., & Vase, D. (1984). Determination of continuous atracurium infusion rate in dogs undergoing whole-body hyperthermia. Cancer Research (suppl), 46 (11), 5599s-5601s.
- Miller-Catchpole, R., & Rapoza, N. (1990). Prophylactic treatment for opportunistic infections in HIV-positive patients: aerosolized pentamidine. Journal of the American Medical Association, 263, 2510-2514.

Milligan, A. (1984). Whole-body hyperthermia induction techniques. Cancer Research (suppl), 44s, 4869s-4872s.

Modest, E., Nosedá, A., Wallen, D., Kucera, L., & Pitantadosi, C. (1990). Combination chemotherapy studies with antitumor and antiviral ether lipid analogs. As reported at the Annual meeting of the American Association of Cancer Research. Abstract 31:A2471.

Morgan, G., Wilkins, H., Pepin, J., & Jobe, O. (1990). Aids following mother-to-child transmission of HIV-2. Acquired Immune Deficiency Syndrome, 4 (9), 8789-882.

Neil, R. (1990). Ag research touches everyone. Progressive Farmer, 105 (11), 16.

NIH, (1989a). Parallel track system to expand access to drugs--Dr. Fauci. As reported in the NIAID AIDS agenda 1, July.

NIH, (1990b). Summary of findings-site visit report--clinical use of hyperthermia in AIDS. Backgrounders, September,

O'Shaughnessy, M. (1989, June). Serology tests for the diagnosis of AIDS. (Meeting abstract) Reported in The Scientific and Social Challenge.

Page, R., Thrall, D., Dewhirst, M., & Meyer, R. (1987). Whole-body hyperthermia. Rationale and potential use in cancer treatment. Journal of Veterinary Internal Medicine, 1 (3), 110-120.

Parry, J., McAlpine, L., & Avillez, M. (1990). Sensitivity of six commercial enzyme immunoassay kits that detect both anti-HIV-1 and anti-HIV-2. Acquired Immune Deficiency Syndrome, 4 (4), 355-360. (Abstract).

Pellegrino, E. (1990). Ethics. Journal of the American Medical Association, 263 (19), 2641-2642.

Pinching, A. (1988). Factors affecting the natural history of human immunodeficiency virus infection. Immunology Reviews, 1 (1), 23-38.

Rapin, A. & Erickson, P. (1990). Differences in knowledge of and risk factors for AIDS between Hispanic and non-Hispanic women attending an urban family planning clinic. Journal of Acquired Immune Deficiency Syndrome, 4 (9), 889-899. (abstract)

- Raymond, M. (1990). AIDS education in the workplace: the European experience. Reported at the International Conference on AIDS. (Abstract no. 4115). 6 (2), 467.
- Robins, H., Dennis, W., Neville, A., Shechterly, L., & et al, (1985). A non-toxic system for 41.8 degrees C whole-body hyperthermia: Results of a phase 1 study using a radiant heat device. Cancer Research, 45 (8), 3937-3944.
- Robins, H., Hugander, A., & Cohen, J. (1989). Whole body hyperthermia in the treatment of neoplastic disease. Radiological Clinics of North America, 27 (3), 603-610.
- Romieu, I., Marlink, R., M'Boup, S., Kanki, P. (1989). HIV-2 link to AIDS. Presented at the International Conference on AIDS. (Abstract no. T.G.P.27).
- Rouzious, D., Chamaret, S., Montagnier, L., Carnelli, V. (1985). The Lancet, 1 (8423), 2718423-272.
- Rouzioux, C. (1985). Absence of antibodies to AIDS virus in haemophiliacs treated with heat-treated factor V111 concentrate [Letter to the Editor]. The Lancet, 1 (8423), 272.
- Rutherford, G. & Werdegar, D. (1989). The epidemiology of acquired immunodeficiency syndrome. Immunology Service, 44, 1-36.
- Schram, N. (1990). Let's offer HIV testing and services to more patients. Reported in American Medical News, November 9.
- Shen, R., Mornback, N., Shidnia, H., Lu, L., & et al, (1988). Effect of whole-body hyperthermia and cyclophosphamide on natural killer cell activity in murine erythroleukemia. Cancer Research, 48 (16), 4561-4563.
- Shidnia, H. (1990). Microwave hyperthermia for the tratment of AIDS. Presented at the 7th annual meeting of the American Society of Hyperthermic Oncology (ASCHO) November. Abstract p. 29.
- Smith, M. (1991). An investigation of school administrators' beliefs and the relationship between HIV and special education. Health Education, 22 (1), 35-42.
- Staff, (1990a). HIV Progression and Survival. American Society of Addiction Medicine, 5 (2).

Staff (B), (1990, September). Studies, treatment programs, new drugs aimed at AIDS virus. Reported in The Psychiatric Times-Medicine and Behavior, p. 26-27.

Stanley, S., Bressler, P., Poli, G., Fauci, A. (1989). Heat shock induces production of HIV from chronically infected promonocytic and T cell lines. Presented at the Sixth International Conference on AIDS, Abstract FA314.

Staver, S. (1990, December 14). Surgeons death renews concerns over HIV-positive health care workers. Reported in American Medical News. p. 8-9.

Staver, S. (1991, March 15). Drug firm seeks approval of DDC for AIDS care. American Medical News, p. 2.

Stewart, J., Bibbs, F. (1984). Hyperthermia in the treatment of cancer. Perspectives on its promise and its problems. Cancer (suppl), 5 (4), 2823s-2830s.

Stuchin, J., Taylor, M., & Wang, M. (1990). Differences among health professionals in attitudes toward persons with AIDS. Health Education, 21 (4), 32-35.

Terwilliger, E., Sodroski, J., Haseltine, W. (1990). Mechanisms of infectivity and replication of HIV-1 and implications for therapy. Annals of Emergency Medicine, 19 (3), 233-241.

Thomas, S. (1991a). Evaluation and risk reduction projects in ethnic and racial minority communities. Health Education, 22 (1), 24-29.

Thomas, S., Gilliam, A., & Iwrey, C. (1991b). Evaluation of community based AIDS education risk reduction programs in minority populations. Presented at the National Conference on the Prevention of HIV infection and AIDS among Racial and Ethnic Minorities in the United States. CDC.

Thrall, D., Page, R., & McLeod, D. (1987). Use of insulation to reduce extremity temperature nonuniformity during whole body hyperthermia in dogs. Cancer Research, 47 (22), 588-592.

U.S. Preventive Services Task Force, (1990). Counseling to prevent HIV infection and other sexually transmitted diseases. American Family Physician, 41 (4), 1179-1187.

- van der Groen, G., van Kerckhoven, I., Vercauteren, G., & Piot, P. (1990). Operational characteristics of commercially available assays to determine antibodies to HIV-1 and/or HIV-2 in human sera. Reported at the International conference on AIDS (Abstract No. S.C.213).
- van Haastrecht, H., van den Hoek, J., Bardous, C., Leentvaar-Kuypers, D., & Coutinho, R. (1991). The course of the HIV epidemic among intravenous drug users in Amsterdam, The Netherlands. American Journal of Public Health, 81 (1), 59-62.
- Viscarello, R. (1990). AIDS. Natural history and prognosis. Obstetrical and Gynecological Clinics of North America, 17 (3), 545-555.
- Voelker, R. (1990, December 14). Puerto Ricans tell AIDS group of many needs, few resources. Reported in the American Medical News, p. 1.
- Voelker, R. (1991, January 21). Access to care tops state legislative agendas for 2nd year in a row. Reported in the American Medical News, p. 3.
- Volberding, P., Lagakos, S., Koch, M., & Pettinelli, C. (1989). Zidovudine in asymptomatic human immunodeficiency virus infection. A controlled trial in persons with fewer than 500 CD4 positive cells per cubic millimeter. New England Journal of Medicine, 322 (14), 941-949.
- Wabitsch, K., Mills, J., Malkin, J., & Gottlieb, L. (1990). Clinical management guidelines of HIV infection and AIDS, an algorithm approach. Reported at the International Conference on AIDS. Global Programme on AIDS, World Health Organization. (Abstract no. S.D.911).
- Wertheimer, W. (1990). The politics of STDs. Dwindling resources for a growing problem. Primary Care, 17 (1), 183-194.
- Weshler, Z., Kapp, D., Lord, P., & Hayes, T. (1989). Development and decay of systemic thermotolerance in rats. Israel Journal of Medical Science, 25, 15-19. (Abstract).
- WHO, (1990a). Abstract. The Lancet, 28; 336(8709), 221-224.

WHO, (1990b). Global Programme on AIDS. Reported at the International Conference on AIDS, June 20-23. Abstract No. S.D.848.

WHO, (1991c) Global Programme on AIDS. Update: Cases reported to surveillance, forecasting and impact assessment unit.

Wong, G., McHugh, T., Stites, D., Goeddel, D. (1989, Nov.). HIV infected cells are more susceptible than uninfected cells to killing by irradiation, heat, or tumor necrosis factor. Presented at the NIH/NY Academy of Sciences Conference on AIDS, Crystal City, Va.

Wysocki, D. & Harrison, R. (1991). Aids and the media: A look at how periodicals influence children and teenagers in their knowledge of AIDS. Journal of Health Education, 22 (1), 20-23.

Yatvin, M. (1988). An approach to AIDS therapy using hyperthermia and membrane modification. Medical Hypotheses, 27 (3), 163-165. (Abstract).

Zarling, J., Moral, P., Haffar, O., Sias, J., Richman, D., Spina, C., Myers, D., Kuebelbeck, V., & Ledbetter, J. (1990). Inhibition of HIV replication by pokeweed antiviral protein targeted to CD4 cells by monoclonal antibodies. Nature, 347, 92-95. (Abstract)

APPENDIX

KENNETH ALONSO ASSOCIATES, INC.
203 B MEDICAL WAY
RIVERDALE, GEORGIA 30274

September 11, 1991

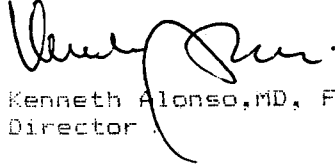
(404)991-1971

Dr. John Parkinson
Route 1, Box 289
Riceville, Tennessee 37370

Dear Dr. Parkinson,

I am happy to have you evaluate the data obtained concerning HIV positive patients with Kaposi's Sarcoma treated with systemic hyperthermia. Any patient data released to you is done so with my knowledge. For the purpose of maintaining patient confidentiality no information which would allow the ready identification of the subjects involved in this investigational study will be provided.

Yours,



Kenneth Alonso, MD, FACP
Director

/k

VITA

John D. Parkinson received his Medical Degree from The University of Tennessee. He is a retired psychiatrist with experience in both the private and public sectors. He also has ten years experience in Emergency Medicine. His interest in education has extended over several years, during which he has taught at both the graduate and undergraduate levels.

In the future, Dr. Parkinson hopes to be involved in the training programs for health care providers, an area that he believes must make some dramatic changes to contain the health care cost while still providing high quality care to all of our population.