

A TRIAL OF SURAMIN IN PATIENTS WITH THE AIDS-RELATED
SYNDROME OF PROLONGED, GENERALIZED LYMPHADENOPATHY

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1.0 OBJECTIVE

- 1.1 To determine the tolerance and toxicity of Suramin in patients with the syndrome of prolonged generalized lymphadenopathy (PGL) associated with acquired immune deficiency syndrome (AIDS).

2.0 BACKGROUND AND RATIONALE

2.1 AIDS and PGL

The acquired immune deficiency syndrome (AIDS) is defined as biopsy-proven Kaposi's sarcoma and/or the occurrence of one or more life-threatening opportunistic infections in persons with no previously documented immune deficiency (1). Patients with AIDS have prominent defects in cell-mediated immunity, and typically have marked reduction of T lymphocytes of the helper phenotype. The first report of AIDS was in the Spring of 1981. As of September 3, 1984, 5896 cases had been reported by physicians and health departments in the U.S. (2). Of these reported cases 2688 or 46% of patients are reported to have died.

Simultaneous with the AIDS epidemic, a syndrome of prolonged unexplained generalized lymphadenopathy (PGL) was recognized in the same population groups at increased risk for AIDS (3). These patients exhibit lymphadenopathy which may be associated with low grade fevers, night sweats, weight loss, and/or fatigue (4). Lymph node biopsies reveal an intense follicular

hyperplasia (4). Peripheral blood T helper/T suppressor ratios are typically reduced in some cases due to reduced numbers of T helper cells (5). Persons with PGL and immunologic abnormality appear to be at increased risk for the development of AIDS (6).

Recently members of the retrovirus family have been strongly implicated in the etiology of AIDS and the PGL syndrome (7,8). In one series retroviruses were isolated from 18/22 lymph nodes from individuals with the PGL syndrome (8). The prototype isolates (LAV and HTLV-III) appear to have a tropism for helper T lymphocytes. Drugs with anti-viral activity against these viruses have the potential to arrest or reverse ongoing injury to the immune system in these patients. LAV and HTLV-III possess an enzyme (reverse transcriptase) which is unique to the retrovirus family. This enzyme is a logical target for antiviral therapy of AIDS and the related PGL syndrome.

2.2 Suramin

Suramin (also known as Bayer 205, Germanin, Moranyl, Fournneau 309, Belganyl, Naphuride, and Antrypol) was introduced in 1920 for the treatment of African trypanosomiasis (9). Presently, Suramin is considered the drug of choice for the therapy of early Trypanosoma rhodesiense sleeping sickness when the central nervous system is not involved (10). It is also the drug of choice for the destruction of the adult worm (Onchocerca

2.2.2 Biologic properties

The mechanism of action of Suramin is unknown, although it is known to inhibit various enzyme systems including the reverse transcriptase enzyme of animal retroviruses (12).

2.2.3 Reverse Transcriptase Inhibitory Activity

Suramin binds strongly to proteins and inhibits a variety of enzymes including ureases, hexokinase, succinic dehydrogenase, beta-glucuronidase, acid phosphatase, and lysozyme. In 1979 De Clerq found that the drug exerts a strong inhibitory effect on the RNA-directed DNA polymerase (reverse transcriptase) activity of several oncornaviruses including Moloney murine leukemia virus, murine Rauscher leukemia viruses, Moloney murine sarcoma virus and avian myeloblastosis virus (12). Suramin effected 50% inhibition of the reverse transcriptase activity of oncornaviruses at a concentration range of 0.1-1 ug/ml. This concentration was far below the concentrations required to inhibit other enzymes. There is evidence that the mechanism of action is interaction with the template-primer binding site of the enzyme. Preliminary evidence indicates that suramin inhibits the reverse transcriptase of LAV.

2.2.4 Use of Suramin in Humans

2.2.4.1 Treatment of African Trypanosomiasis

By 1925 Suramin was found to be an effective drug for early Gambian and Rhodesian sleeping

sickness (14). It remains the drug of choice for T. rhodiense sleeping sickness when the central nervous system is not involved (11). Maclean (14) found that 82% of patients with early T. rhodiense sleeping sickness were cured when Suramin was given weekly IV to a total dosage of 4.5 gm. Presently Suramin is recommended by the WHO Expert Committee on Trypanosomiasis for therapy of T. rhodiense sleeping sickness (10).

2.2.4.2 Treatment of Onchocerciasis

The efficacy of Suramin in onchocerciasis was demonstrated by Van Hoof in 1942 (15). Studies revealed that a course of 7 gm. given at the rate of 1 gm. IV per week caused the disappearance of both microfilarial and adult O. volvulus within 1-2 months. Ocular involvement due to onchocerciasis may respond to Suramin with disappearance of microfilariae from the anterior chamber and improvement of vision.

3.0 STUDY SUMMARY

This is a phase I study of Suramin (1 gram IV) administered once a week for 6 weeks. Toxicity, immunologic, and virologic studies will be conducted.

3.1 Patient Selection

12 patients with the syndrome of prolonged unexplained lymphadenopathy will be entered on study. Prior to selection a complete medical history will be taken, a complete physical examination performed,

pathology material reviewed and various laboratory analyses made in order to insure that all patients meet the enrollment criteria. Patients who meet the following inclusion criteria will be enrolled.

3.1.1 Eligibility Criteria

All patients must:

3.1.1.1 Be 18 years of age or older.

3.1.1.2 Lymphadenopathy with pathologic clinical appearance (1-3 cm diameter) and involving at least two regional chains above the diaphragm.

3.1.1.3 Lymphadenopathy for greater than 6 months duration.

3.1.1.4 Biopsy-proven follicular hyperplasia, and absence of involution and malignancy.

3.1.1.5 T helper numbers less than 600 per cubic millimeter.

3.1.1.6 Stable clinical condition defined as prognosis for survival of at least 6 months.

3.1.1.7 No persisting symptoms of any toxic effect resulting from previous therapy.

3.1.2 Exclusions

3.1.2.1 Previous opportunistic infection or Kaposi's sarcoma.

3.1.2.2 The following abnormal laboratory findings:

Serum creatinine greater than 1.5 mg/dl.

AST or ALT greater than 5 times the upper limit of normal.

Total bilirubin greater than 2.5 mg/dl.

Alkaline phosphatase greater than 2 times
upper limit of normal.

3.1.2.3 Incapable of giving meaningful informed
consent.

3.1.3 Subsequent Exclusion Criteria

After enrollment a patient will be excluded from further participation in the study for any of the following reasons:

3.1.3.1 Has idiosyncrasy (collapse) following the test dose or any dose of Suramin.

3.1.3.2 Develops nephritis or renal shutdown.

3.1.3.3 Develops bilirubin greater than 2.5 mg/dl.

3.1.3.4 Desires to be withdrawn from the study.

4.0 THERAPEUTIC AGENT

4.1 Product description

Suramin is a symmetrical urea compound with the chemical formula shown under 2.2.1.

4.2 Formulation and stability

Suramin is supplied in ampules containing 0.5 gm of the dry powder. A 10% solution for injection is made up by adding 5 ml. of distilled water to each 0.5 gm. dry powder. The solution is prepared immediately before use.

4.3 Pharmacology

The LD 50 for mice given IV Suramin is 620 mg./kg.
The LD 10 is 420-500 mg/kg. In mice 0.0000g gm. is a

curative dose and 0.01 gm is a toxic dose; the chemotherapeutic index is therefore 1/167. (16). The chief toxic effect of Suramin on laboratory animals is upon the kidney where there are minute hemorrhages and degenerative changes. Such changes may also be noted in the liver, lungs, and central nervous system (9).

Suramin is absorbed from the gastrointestinal tract to a limited extent. The IV route is recommended as Suramin causes intense local irritation when given by the subcutaneous and intramuscular routes. Following IV administration, a high concentration of Suramin is found in plasma. The plasma concentration falls over the first few hours and then becomes almost constant for a period of days (17). Suramin combines with plasma proteins and may persist in the blood stream for 3 months. It does not enter red blood cells or cross the blood-brain barrier. Metabolic destruction of Suramin is believed to be negligible and the drug is excreted very slowly. Consequently repeated doses have a cumulative effect (9).

4.5 Side Effects and Toxicity

Suramin is a potentially toxic drug which requires close supervision of the patient when the compound is administered (10). Side effects include immediate collapse, nephrotoxicity, fever, hepatotoxicity, rash and pruritis, local edema, malaise, and ocular reactions. Relative adrenal insufficiency, severe exfoliative dermatitis, agranulocytosis, hemolytic anemia, and death are rare

associations.

4.5.1 Immediate Collapse

Nausea, vomiting, and loss of consciousness accompanied by seizure activity occurred in 12 of 4500 patients given IV Suramin for prophylaxis of sleeping sickness (18). A test dose of 0.2 gm IV is useful in identifying individuals with marked idiosyncrasy to Suramin (19).

4.5.2 Nephrotoxicity

Albuminuria is common after Suramin administration. Alone it does not necessitate cessation of therapy (10). Nephritis with renal failure has been reported (20).

4.5.3 Adrenal Insufficiency

Adrenal insufficiency was observed in patients treated for pemphigus (21). It has not been observed in patients with trypanosomiasis or onchocerciasis.

4.5.4 Hematologic Toxicity

Hemolytic anemia and agranulocytosis are extremely rare complications of therapy (22).

4.5.5 Fever

Fever to 100-101 may follow injections. Severe fever with prostration and diarrhea lasting weeks occurs rarely (23).

4.5.6 Hepatotoxicity

Jaundice and transient hepatitis have been reported (24).

4.5.7 Rash, Pruritis, Edema

Rash with itching is common, however severe exfoliative dermatitis is rare. Edema is observed in patients with sleeping sickness or onchocerciasis presumably due to death of parasites.

4.5.8 Pain

Burning in the palms and soles has been noted (19).

4.5.9 Ocular Reactions

Blepharitis, conjunctivitis, photophobia, and lacrimation have been observed (19).

4.5.10 Death

Deaths due to immediate hypersensitivity have occurred when a test dose of Suramin was not used (15).

5.0 TREATMENT REGIMEN

5.1 Patient Entry/Treatment Assignment

All patients will be treated with the treatment regimen recommended for onchocerciasis. This consists of Suramin administered 1 gram intravenously per week for 6 weeks. A test dose of 0.1 gram IV will be given initially to all patients to exclude hypersensitivity.

5.2 Assessment of Response/Toxicities

Side effects and toxicities related to Suramin are to be assessed weekly.

5.3 Removal from Study

Toxicities - Patients developing unmanageable or life-

threatening toxicities may be removed from the study at the discretion of the principal investigator.

6.0 OBSERVATIONS/STUDIES TO BE RECORDED

6.1 Study Schedule

Laboratory studies, disease evaluations and other observations are to be performed as outlined in the Activities Chart (see next page).

6.2 Prestudy Evaluations

Studies at entry should be performed within 1 week prior to initiation of Suramin.

6.3 Patient Performance/Side Effects

Karnovsky performance status will be determined prestudy and every other week thereafter. Drug-related side effect and disease symptoms will be evaluated weekly.

6.4 Laboratory Data

Patients will be evaluated with the following:

6.4.1 Hematology: Hemoglobin, hematocrit, WBC with differential, and platelet count at Entry and weekly.

6.4.2 Chemistry: AST, ALT, alkaline phosphatase, bilirubin, BUN, and creatinine weekly.

6.4.3 Serum: for anti-HTLV-III antibody will be obtained every 2 weeks. Additional serum will be frozen for use in measuring HTLV-III antigen when such tests are developed.

ACTIVITIES CHART

STUDY OF SURAMIN IN ACQUIRED IMMUNODEFICIENCY SYNDROME

Week	Pre	1	2	3	4	5	6	7	8	9	10
Interval History	X	X	X	X	X	X	X	X	X	X	X
Physical Exam	X	X	X	X	X	X	X	X	X	X	X
Hematology											
CBC, differential	X	X	X	X	X	X	X	X	X	X	X
Platelet count	X	X	X	X	X	X	X	X	X	X	
Chemistries											
SMAC panel (inc. AST,ALT,alkaline phosphatase, bili, BUN, creatinine)	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X		
T cell subsets	X		X		X		X		X		X
LAV isolations	X		X		X		X		X		X

6.4.4 Immunologic Studies: Blood will be drawn for determination of absolute numbers of T-helper and T-suppressor lymphocytes at Entry and weekly,

6.5.5 Virologic Studies: Blood lymphocytes will be harvested weekly for retrovirus culture.

7.0 TREATMENT MODIFICATIONS/TOXICITY MANAGEMENT

7.1 General Principles

7.1.1 upportive Management

Every effort will be made to manage dermatologic and minor gastrointestinal toxicities with supportive care.

7.2 Severe or Life-Threatening Toxicities

Major toxicities may require patient withdrawal..

7.2.1 Hypotension or collapse on the first or subsequent dose of Suramin will require withdrawal.

7.2.2 Doses will be withheld at the discretion of the investigator for serum creatinine greater than 1.5, serum ALT or AST greater than 5 times normal, reduction of hemoglobin, total leukocyte count or platelet count of greater than 25% of Entry level.

8.0 STUDY MANAGEMENT AND REPORTING PROCEDURES

8.1 Patient Consent and IRB Approval

The investigator is responsible for patient care and consent by the patient. Written informed consent must be obtained prior to entry of any patient.

No patients will be entered on this protocol until it has been approved by the UCLA Human Subject Protection Committee.

8.2 Drug Acquisition and Inventory Control

Suramin will be obtained from the Parasitic Diseases Service, Centers for Disease Control. Records of all Suramin dispensed will be maintained by the Investigator. All unused drug will be returned to CDC or destroyed.

9.0 PATIENT RECORDS

9.1 Hospital Records

Hospital charts will be maintained by the Investigator.

9.2 Data Collection Form

A data collection form will be developed by the Investigator. Forms will be confidential.

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APPENDIX II

KARNOFSKY PERFORMANCE SCALE

Able to carry on normal activity; no special care is needed.

Unable to work; able to live at home and care for most personal needs; a varying amount of assistance is needed

Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly

100 Normal; no complaints; no evidence of disease

90 Able to carry on normal activity; minor signs or symptoms of disease

80 Normal activity with effort; some signs or symptoms of disease

70 Cares for self; unable to carry on normal activity or to do active work

60 Required occasional assistance but is able to care for most of his needs

50 Requires considerable assistance and frequent medical care

40 Disabled; requires special care and assistance

30 Severely disabled; hospitalization is indicated although death not imminent

20 Very sick; hospitalization necessary; active supportive treatment is necessary

10 Moribund; fatal processes progressing rapidly

0 Dead

Mike's Copy

Protocol 26,541-003

Project P53

A Multi-Center, Placebo-Controlled Trial to Evaluate Azidothymidine (AZT) in the Treatment of Human T Lymphotropic Virus Type-III (HTLV-III) Infection in Patients with AIDS Related Conditions (ARC) or Acquired Immune Deficiency Syndrome (AIDS)

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1.0 INTRODUCTION

1.1 Study Rationale

The acquired immunodeficiency syndrome (AIDS) is a human disease first described in the United States in 1981 which has recently been described as a major human epidemic in isolated pockets worldwide. It is characterized by profound alterations in immune function predominantly affecting T cell function and the regulation of cell mediated immunity. AIDS is almost always fatal within one to two years of the first clinical manifestations of illness.

Although AIDS was initially described and characterized in three high risk groups, (homosexual men, hemophiliacs, and intravenous drug abusers), other nonrisk individuals have developed the disease. It has been shown to be spread by intimate sexual contact, by the administration of blood products, and occasionally by the maternal-fetal route. Many patients who develop AIDS are asymptomatic when they transmit their disease to contacts because a 1-5 year (or more) latency period exists between infection and clinical manifestations of illness.

In 1983 and 1984 several groups of investigators reported the association of a new virus (HTLV-III/LAV) with AIDS. Three lines of evidence point to this virus as the etiologic agent of AIDS: 1) it infects and kills the T₄+ helper-inducer T cells which are depleted in AIDS, 2) it has been reproducibly isolated from patients with AIDS and the AIDS-related conditions (ARC) of diseases which precede frank AIDS, and 3) there is a high (>90%) incidence of HTLV-III seropositivity in affected patients.

Evidence therefore indicates that AIDS is a serious infectious disease caused by a new family of human retrovirus which is spread primarily through sexual contact and administration of blood products. A long latency or persistent viremic period may precede symptomatic illness. Individuals who are infected could therefore benefit from therapy with an effective anti-AIDS virus agent.

Azidothymidine (AZT) has been shown to be a potent inhibitor of human retrovirus replication in vitro (see Investigator's Brochure for complete information). Preliminary animal and human data regarding the pharmacology and toxicology of this compound indicate that it is safe at the dose planned for this trial. The prevention and treatment of AIDS has been identified as a major priority within the medical community and by the U.S. Department of Health and Human Services, and the World Health Organization (WHO). This study will enable investigation of a drug on a double-blind basis with potential benefit for the treatment of specific AIDS patients and patients with AIDS Related Conditions (ARC).

1.2 Animal and In Vitro Testing

By the intravenous route, the LD50 of Azidothymidine (AZT) is greater than 750 mg/kg in rats and mice. No significant alterations were seen when the compound was administered to dogs, intravenously, at dose levels of up to 85 mg/kg/day for 2 weeks. Similarly, no changes were noted in rats given BW 0509U81 intravenously, at dose levels of up to 150 mg/kg/day for one month.

In an oral dose range-finding study in rats which were given the compound at dose levels of up to 500 mg/kg/day, the only alterations observed were very minimal histologic changes in the liver and kidney of a few high dose animals.

More notable effects were seen in an oral DRF in Beagle dogs which were given 0, 125, 250, or 500 mg/kg/day of AZT daily for 2 weeks. Vomiting and fecal alterations (with blood) were seen in high dose dogs and the high dose female was sacrificed in moribund condition on dose day 14. This animal also lost a significant amount of weight in the treatment period. There was a moderate to marked leucopenia and thrombocytopenia at all dose levels and alkaline phosphatase, BUN and CRE levels were elevated in the high dose female sacrificed on day 14. Grossly, hemorrhage in the gastrointestinal tract in the high dose dogs and a mid-dose female, as well as a maturational

defect with mucosal atrophy in the intestinal tract of the high dose female. Slight to moderate hypoactivity was seen in lymphoid tissues at all treatment levels and mild to marked (dose-related in severity) hypocellularity of the bone marrow was noted in dogs at all dose levels.

In an oral DRF, *Cynomolgus* monkeys (a species which unlike dogs metabolizes the drug more like man), were given AZT at dose levels of 125, 250, 500 mg/kg/day for 2 weeks. The only changes seen that may have been treatment-related were frequent vomiting in the high dose male, a slight nondose-related decrease (values still within normal limits) in RBC, HCT, and H_{3b} at all treatment levels, and a slight increase in SGPT (values still within normal limits) in treated males and the high dose female.

In an oral DRF in pregnant rats given the test compound at dose levels of up to 500 mg/kg from gestation day 6 through 15, only a slight decrement in maternal body weight was noted.

In genetic toxicology experiments, the Ames test was negative, whereas the drug was a weak mutagen at the highest concentrations tested (1000 to 5000 micrograms/ml) in the mouse lymphoma assay. In an in vitro cytogenetics assay in cultured human lymphocytes, AZT was clastogenic, with the no-effect level being between 3 and 10 micrograms/ml.

1.3 Human Pharmacokinetics

1.4 Summary of Human Phase I Safety and Clinical Experience

The first clinical trial was conducted in 23 patients with AIDS or ARC and HTLV-III viremia. Four doses were studied:

- A. 1 mg/kg every 8 hours x 28 days iv plus 2 mg/kg every eight hours x 30 days orally
- B. 2.5 mg/kg every 8 hours iv x 14 days plus 5 mg/kg every 8 hours x 30 days orally
- C. 2.5 mg/kg every 4 hours iv x 14 days plus 5 mg/kg every 4 hours x 30 days orally
- D. 5 mg/kg every 4 hours iv x 14 days plus 10 mg/kg every 4 hours x 30 days orally.

All patients tolerated azidothymidine well. Two patients developed anemia and were removed from the study. One patient in group D developed a relative leukopenia (WBC dropped from 4000 to 1900) which resolved when drug was discontinued.

There was a 1-2 gm/dl fall in hemoglobin in most patients. This stabilized after three weeks despite continued treatment. Hemolysis was not a factor. The change in hemoglobin was unrelated to the amount of drug given.

There was no effect on renal or hepatic function at any dose.

1.5 Study Purpose

The purpose of this protocol is to determine whether azidothymidine (AZT) is useful as a treatment for the Acquired Immune Deficiency Syndrome (AIDS) and the AIDS-Related Conditions (fever, weight loss, lymphadenopathy). Patients with documented HTLV-III viremia will be evaluated for decrease, suppression or disappearance of virus. Drug effects on virus replication, immune function and clinical condition will be monitored with periodic virus cultures and estimates of lymphocyte type and numbers, cell surface markers, and in vitro responses to stimuli.

2.0 STUDY OBJECTIVES

- 2.1 Clinical improvement as measured by weight gain, increased Karnofsky performance status (see Appendix II), improved CNS status (see Appendix III), decrease in fever and reduction in frequency and severity of opportunistic infections.
- 2.2 Restoration of immune response as measured by reactivation of cutaneous hypersensitivity, significant and consistent increase in absolute T4 lymphocyte counts and T4/T8 ratios. Increase in absolute lymphocyte counts.
- 2.3 Antiviral effect as measured by a reduction in the ability to detect virus-coded products (e.g. reverse transcriptive gag antigen or RNA transcripts) or disappearance of virus from the blood or other body fluids (e.g. CSF, semen, etc.).
- 2.4 Decreased incidence of progression to less favorable categories.

3.0 INVESTIGATORS/FACILITIES

3.1 This will be a multi-center trial with emphasis on a broad geographic distribution.

3.2 A list of investigators and facilities is provided in Appendix IV.

4.0 STUDY OUTLINE

4.1 Type of Study

This will be a double-blind placebo-controlled clinical trial of AZT in specific categories of ARC and AIDS patients.

The trial will include 6 months of treatment with periodic review of data (at least every 2 months) by an independent Scientific Review Board. There will be a follow-up evaluation 30 days following discontinuation of treatment.

5.0 PATIENT SELECTION

5.1 Inclusion Criteria

5.11 AIDS Related Conditions (ARC)

5.111 Patients must be symptomatic (see Appendix VIII for definitions of specific symptoms).

5.112 Clinical parameters (at least one of the first 2 but may include any of the others listed).

5.1121 unexplained weight loss $> 10\%$ or ≥ 15 lbs within the previous 3 months. Documentation by hospital records.

5.1122 documented history of mucocutaneous oral candidiasis

5.1123 fever $> 100^{\circ}\text{F}$ without infectious cause present greater than 3 weeks

5.1124 lymphadenopathy ≥ 4 extrainguinal regions; present at entry

5.1125 biopsy proven hairy leukoplakia

5.113 Laboratory parameters - All patients will have at least the first 3 parameters present at entry.

5.1131 total white blood cell count (WBC) $> 2000/\text{cubic millimeter}$

- 5.1132 absolute T4 counts: Group A $>100 \leq 150$, Group B $>150 < 500$ /cubic millimeter. Patients will be prestratified and randomized according to these categories.
- 5.1133 T4/T8 ratio < 1.0
- 5.1134 cutaneous anergy to the following antigens: including at a minimum trichophyton, tetanus toxoid, candida, and PPD. Standard lots of antigen will be purchased from a central source and distributed to all study centers. A standard protocol will be followed in all centers (see Appendix IX).
- 5.1135 one positive HTLV-III culture within 3 months prior to entry into the study or blood obtained and culture pending. Patient with negative cultures will be poststratified and analyzed separately. For entry patients must have 5.1131, 5.1132, 5.1134, and 5.1135.

5.12 Acquired Immune Deficiency Syndrome (AIDS)

- 5.121 Patients with AIDS should be only those who are status post and recovered from 1st pneumocystis carinii pneumonia (PCP) no greater than 90 days
- 5.122 There should be no history of other opportunistic infections and no evidence of active opportunistic infections (e.g. culture proven mycobacterium avium intracellulai, histoplasmosis; PCP by biopsy, etc.).
- 5.123 All patients will be treated with standard suppressive regimens of TMP/SMX (SEPTRA) unless intolerance to sulfaminimides, leucovorin anti-fungal agents and antihistamines will be added as needed. These treatment regimens will be outlined in Appendix V.
- 5.124 All patients must have life expectancy of 6 months.

5.2 Exclusion Criteria

- 5.21 AIDS patients with Kaposi's sarcoma (they will be considered in a separate protocol)
- 5.22 Intravenous drug abusers (will be considered in a separate protocol)
- 5.23 Patients who have received other anti-retroviral agents within 6 weeks prior to entry and Suramin within 12 weeks.
- 5.24 Immunomodulating agents within 4 weeks prior to entry in the study.
- 5.25 Asymptomatic patients (both ARC and AIDS).
- 5.26 Chemotherapeutic agents within 2 weeks (some treatment will be allowed on study), which include all cytolytic agents. Exceptions will be made for suppression of PCP, oral candida and herpes simplex infections; however, these therapies will be standardized.
- 5.27 Children younger than 12 years old (considered in a separate protocol).

5.3 Demographics of Patient Population

- 5.31 Age: $\geq$ 12 years old
- 5.32 Race: No limitation
- 5.33 Sex: No limitation

5.4 Number/Source/Management of Patients

- 5.41 Number of patients to be studied: A total of 200 patients will complete the study (133 will receive AZT and 67 will receive placebo).
- 5.42 Source of patients: AIDS clinics within the study centers.
- 5.43 Management of patients: This will be an outpatient study and patients will be seen weekly for the first month and every other week (twice a month) thereafter. There will be a follow-up at one month after end of therapy.

6.0 STUDY MEDICATION, DOSAGE AND ADMINISTRATION

6.1 Study Medication Supply

6.21 Patients will receive three, 250 mg capsules 6 times per day (every 4 hours) or the closest increment to 10 mg/kg (dosing not exceed 11.0 mg/kg) every four hours.

6.22 Medication will be dispensed on a weekly basis for the first month and every other week (a 2 week supply) thereafter.

6.23 The total duration of treatment will be 6 months with a follow-up at 1 month after the end of therapy.

7.0 CLINICAL EVALUATION

7.1 Enrollment

Once it has been determined that the patient qualifies, the study details will be discussed, questions will be answered and informed consent will be obtained from the patient as documented by a signed statement of informed consent approved by the institutional human experimentation review committee(s). A copy of the IRB approval informed consent form will be forwarded to the sponsor. The sponsor will be notified of IRB approval and study medication will be shipped.

Prior to administration of the first dose of study drug, a history and general physical exam will be completed and recorded on the case report form provided by the sponsor and results of pregnancy tests (for female patients) will be available.

It is recognized that patients may improve while receiving study medication. Efficacy may be indicated by improved clinical status, elimination of virus or decrease in amount of virus detectable, and improvement in parameters of immune function. Relapse in clinical, virologic or immune status may occur when study medication is discontinued.

7.2 Concomitant Medications

Any other treatments/medications/biologicals/blood products the patient is receiving at the time of enrollment,

has received within 4 weeks prior to enrollment, or receives during the study will be recorded at each visit.

7.3 Treatment Phase and Follow-up

7.31 Efficacy Evaluation

7.311 Subjective symptoms to be evaluated weekly during the first month include headache mental acuity, malaise, fatigue, dyspnea, nausea, abdominal discomfort, loss of appetite, tremors and lethargy. These symptoms will be evaluated weekly during the first month and every other week until the end of the study.

7.312 Objective signs for each patient will be weight gain or loss changes in vital signs, Candida, and cutaneous skin eruptions. These observations, including vital signs, will be made weekly during the first month and every other week during the remainder of the study. Evaluation of size and appearance assessment of lymphadenopathy will be documented every other week in those patients with this disease manifestation. These observations will be made by the same observer at each visit.

7.32 CNS Evaluation - Patients with evidence of CNS disease will be evaluated at entry and monthly during treatment (see Appendix VII). CT scans will be performed at entry, end of treatment and at one month follow-up. Magnetic Resource Imaging will be performed in centers where the technology is available. This will be performed at entry, if an abnormality is detected evaluations will be repeated every 3 months and at follow-up.

7.33 Adverse effects of both a local and generalized nature will be assessed on a daily basis during drug administration. Patients will be evaluated clinically within 24 hours of discontinuation of study drug and at one month following end of treatment.

7.34 Periodic Review

Data will be reviewed every 2 months by an independent scientific review committee to assess safety and efficacy.

7.35 Treatment Success and Failures

7.351 Treatment successes will be those persons who have two or more of the following after 6 months of therapy:

7.3511 Absolute T_4 counts of greater than 500/cu mm for 3 successive determinations.

7.3512 Anergic patients who react to at least 2 antigens and remain positive through end of therapy.

7.3513 Febrile patients who remain afebrile for >3 months.

7.352 Treatment failures will be defined as those persons who have two or more of the following:

7.3521 Absolute T_4 counts falling below 100/cu mm for >3 months.

7.3522 Anergic patients who remain anergic

7.3523 Febrile patients who remain consistently so during the treatment period.

7.3524 Patients who develop an opportunistic infection never before experienced or more the 2 previously experienced opportunistic infections during the treatment period.

7.3525 Patients with AIDS who experience PCP that is not treatable by standard therapy or more than one episode during the treatment period.

8.0 LABORATORY STUDIES

8.1 Evaluations to be Performed

The following laboratory studies will be performed on a weekly schedule during the first month of trial and every other week thereafter:

- 8.11 Chemistries: serum creatinine, BUN, electrolytes (Na, K, Cl, HCO₃), cholesterol, bilirubin, SGOT, alkaline phosphatase, CPK, amylase and glucose.
- 8.12 Hematologic studies: RBC, WBC, differential platelet count, reticulocyte count, hemoglobin, hematocrit, erythrocyte sedimentation rate.
- 8.13 Urinalyses: appearance, pH, sp. gr., color, glucose, protein, bilirubin, occult blood, ketones and microscopic exam for cells, casts, crystals (describe and estimate quantity), bacteria.

The laboratory studies listed below will be performed as indicated:

- 8.14 Virology: Samples for isolation of HTLV-III from blood (and saliva and semen if appropriate) will be collected at entry and monthly thereafter. Samples will be collected at entry for CMV culture (preferably blood, urine, throat and semen); if cultures become positive, they will be collected monthly thereafter.
- 8.15 Serologies: HTLV-III Ab at entry and monthly during drug administration. All antibody tests will be performed by ELISA and Western Blot.
Hbs Ags and Ab, eAg and Ab, polymerase, CMV and EBV will be performed at entry, 3 months, end of treatment and end of followup.
Immunoglobulins, specifically IGg, IgA and IgM (radial Immunodiffusion-Mancini Method) will be performed at entry, after 3 months of therapy, end of therapy and end of follow-up. Sera of these tests will be saved frozen, and performed at on central laboratory.
- 8.16 Assessment of Immune Function: Delayed hypersensitivity

skin tests will be performed at least once prior to therapy, and every other month during therapy, and at the end of therapy. Analysis of lymphocyte subsets (FACS) will be performed twice prior to entry and monthly thereafter.

In vitro assays of cellular immune function (blastogenic response, mitogen testing) will be performed prior to therapy, and end of therapy to PWM and tetanus.

8.17 Other: Serum will be drawn at entry and monthly according to section 8.14 for measurement of alpha interferon levels (heat labile) and stored frozen for future analysis.

8.18 Drug plasma will be drawn weekly for the first month and monthly thereafter for peak and trough AZT levels.

9.0 FOLLOW-UP

All patients will return for a follow-up visit 30 days after completion of treatment. They will have all tests performed that are outlined in sections 7.0 to 8.0 including another comprehensive physical examination.

10.0 ADVERSE EXPERIENCES

The attending staff will observe and query each patient and/or review nursing notes, progress notes and vital signs charted at each visit to discover any adverse experiences. These will be reported as definitely drug-related, probably drug-related, possibly drug-related or not drug-related, based on the principal investigator's judgment and graded as mild Grade 1 (no treatment required), moderate Grade 2 (treatment required but study drug continued with possible dosage adjustment), or severe Grade 3 (study drug discontinued because of reaction). See Appendix II for grading of toxicity. Any treatment required will be carried out on instruction of the principal investigator.

ANY SERIOUS OR ALARMING REACTION INCLUDING DEATH DUE TO ANY CAUSE WHICH OCCURS DURING THIS STUDY MUST BE REPORTED TO BURROUGHS WELLCOME CO. WITHIN 48 HOURS, WHETHER OR NOT THIS REACTION IS RELATED TO THE INVESTIGATIONAL DRUG. In such an event, the investigator will notify:

Joan L. Drucker, M.D.
Burroughs Wellcome Co.
Research Triangle Park, NC 27709
(919) 248-4965 (office)
(919) 248-4965 (home)

or

David W. Barry, M.D.
Director, Division of
Clinical Investigation
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or

Sandra Nusinoff-Lehrman, M.D.
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or

Dannie H. King, Ph.D.
Head, Department of
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Gloria S. Boone, M.S., M.B.A.
Clinical Research Associate
Burroughs Wellcome Co.
(919) 248-4406 (office)
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APPENDIX I **Dosing/Kinetics** **Laboratory Tests**

Test																										End of Treatment	Off Drug				End of Study Follow-up															
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31														
Multiple Dosing (750 mg 6 x Day)		X	----->																								X																			
CBC including absolute lymphs T4, T4/T8	¹ X	X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X	X		X														
Clinical Chemistries		X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X	X		X														
Urinalysis		X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X	X		X														
Virology HTLV-III		X			X				X				X				X				X				X		X					X														
Serology HTLV-III		X			X				X				X				X				X				X		X					X														
EBV CMV Hepatitis B		X											X														X					X														
Immunology α interferon Levels		X			X				X				X				X				X				X		X					X														
Cutaneous anergy		X			X				X				X				X				X				X		X					X														
Blastogenic response to PWM and tetanus		X																									X					X														
CNS evaluation		X											X														X																			
Peak and Trough AZT levels					X				X				X				X				X				X			X		X																

NOTE: Comprehensive physical including chest x-ray at entry.

¹Entry baselines including CBC, absolute lymphocytes, T4 count, T4/T8 ratio to be evaluated 3 times at least 48 hours apart prior to initiation of drug.

Appendix I - star.

APPENDIX II
TOXICITY GRADING FOR DOSE REDUCTIONS

Toxicity	Toxicity Grading			
	(Mild) Grade 1	(Moderate) Grade 2	(Severe) Grade 3	(Life-threatening) Grade 4
Fever*	1°C over pretreatment to 38.6°C	38.7°C-39.7°C	>39.7°C	
Chills*	mild to moderate shaking	severe shaking	rigors	
Fatigue*	100% performance status feeling fatigue	50-100 performance status significant fatigue	<50% performance status depression extreme discomfort lethargy	
Malaise*	[Flu-like syndrome (myalgia, arthralgia)]			
	<6 hrs duration	6-24 hrs duration	>24 hours duration	
Nausea/* vomiting	Nausea only	Emesis <6 no antiemetics	Emesis >6 with antiemetics	
Headache*	<2 hrs not requiring analgesic	>2 hrs, but less than 24 or requiring analgesic	>24 hrs with or without analgesic	
Granulocytes	1000-1500	500-999	<500	Grade 3 plus infection
Platelets	75-100,000	50-74,999	<50,000	Grade 3 plus bleeding
SGOT	<2 x normal or patient's baseline	<3 x normal or patient's baseline	>3 x normal or patient's baseline	
Creatinine	1.5-1.9	2.0-2.5	>2.5	
Peripheral Nerves	Any of the following: decreased DTR's and/or mild parathesias, mild constipation	Any of the following: absent DTR's and/or moderate parathesias; can hold objects	Either of the following: paralysis, severe constipation	Ileus

*Dose reductions may be made at the discretion of the investigator.

APPENDIX V

Suggested Informed Consent for Patients Receiving BW A509U

NATURE OF THE STUDY:

Human T-cell leukemia virus (HTLV-III) infects and inactivates certain blood cells which are part of the body's immune system. The damage to the body's immune system can result in the acquisition of unusual infections and/or unusual forms of cancer. While therapies exist for many, but not all of the infections which might occur, there is no known cure for the immunologic defects caused by the HTLV-III virus. Infection with this virus has been associated with the development of the acquired immune deficiency syndrome (AIDS) in some patients, while in others its presence has not led to any discernible illness over the period of time the patients have been observed. Although it is impossible at this time to predict which patients infected with the HTLV-III virus will go on to develop serious illness, the presence of certain symptoms place certain patients in a higher risk category. Individuals at higher risk are more likely to acquire recurrent and, at times, fatal infections.

You have been referred to this medical center because you have evidence of infection with the HTLV-III virus. Because of this, you are being offered the opportunity to participate in a clinical study designed to test a new drug, known as azidothymidine (AZT). This drug may have some effect in stopping or slowing HTLV-III infection. It is hoped that, eventually, this drug will be utilized in the right way to stop HTLV-III infection and the progress of AIDS. If you decide to participate in this trial, you will be treated as described below. Be sure you read this document carefully and ask any questions that may occur to you about what we are requesting of you.

Before beginning any treatment, you will be carefully examined and have routine tests (complete blood count, blood chemistries, urinalysis, chest x-ray and electrocardiogram) performed. If, on the basis of these studies, we find any evidence of heart disease, kidney disease, or other conditions that may make it dangerous for you to participate in this study, we will advise you of these findings and what alternatives you may have.

If you decide to participate in this study, you will receive either the new drug AZT or placebo. The test agent will be administered as an oral capsule. You will take 3 capsules every 4 hours (or 6 times per day around the clock). You will be required to visit the clinic or hospital weekly during the first month of treatment and every other week (twice per month) for the next 5 months. You will receive the test agent for a total of 6 months. Approximately every 2 months data for all participating centers will be evaluated by an independent scientific review board to determine safety and effectiveness of the test agent. If undue toxicity is observed or dramatic efficacy the study will be stopped.

In addition to the tests performed on admission to the study, we will perform a number of laboratory tests that will help us in your evaluation; blood will be obtained once a week for the first month and every other week thereafter to be sure you are not having any side effects from the treatment. Additionally, we will take blood and urine to measure the levels of the drug in your blood and urine. These tests will require two to three tablespoons of blood per sample and the total amount of blood obtained for these tests over the 6 months of treatment will be less than 450 ml, a volume equal to that taken when you donate a unit of blood.

After completing treatment, you will be scheduled to return for a follow-up visit at 7 months (one month after completion of treatment). At that time, we will reevaluate the presence of HTLV-III infection. If your infection has stopped, we will ask you to return for various follow-up visits. It will be very important to maintain close follow-up because you may be at risk for recurrence of infection. If the infection is still present, there are no proven treatments for HTLV-III infection which can be recommended at this time, but we will discuss your case with you.

BENEFIT:

This study will help determine if AZT, a new orally administered drug, will be useful in the treatment of infection with HTLV-III virus

and will therefore be useful to other persons who may acquire this infection. If your infection is cured by treatment, this study will also be of direct benefit to you.

DURATION OF THE STUDY:

The duration of the study will be 7 months (approximately 210 days). You will be asked to return for reevaluation following to determine the status of your infection. Additional follow-up evaluations may be required following completion of treatment. If relapse is determined at any point, it may be recommended that you be treated with additional courses of the drug.

RISKS, INCONVENIENCES, AND DISCOMFORTS:

The major risk associated with participation in this study is in receiving a new drug which has extremely limited use in humans. Studies in laboratory animals have been conducted to determine the possible side effects of administering this new drug. Although no serious effects on any bodily organs, blood counts, or other body functions have been found, more serious side effects might be detected with more extensive study of the drug in animals and humans. You have been informed that, in the judgment of the principal investigator, the risk of not treating the HTLV-III virus infection outweighs the risk associated with receiving AZT therapy.

You have been informed that treatment with this drug may mean that you will be ineligible for treatment with other experimental drugs for HTLV-III infection for a limited period of time.

You will have blood drawn several times during the course of treatment, as well as before and after therapy, to determine if the treatment is having any adverse effect or is having an effect on your infection; there will be some temporary minor discomfort associated with these procedures.

POLICY REGARDING RESEARCH-RELATED INJURIES:

If physical injury results from your participation in this research, immediate necessary medical care will be provided. However, there is no

provision for free medical care or for monetary compensation for such injury.

POLICY REGARDING PREGNANCY:

The safety of AZT has not been established during pregnancy. Therefore, any sexually active woman of childbearing age will have a pregnancy test performed and evaluated; those pregnant will be excluded from the study, as would any female who has engaged in sexual activity during the past month that could culminate in pregnancy or in which appropriate barrier contraception (diaphragm, condom and foam) was not used. Female patients must agree to abstain or use barrier contraception, if needed, during and for four weeks after the end of drug treatment.

CONFIDENTIALITY OF RECORDS:

Records will be maintained that identify you by name, and these records may be inspected by the Food and Drug Administration (FDA). You will not be identified by name in any presentation or publication of the data to be collected by us. The medical information from this study will be submitted both to the FDA of the United States Government and to Burroughs Wellcome Co. under the regulations established by the Federal Privacy Act. Representatives of Burroughs Wellcome Co. may review your records pertaining to this study.

INVESTIGATIONAL DRUG:

AZT is an investigational drug which means that the FDA has not yet approved it for use in the United States. Studies such as this one will provide the data upon which the drug may one day be approved for use in this disease.

SAFEGUARDS:

In order to minimize or prevent risks and hazards associated with this study, we will perform the following:

1. Frequent physical exams and lab tests will be performed as outlined above.

2. There will be constant attendance by a physician when you are hospitalized for this study.
3. If at any time your physicians feel it would be best for you, you will be withdrawn from this study and the drug will be discontinued.
4. There will be follow-up after the completion of treatment at which time any evidence of delayed side effects will be looked for.
5. You should report any side effects that you think may be due to the therapy you are receiving.
6. In order to safeguard against blood, liver, or kidney damage by the treatment, blood and urine tests will be performed regularly.

ALTERNATIVES TO PARTICIPATION IN THIS STUDY:

If you decline to participate in this study, you may qualify for other studies being conducted to evaluate new treatments for HTLV-III infection. Each of these agents is also an investigational drug.

There is some evidence that infection with the HTLV-III virus may not lead to discernible illness over the period of time patients have been observed.

CIRCUMSTANCES UNDER WHICH YOUR PARTICIPATION MAY BE TERMINATED WITHOUT YOUR CONSENT:

1. Health conditions under which your participation probably would be dangerous.
2. Other conditions which might occur that would make your participation detrimental to you or to your health.

COST TO YOU FROM PARTICIPATION:

There is no cost to you for the hospitalization and procedures associated with the clinical study. However, routine medical care for your condition, if you are a patient, will be charged to you or to your insurance.

SIGNIFICANT NEW FINDINGS:

Any significant new findings developed during the course of this research, which may bear upon your condition (if you are a patient) or your willingness to continue participation in the research, will be provided to you and your attending physician.

APPENDIX VIII

Symptoms to be described under section 5.111 are:

- 1) Fever $>100^{\circ}\text{F}$ at entry
- 2) Karnofsky Performance status $<50\%$
- 3) Cutaneous skin eruptions of unexplained origin
- 4) Decreased Mental Status as measured by Appendix VII
- 5) Evidence of oral candidiasis
- 6) Weight loss 10% or >15 lbs.
- 7) Lymphadenopathy ≥ 4 extrainguinal regions present at entry
- 8) Biopsy proven hairy leukoplakia

**Multiple Dose, Open-Label Clinical Trial to Determine the
Tolerance and Preliminary Efficacy of HPA-23
for Patients with the Acquired Immune
Deficiency Syndrome (AIDS)**

Drug: HPA-23

Protocol No.: BBA201B00

Phase : 2

.Dose Form: 2 ml ampules for
I.V. injection

Strength: 25 mg/ml

IND No.: 26,876

Date: August, 1985

Background

HPA-23 is an antimony-polyoxotungstate heteropolyanion of cryptate structure, with a central sodium ion.

It has been established that the main effect of HPA-23 is the inhibition of nucleic acid polymerases, be they of viral, bacterial or host cell origin. Available data indicate that it exerts its effect by binding to polymerase enzyme molecules before synthesis of polynucleotide chains can take place. So far two mechanisms of HPA-23 enzyme binding have been detected. HPA-23 competitively binds to the attachment site of the template-primer on the polymerase, and interferes with the initiation step. HPA-23 also binds, probably by electrostatic attachment, in a noncompetitive manner to polymerases and inhibits their activity.

In vitro studies examining the antiviral activity of HPA-23 in tissue culture gave erratic results. Murine sarcoma virus, human adenovirus, herpes simplex, vaccinia, Coxsackie virus, influenza, rabies, and rhinovirus were inhibited in different primate cell culture systems with HPA-23 concentrations ranging from 2 to 100 mcg/ml. HPA-23 had an enhancing effect on vesicular stomatitis virus.

A considerable number of animal protection studies utilizing HPA-23 have been performed, most commonly in mice. The various trials demonstrated good activity in mice against several oncogenic viruses, such as Friend leukemia virus, the plasma variant of murine sarcoma virus, and against spontaneously-occurring mouse mammary tumors.

HPA-23 has also been found to inhibit in vitro the reverse transcriptase necessary for lymphadenopathy associated virus (LAV)/human T-cell lymphotropic virus type III (HTLV III) replication, the presumptive etiologic agent of the acquired immune deficiency syndrome (AIDS).

In a report summarizing preliminary observation of the safety and efficacy of HPA-23 (Rozenbaum et al: Lancet 1985; 450-451) inhibition of LAV was demonstrated in four patients with either AIDS or an AIDS-related condition.

Data obtained for 28 patients with AIDS and 19 patients with an AIDS-related condition (on file) indicate that 200 mg daily for extended periods is associated with unacceptable toxicity, particularly hematopoietic. Lower doses of 50 to 100 mg were better tolerated, although limited data regarding the efficacy of these doses in inhibiting LAV/HTLV III replication are inconclusive. Viral inhibition was shown for two patients treated with 50 mg of HPA-23 daily, although 200 mg daily failed to inhibit viral replication in other patients.

For these reasons, clinical trials to assess the pharmacokinetics, safety, and efficacy of HPA-23 in patients with AIDS using doses of 0.25 mg/kg to 2 mg/kg (17.5 mg to 140 mg for a 70 kg man, respectively) are warranted.

I. OBJECTIVE OF STUDY

This clinical trial will assess the tolerance and preliminary efficacy of HPA-23, given intravenously as single 0.25, 0.5, 1.0 or 2.0 mg/kg daily doses for 8 weeks in patients with the acquired immune deficiency syndrome (AIDS).

II. DESIGN

This will be an open label, parallel, multiple dose study in patients with CDC-defined AIDS who will be assigned to receive one of four dosing regimens of HPA-23.

All patients within a single dosage group per center will begin HPA-23 treatment at the same time. The lowest dosage will be studied first. Subsequent dosages will begin at intervals sufficient to evaluate potential adverse events noted at the previously tested lower dosages.

III. STUDY POPULATION

A. Number of Centers and Patients

This study will be a multicenter study performed in several geographical areas. One or more investigators may conduct this study per geographical area. A total of approximately 80 evaluable patients (20 per dosage regimen) will be enrolled.

B. Inclusion Criteria: Patients meeting the following criteria are eligible for entry into this study:

1. Age: 18 to 60 years of age
2. Sex: Male or female (post-menopausal or surgically sterile females only)
3. Diagnosis: Each patient must have AIDS. AIDS is defined as a disease, at least moderately predictive of a defect in cell-mediated immunity, occurring in a person with no known cause for diminished resistance to that disease. Such diseases include Kaposi's Sarcoma, Pneumocystis carinii pneumonia, and other serious opportunistic infections. These infections include pneumonia, meningitis, or encephalitis due to one or more of the following: aspergillosis, candidiasis, cryptococcosis, cytomegalovirus, nocardiosis, strongyloidosis, toxoplasmosis, zygomycosis or atypical mycobacteriosis (species other than tuberculosis or lepra), esophagitis due to candidiasis, cytomegalovirus, or herpes simplex virus, progressive multifocal leukoencephalopathy,

chronic enterocolitis (more than four weeks) due to cryptosporidiosis, or unusually extensive mucocutaneous herpes simplex of more than five weeks duration.

4. General Condition: Patients must be clinically stable (no active life-threatening infection) with an anticipated life expectancy of at least 8 weeks. Opportunistic infections (OI's), if present prior to beginning treatment with HPA-23, must be under control (e.g., mycobacterium avium-intracellulare) or cured (e.g., Pneumocystis carinii pneumonia).

Patients must also have a performance grade of 0 or 1 (Karnofsky 70-100, See Appendix 1).

5. All patients must give signed informed consent indicating that they understand the purpose of the study and are willing to adhere to the procedures of this protocol.

C. Exclusion Criteria. Patients with the following will be excluded from the study:

1. Female patients of childbearing potential.
2. Hemophiliac patients with AIDS (because of the risk of thrombocytopenia, bleeding or both with HPA-23 treatment).
3. Patients with a confirmed diagnosis of lymphoma.
4. Patients with known visceral Kaposi's sarcoma.
5. Patients with a neutrophil count of less than $1000/\text{mm}^3$ within 7 days of the start of HPA-23 treatment.
6. Patients with a platelet count below $100,000/\text{mm}^3$ within 7 days of the start of HPA-23 treatment.
7. Patients with a prothrombin time (PT) 2 seconds above control or partial thromboplastin time (PTT) 8 seconds above control within 7 days of the start of HPA-23 treatment.
8. Patients with SGOT, SGPT or alkaline phosphatase test values greater than 2 times the upper normal limit, or a pre-treatment total bilirubin value above the upper normal limit within 7 days of the start of HPA-23 treatment.

9. Patients who have received biologic response modifiers during the four weeks prior to beginning HPA-23 treatment.
10. Patients who have received cytotoxic chemotherapy or radiation therapy (other than local radiation to a limited area of Kaposi's sarcoma lesions) within four weeks prior to treatment with HPA-23 or have residual chemotherapy or radiation-induced toxicity.
11. Patients who have received other investigational drugs within the past four weeks.
12. Patients who have received aspirin, aspirin-containing products or systemic medications other than topical antifungals, mild sedatives/hypnotics, or acetaminophen within 7 days prior to beginning treatment.

IV. INVESTIGATIONAL MATERIALS

HPA-23 will be supplied in ampules containing 50 mg HPA-23 dissolved in 2 ml of an isotonic saline solution (25 mg/ml). These ampules must be refrigerated between 8 and 15 degrees centigrade.

V. DOSAGE REGIMEN AND DURATION

- A. Test medication. Patients will be consecutively assigned to one of the following treatment groups:

Group A	0.25 mg/kg/day
Group B	0.50 mg/kg/day
Group C	1.00 mg/kg/day
Group D	2.00 mg/kg/day

All patients will receive HPA-23 as a rapid intravenous infusion over 5 minutes, 5 days/week (Monday-Friday) for a period of 8 weeks.

- B. Dosage adjustments. No dosage adjustments are permitted.
- C. Discontinuation. If the patient experiences a serious adverse drug event (clinical or laboratory) drug will be discontinued.

Serious laboratory adverse events requiring discontinuation of treatment include the following:

Neutrophils	- fewer than 500/mm ³
Platelets	- fewer than 40,000/mm ³

PT	- greater than 1.5 times control
PTT	- greater than 1.5 times control
SGOT/SGPT	- greater than 5 times the upper normal limit
Alkaline phosphatase	- greater than 3 times the upper normal limit
Bilirubin	- greater than 3.0 mg%
Creatinine	- greater than 2.0 mg%
Urinalysis	- proteinuria of 4+ by dipstick

Immediately prior to discontinuation on the basis of any abnormal laboratory test value, confirmation of such abnormality should be made.

Patients who are discontinued from the study due to decreased platelet count should have a bone marrow biopsy performed and must be monitored closely until the platelet count stabilizes or returns to the baseline value.

Patients discontinuing treatment due to other abnormal laboratory test values will continue to be evaluated weekly until the abnormal value returns to the baseline level or is adequately explained.

- D. Concomitant medication. The only concomitant medications allowed during the study will be topical antifungals (e.g., Nystatin), mild sedatives/hypnotics or acetaminophen. Patients who require any additional systemic concomitant medications during the course of this study will be discontinued. All concomitant medications will be recorded in the appropriate section of the Case Report Form (CRF).

VI. STUDY PROCEDURES

During the week preceding the initiation of HPA-23 treatment, patients must be thoroughly screened for eligibility according to the criteria in Section III.B and C. Patients will return to the study site on Monday of Week 1 for baseline evaluation immediately prior to the first administration of HPA-23.

CDC guidelines for handling blood and urine samples are described in Appendix 2.

- A. Study Schedule. At each center all patients enrolled for each dosing regimen will be treated concurrently on Monday beginning with Group A. Patients assigned to Group B will begin treatment 2 weeks following initiation of treatment for Group A providing clinically significant adverse events are not noted in Group A. Likewise, patients assigned to Group C will begin treatment 2 weeks following initiation of treatment for Group B. Patients assigned to Group D will begin treatment 4 weeks following initiation of treatment for Group C providing no clinically significant adverse events were noted.
- B. Prestudy evaluation. For patients who have met the entry criteria the following will be performed within 24 hours prior to initiation of treatment with HPA-23:
1. Complete medical history with particular emphasis on the presence of opportunistic infections and the patient's general condition including a history of fevers, night sweats, fatigue, weight loss greater than 10% of normal body weight, or diarrhea.
 2. Complete physical examination with particular attention to the location and size of any Kaposi's sarcoma lesions and lymphadenopathy.
 3. Chest x-ray.
 4. 12 lead electrocardiogram.
 5. Complete clinical hematology including hematocrit, hemoglobin, WBC count and differential, and platelet count.
 6. Prothrombin time, partial thromboplastin time, thrombin time and fibrinogen concentration.
 7. Clinical biochemistry including serum electrolytes, BUN, creatinine, albumin, SGPT, SGOT, alkaline phosphatase, total bilirubin, total protein and blood glucose.
 8. Complete urinalysis.
 9. Hepatitis B surface antigen.
 10. Immunologic studies to include total lymphocyte number, enumeration of T_4 and T_8 lymphocyte subsets, and determination of the T_4/T_8 ratio.
 11. Performance status.

12. LAV/HTLV III reverse transcriptase activity assay (RTA). Two 30 ml blood samples for an RTA assay should be collected. One sample should be collected and analyzed according to procedures established by the investigator's local laboratory. The second sample should be collected and handled for analysis by a central laboratory according to the procedures outlined in Appendix 3 and 4.

C. Monitoring During Treatment (See Section XVI, Study Summary - Schedule of Events).

With each dose: Pulse, respiratory rate, and blood pressure prior to and immediately after each infusion until stable.

Week 1: On Friday blood for determination of peak and trough HPA-23 concentrations will be obtained. A sample for the trough concentration should be drawn immediately prior to HPA-23 administration; the sample for the peak concentration should be drawn from the arm opposite the infusion site 5 minutes following the infusion.

- Week 2:
- Complete hematological, coagulation, biochemical and urinalysis profile (See Section VI.B.5-8)
 - Interim medical history and physical examination
 - Evaluation of symptoms to assess potential adverse effects
 - Blood for determination of peak and trough HPA-23 plasma concentrations will be obtained on Monday. Samples should be prepared as specified in Section VI.C. Week 1.
 - LAV/HTLV III RTA assay (see Section VI.B.11). This sample should be drawn on either Tuesday or Wednesday.

Week 3: - Complete hematological, coagulation, biochemical and urinalysis profile (see Section VI.B.5-8).

- Evaluation of symptoms to assess potential adverse effects.
- Week 4:
- Complete hematological, coagulation, biochemical and urinalysis profile (see Section VI.B.5-8)
 - Interim medical history and physical examination
 - 12 lead electrocardiogram
 - LAV/HTLV III RTA assay (see Section VI.B.11). This should be drawn on either a Tuesday or Wednesday.
 - Evaluation of symptoms to assess potential adverse effects.
 - Blood for determination of HPA-23 plasma concentrations will be obtained on Friday. Samples should be prepared as specified in Section VI.C. Week 1.
- Week 5:
- Complete hematological, coagulation, biochemical and urinalysis profile (see Section VI.B.5-8)
 - Evaluation of symptoms to assess potential adverse effects.
 - Blood for determination of HPA-23 plasma concentrations will be obtained on Monday. Samples should be prepared as specified in Section VI.C. Week 1.
- Week 6:
- Complete hematological, coagulation, biochemical and urinalysis profile (see Section VI.B.5-8)
 - Interim medical history and physical examination.
 - Evaluation of symptoms to assess potential adverse effects.

Week 7: - Complete hematological, coagulation, biochemical and urinalysis profile (see Section VI.B.5-8).

- Evaluation of symptoms to assess potential adverse effects.

- Blood for determination of HPA-23 plasma concentrations will be obtained on Friday. Samples should be prepared as specified in Section VI.C. Week 1.

Week 8: - Complete hematological, coagulation, biochemical and urinalysis profile (see Section VI.B.5-8).

- Evaluation of symptoms to assess potential adverse effects.

- Blood for determination of HPA-23 plasma concentrations will be obtained on Monday. Samples should be prepared as specified in Section VI.C. Week 1.

- LAV/HTLV III RTA assay (see Section VI.B.11). This sample should be drawn on either Tuesday or Wednesday.

D. Termination evaluation to be performed within 72 hours following discontinuation of treatment:

- Complete hematological, coagulation, biochemical and urinalysis profile (see Section VI.B.5-8).

- Evaluation of symptoms to assess potential adverse effects.

- Assessment of performance status.

- Immunologic studies (see Section VI.B.10).

- Medical history and physical examination.

- Chest x-ray.

- 12 lead electrocardiogram.

- E. Follow-up. LAV/HTLV III reverse transcriptase activity assay should be performed on the second Tuesday or Wednesday following discontinuation of treatment.

Patients with abnormal laboratory test values will be followed at least once weekly until affected values stabilize or return to baseline levels.

VII. STUDY EXTENSION/TERMINATION

- A. Extension. This study may be extended to include additional patients only with the mutual consent of the investigator and the sponsor.

If the investigator and sponsor, upon review of the data, feel that a patient has benefitted significantly from HPA-23, administration of this drug may continue at the discretion of the investigator and sponsor.

- B. Termination. This study may be terminated for any of the following reasons:

1. Clinical Adverse Drug Event (ADE) that dictates discontinuation of treatment.
2. Abnormal laboratory test values as specified in Section V. C.
3. Patients who do not adhere to the dosing schedule.
4. Patient request.
5. Decision of the investigator.
6. Decision of the sponsor.

The reason for termination of the study for each patient who does not complete the study will be recorded on the Case Report Form. The investigator will perform the termination procedures described in Section VI.D. immediately following discontinuation of therapy.

VIII. QUALIFYING DATA

All patients who receive HPA-23 will be included in the safety analysis.

The following criteria are the minimal requirements to consider a patient valid for efficacy analysis:

- A. Patient selection - Only patients meeting all inclusion and exclusion criteria.
- B. Pretherapy evaluation - Documentation of baseline laboratory values without clinically significant abnormalities (refer to Section III.C.5-8).
- C. Compliance - Patients who do not adhere precisely to the dosing schedule will have treatment discontinued. Peak and trough HPA-23 concentrations and RTA will be assessed for these patients up to the point of non-compliance. Patients who are discontinued for non-compliance prior to week 4 will be replaced.
- D. Efficacy - RTA studies performed prestudy and according to the schedule outlined in Section VI. Additional parameters to be assessed are described in Section XI.

IX. EFFICACY CRITERIA

See Section XI.

X. DRUG EVENTS

All drug events encountered during the study will be reported on the Case Report Form. The side effects will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the Case Report Form. Relationship of the adverse reaction to the test drug must be assessed by the investigator. These assessments by the investigator may be made in recognition of the general outline presented in Appendix 5.

ANY DEATH, ANY UNUSUAL OR SERIOUS EVENT, OR ANY UNUSUAL FREQUENCY OF EVENTS MUST BE REPORTED PROMPTLY BY TELEPHONE TO THE SPONSOR, EVEN THOUGH THE EXPERIENCE MAY NOT APPEAR TO BE DRUG RELATED.

RHONE-POULENC PHARMACEUTICALS
P.O. Box 125
Black Horse Lane
Monmouth Junction, NJ 08852

Telephone: Monday through Friday - 8:30 a.m. to 5:00 p.m.
(201) 297-0100 x309 Kara E. Smith or
x305 Bruce L. Moskovitz, M.D.

Emergency telephone numbers for use during non-business hours will be given to the investigator at the beginning of the study.

Such preliminary reports will be followed by detailed descriptions as promptly as possible and will include copies of case reports, autopsy summary reports, and other documents when requested.

XI. ANALYSIS OF DATA

The mean $\pm$ SD peak and trough serum concentrations will be calculated for each dose.

Inhibition of LAV/HTLV III replication as determined by RTA assay will be tabulated for each collection time specified in Section VI, and appropriate evaluations will be made.

Post-study evaluations will be compared to the baseline evaluations for the following:

- KS lesions
- Opportunistic infections
- Performance status
- Immunologic parameters

Assessment of safety parameters will be performed for all patients.

XII. CONDITIONS FOR MODIFYING THE STUDY

If preliminary or interim analysis indicates that modifications should be made in the experimental design, dosages, parameters, patient selection, etc., these changes will be made after appropriate consultation between the sponsor and the investigator, and through amendments to this protocol after approval by appropriate reviewers and submission to the Food and Drug Administration.

XIII. WARNINGS

Preliminary data suggest that HPA-23 has the potential to cause severe thrombocytopenia, abnormalities of coagulation parameters, neutropenia and elevation of liver enzyme test values, particularly in patients with AIDS.

XIV. REVIEW AND CONSENT

A. Institutional Review

It is the responsibility of the investigator to obtain review and approval of this protocol and any changes thereto by an

Institutional Review Committee (IRB) which operates in accordance with the Federal Regulation published in the Federal Register of January 27, 1981. The investigator must submit a copy of his IRB approval document to the sponsor prior to shipment of drug.

B. Patient Consent

It is the responsibility of the investigator to obtain IRB approval of his written informed consent document; and further, to obtain a signed copy of this from each patient before entry into the study. This document must reflect the information contained in the Clinical Investigation Manual which the sponsor has given to the investigator and the elements of informed consent contained in Federal Regulations published in the Federal Register of January 27, 1984. If a patient is below the age of legal consent, written counsel must be obtained from the legal parent or guardian.

XV. INVESTIGATOR'S RESPONSIBILITIES

A. Case Report Forms

Individual Case Report Forms must be completed in black ink or typewritten. All data must be carefully completed to permit a meaningful interpretation. Case Report Forms are designed for computer processing and analysis.

Corrections of data on the Case Report Forms can be made only by crossing out the incorrect data (using a single line) and writing the correct entry next to the one crossed out. Each correction must be initialed and dated by the person making the revision.

A Case Report Form is required for each patient who has received or taken any test medication prepared for this protocol. A copy of the Case Report Form will be retained in the investigator's file until two years after all investigational use of the drug is discontinued and the FDA so notified or until two years after a New Drug Application is approved.

B. Laboratory Reports

Prior to initiation of this study, the investigator must supply the sponsor with the ranges of laboratory normal values for the laboratory utilized, also noting its certification.

Laboratory test results required by the protocol are to be recorded on the appropriate pages of the Case Report Form. When required by the protocol, additional reports will be attached to the Case Report Form. If unexplained laboratory abnormalities occur, corroborative tests will be done until these have returned to normal and/or adequate explanation of the abnormality is found.

C. Other Reports

Copies of records pertinent to the study (e.g. laboratory data, x-ray reports, patient charts) must be made available to the sponsor, if requested, with due precaution to confidentiality for the patient.

D. Monitoring Requirements

This study will be monitored (by personal visit or telephone) periodically at appropriate intervals by the representatives of the sponsor.

E. Drug Dispensing Log

Patients entered into the test drug trial will be assigned test drug in the chronological order in which they begin drug therapy. A clear record of each container of drug dispensed must be maintained by each investigator.

Unused drug supplies must be returned to the Sponsor at the completion of the study.

F. Patient Exclusion Record

A record must be kept by the investigator listing all subjects considered for entry and subsequently excluded. Subjects excluded from the study will have the reason for exclusion recorded on the form provided by the sponsor.

XVI. STUDY SUMMARY - SCHEDULE OF EVENTS

SCREENING EVALUATION (to be performed within 7 days prior to initiation of treatment)

- Complete medical history and physical examination
- Chest x-ray
- 12 lead electrocardiogram
- Laboratory safety tests (hematology, blood chemistry and urinalysis)
- Coagulation studies
- Performance status

WITH EACH DOSE: Pulse, respiratory rate, blood pressure.

WEEK 1

	M ^a	T	W	TH	F
COMPLETE PHYSICAL EXAMINATION AND RECENT MEDICAL HISTORY	X				
LABORATORY SAFETY TESTS (HEMATOLOGY, BLOOD CHEMISTRY AND URINALYSIS)	X				
COAGULATION STUDIES	X				
HEPATITIS B SURFACE ANTIGEN					
IMMUNOLOGIC STUDIES	X				
LAV/HTLV III REVERSE TRANSCRIPTASE ACTIVITY ASSAY (RTA)	X				
PERFORMANCE STATUS (KARNOFSKY SCALE)	X				
BLOOD FOR PEAK AND TROUGH EVALUATIONS					X
OBSERVE/INTERVIEW FOR ADVERSE DRUG EVENTS	X	X	X	X	X

^a To be performed prior to initiation of treatment

WEEK 2

	M	T	W	TH	F
COMPLETE PHYSICAL EXAMINATION AND MEDICAL HISTORY					ANY DAY
LABORATORY SAFETY TESTS (HEMATOLOGY, BLOOD CHEMISTRY AND URINALYSIS)					ANY DAY
COAGULATION STUDIES					ANY DAY
LAV/HTLV III REVERSE TRANSCRIPTASE ACTIVITY ASSAY (RTA)					X or X
BLOOD FOR PEAK AND TROUGH EVALUATIONS	X				
OBSERVE/INTERVIEW FOR ADVERSE DRUG EVENTS	X	X	X	X	X

WEEK 3

	M	T	W	TH	F
LABORATORY SAFETY TESTS (HEMATOLOGY, BLOOD CHEMISTRY AND URINALYSIS)					ANY DAY
COAGULATION STUDIES					ANY DAY
OBSERVE/INTERVIEW FOR ADVERSE DRUG EVENTS	X	X	X	X	X

WEEK 4

	M	T	W	TH	F
COMPLETE PHYSICAL EXAMINATION AND RECENT MEDICAL HISTORY			ANY DAY		
LABORATORY SAFETY TESTS (HEMATOLOGY, BLOOD CHEMISTRY AND URINALYSIS)			ANY DAY		
COAGULATION STUDIES			ANY DAY		
ELECTROCARDIOGRAM			ANY DAY		
LAV/HTLV III REVERSE TRANSCRIPTASE ACTIVITY ASSAY (RTA)		X or X			
BLOOD FOR PEAK AND TROUGH EVALUATIONS					X
OBSERVE/INTERVIEW FOR ADVERSE DRUG EVENTS	X	X	X	X	X

WEEK 5

	M	T	W	TH	F
LABORATORY SAFETY TESTS (HEMATOLOGY, BLOOD CHEMISTRY AND URINALYSIS)			ANY DAY		
COAGULATION STUDIES			ANY DAY		
BLOOD FOR PEAK AND TROUGH EVALUATIONS	X				
OBSERVE/INTERVIEW FOR ADVERSE DRUG EVENTS	X	X	X	X	X

WEEK 6

	M	T	W	TH	F
COMPLETE PHYSICAL EXAMINATION AND RECENT MEDICAL HISTORY			ANY DAY		
LABORATORY SAFETY TESTS (HEMATOLOGY, BLOOD CHEMISTRY AND URINALYSIS)			ANY DAY		
COAGULATION TIMES			ANY DAY		
OBSERVE/INTERVIEW FOR ADVERSE DRUG EVENTS	X	X	X	X	X

WEEK 7

	M	T	W	TH	F
LABORATORY SAFETY TESTS (HEMATOLOGY, BLOOD CHEMISTRY AND URINALYSIS)			ANY DAY		
COAGULATION STUDIES			ANY DAY		
BLOOD FOR PEAK AND TROUGH EVALUATIONS					X
OBSERVE/INTERVIEW FOR ADVERSE DRUG EVENTS	X	X	X	X	X

WEEK 8

	M	T	W	TH	F
LABORATORY SAFETY TESTS (HEMATOLOGY, BLOOD CHEMISTRY AND URINALYSIS)			ANY DAY		
COAGULATION STUDIES			ANY DAY		
LAV/HTLV III REVERSE TRANSCRIPTASE ACTIVITY ASSAY (RTA)			X or X		
BLOOD FOR PEAK AND TROUGH EVALUATIONS	X				
OBSERVE/INTERVIEW FOR ADVERSE DRUG EVENTS	X	X	X	X	X

WEEK 9 (Termination: within 72 hours following discontinuation of therapy)

- Complete physical examination and recent medical history
- Chest x-ray
- Electrocardiogram
- Laboratory safety tests (hematology, blood chemistry and urinalysis)
- Coagulation studies
- Immunologic studies
- Performance status

WEEK 10

LAV/HTLV III REVERSE TRANSCRIPTASE
ACTIVITY ASSAY (RTA)

M T W TH F

X or X

APPENDIX 1

CRITERIA FOR ESTIMATION OF PERFORMANCE STATUS

<u>Grade</u>	<u>Scale</u>
0	Fully active, able to carry on all predisease performance without restriction. (Karnofsky 90-100)
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work. (Karnofsky 70-80)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. (Karnofsky 50-60)
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. (Karnofsky 30-40)
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. (Karnofsky 10-20)
5	Dead.

APPENDIX 2

Acquired Immune Deficiency Syndrome (AIDS):

Precautions for Clinical and Laboratory Staffs (Published in Morbidity and Mortality Weekly Reports 1982 Nov 5;31:577-80)

The etiology of the underlying immune deficiencies seen in AIDS cases is unknown. One hypothesis consistent with the current observations is that a transmissible agent may be involved. If so, transmission of the agent would appear most commonly to require intimate, direct contact involving mucosal surfaces, such as sexual contact among homosexual males, or through parenteral spread, such as occurs among intravenous drug abusers and possibly hemophilia patients using Factor VIII products. Airborne spread and interpersonal spread through casual contact do not seem likely. These patients resemble the distribution of disease and modes of spread of hepatitis B virus, and hepatitis B virus infections occur very frequently among AIDS cases.

There is presently no evidence of AIDS transmission to hospital personnel from contact with affected patients or clinical specimens. Because of concern about a possible transmissible agent, however, interim suggestions are appropriate to guide patient-care and laboratory personnel, including those whose work involves experimental animals. At present, it appears prudent for hospital personnel to use the same precautions when caring for patients with AIDS as those used for patients with hepatitis B virus infection, in which blood and body fluids likely to have been contaminated with blood are considered infective. Specifically, patient-care and laboratory personnel should take precautions to avoid direct contact of skin and mucous membranes with blood, blood products, excretions, secretions, and tissues of persons judged likely to have AIDS. The following precautions do not specifically address out-patient care, dental care, surgery, necropsy, or hemodialysis of AIDS patients. In general, procedures appropriate for patients known to be infected with hepatitis B virus are advised, and blood and organs of AIDS patients should not be donated.

The precautions that follow are advised for persons and specimens from persons with: opportunistic infections that are not associated with underlying immunosuppressive disease or therapy, Kaposi's sarcoma (patients under 60 years of age), chronic generalized lymphadenopathy, unexplained weight loss and/or prolonged unexplained fever in persons who belong to groups with apparently increased risks of AIDS (homosexual males, intravenous drug abusers, Haitian entrants, hemophiliacs), and possible AIDS (hospitalized for evaluation). Hospitals and laboratories should adapt the following suggested precautions to their individual circumstances; these recommendations are not meant to restrict hospitals from implementing additional precautions.

A. The following precautions are advised in providing care to AIDS patients:

1. Extraordinary care must be taken to avoid accidental wounds from sharp instruments contaminated with potentially infectious material and to avoid contact of open skin lesions with material from AIDS patients.
2. Gloves should be worn when handling blood specimens, blood-soiled items, body fluids, excretions, and secretions, as well as surfaces, materials, and objects exposed to them.
3. Gowns should be worn when clothing may be soiled with body fluids, blood, secretions, or excretions.
4. Hands should be washed after removing gowns and gloves and before leaving the rooms of known or suspected AIDS patients. Hands should also be washed thoroughly and immediately if they become contaminated with blood.
5. Blood and other specimens should be labeled prominently with a special warning, such as "Blood Precautions" or "AIDS Precautions." If the outside of the specimen container is visibly contaminated with blood, it should be cleaned with a disinfectant (such as a 1:10 dilution of 5.25% sodium hypochlorite [household bleach] with water). All specimens should be placed in a second container, such as an impervious bag, for transport. The container or bag should be examined carefully for leaks for cracks.
6. Blood spills should be cleaned up promptly with a disinfectant solution, such as sodium hypochlorite (see above).
7. Articles soiled with blood should be placed in an impervious bag prominently labeled "AIDS Precautions" or "Blood Precautions" before being sent for reprocessing or disposal. Alternatively, such contaminated items may be placed in plastic bags of a particular color designated solely for disposal of infectious wastes by the hospital. Disposable items should be incinerated or disposed of in accord with the hospital's policies for disposal of infectious wastes. Reusable items should be reprocessed in accord with hospital policies for hepatitis B virus-contaminated items. Lensed instruments should be sterilized after use on AIDS patients.
8. Needles should not be bent after use, but should be promptly placed in a puncture-resistant container used solely for such disposal. Needles should not be reinserted into their original sheaths before being discarded into the container, since this is a common cause of needle injury.

9. Disposable syringes and needles are preferred. Only needle-locking syringes or one-piece needle-syringe units should be used to aspirate fluids from patients, so that collected fluid can be safely discharged through the needle, if desired. If reusable syringes are employed, they should be decontaminated before reprocessing.
10. A private room is indicated for patients who are too ill to use good hygiene, such as those with profuse diarrhea, fecal incontinence, or altered behavior secondary to central nervous system infections.

Precautions appropriate for particular infections that concurrently occur in AIDS patients should be added to the above, if needed.

- B. The following precautions are advised for persons performing laboratory tests or studies on clinical specimens or other potentially infectious materials (such as inoculated tissue cultures, embryonated eggs, animal tissues, etc.) from known or suspected AIDS cases:
1. Mechanical pipetting devices should be used for the manipulation of all liquids in the laboratory. Mouth pipetting should not be allowed.
 2. Needles and syringes should be handled as stipulated in Section A (above).
 3. Laboratory coats, gowns, or uniforms should be worn while working with potentially infectious materials and should be discarded appropriately before leaving the laboratory.
 4. Gloves should be worn to avoid skin contact with blood, specimens containing blood, blood-soiled items, body fluids, excretions, and secretions, as well as surfaces, materials and objects exposed to them.
 5. All procedures and manipulations of potentially infectious material should be performed carefully to minimize the creation of droplets and aerosols.
 6. Biological safety cabinets (Class I or II) and other primary containment devices (e.g., centrifuge safety cups) are advised whenever procedures are conducted that have a high potential for creating aerosols or infectious droplets. These include centrifuging, blending, sonicating, vigorous mixing, and harvesting infected tissues from animals or embryonated eggs. Fluorescent activated cell sorters generate droplets that could potentially result in infectious aerosols. Translucent

plastic shielding between the droplet-collecting area and the equipment operator should be used to reduce the presently uncertain magnitude of this risk. Primary containment devices are also used in handling materials that might contain concentrated infectious agents or organisms in greater quantities than expected in clinical specimens.

7. Laboratory work surfaces should be decontaminated with a disinfectant, such as sodium hypochlorite solution (see A5 above), following any spill of potentially infectious material and the completion of work activities.
 8. All potentially contaminated materials used in laboratory tests should be decontaminated, preferably by autoclaving, before disposal or reprocessing.
 9. All personnel should wash their hands following completion of laboratory activities, removal of protective clothing, and before leaving the laboratory.
- C. The following additional precautions are advised for studies involving experimental animals inoculated with tissues or other potentially infectious materials from individuals with known or suspected AIDS.
1. Laboratory coats, gowns, or uniforms should be worn by personnel entering rooms housing inoculated animals. Certain nonhuman primates, such as chimpanzees, are prone to throw excreta and to spit at attendants; personnel attending inoculated animals should wear molded surgical masks and goggles or other equipment sufficient to prevent potentially infective droplets from reaching the mucosal surfaces of their mouths, nares, and eyes. In addition, when handled, other animals may disturb excreta in their bedding. Therefore, the above precautions should be taken when handling them.
 2. Personnel should wear gloves for all activities involving direct contact with experimental animals and their bedding and cages. Such manipulations should be performed carefully to minimize the creation of aerosols and droplets.
 3. Necropsy of experimental animals should be conducted by personnel wearing gowns and gloves. If procedures generating aerosols are performed, masks and goggles should be worn.

APPENDIX 3

COLLECTION OF BLOOD SAMPLES FOR RTA ASSAY

BY A CENTRAL LABORATORY

1. Collect 30 ml of blood in a sterile, preservative-free, heparinized tube at the times specified in the protocol.
2. Each tube must be appropriately labelled with the following information:
 - a. protocol number
 - b. patient initials
 - c. patient ID number
 - d. investigator ID number
 - e. study week and date
3. Blood samples must be securely packaged at room temperature with sufficient protection (i.e., styrofoam) to prevent breakage or tumbling.
4. All samples must be sent via an overnight delivery service to insure delivery to the laboratory within 24 hours.

4. Extraordinary care must be taken to avoid accidental sticks or cuts with sharp instruments contaminated with body fluids or tissues of experimental animals inoculated with material from AIDS patients.
5. Animal cages should be decontaminated, preferably by autoclaving, before they are cleaned and washed.
6. Only needle-locking syringes or one-piece needle-syringe units should be used to inject potentially infectious fluids into experimental animals.

The above precautions are intended to apply to both clinical and research laboratories. Biological safety cabinets and other safety equipment may not be generally available in clinical laboratories. Assistance should be sought from a microbiology laboratory, as needed to assure containment facilities are adequate to permit laboratory tests to be conducted safely.

APPENDIX 4

AIDS ASSOCIATED RETROVIRUS DETECTION

By agreement all centers involved in this study and the SUNY-Upstate Medical Center reference laboratory will detect retroviral reverse transcriptase in the same technique. The reference laboratory will also work on improved techniques for virus detection and quantification.

I. Standard Assay

Peripheral blood mononuclear cells will be obtained from the patients by density sedimentation of 30 ml of heparinized blood on Ficoll-Hypaque. Cells will be stimulated with 5 mcg/ml of PHA and cultured in RPMI-1640 media containing 10% FCS and 20 units/ml T-cell growth factor (recombinant IL-2 provided by Cetus Laboratories) at a seed density of 10^6 cells/ml. At day 7 of the culture, fresh, normal, uninfected cultured T-cells will be added to the culture to a final volume of 200 ml of media (RPMI-1640, 10% FCS units/ml, 20 mcg/ml TCGF, .01 mcg/ml PHA), 10^6 cells/ml.

At day 14, the cell-free supernatant of the cell culture will be subjected to high speed centrifugation (19,900 rpm for 451 in a T 19 rotor). The pelleted material will be suspended in 150 ul of Buffer A, disrupted with 75 ul Solution 2 and 75 ml will be added to 150 ul of reaction mixtures and assayed in duplicate for reverse transcriptase activity mixture.

Solution 2

Buffer A	2.5 ml 1M Tris-HCL pH 7.5
	2.5 ml 2M DTT
	0.25 ml 10% Triton-X 100
	50 ml Glycerol
	33 ml 1.5 M KCl
	11.75 ml H ₂ O

Solution 2	4.5 ml 10% Triton-X 100
	18.75 ml 4M K CL
	26.75 ml H ₂ O

Reaction Mixture	69 ul H ₂ O 10
	26 ul Mg++ (.2M)
	10 ul poly rC-oligo dG
	20 ul d-GTP-H ₃

Samples will be scored as picomoles of GMP incorporated per hour. Positive control samples of low and high HTLV III producing cell lines and negative normal T-cell control cell lines will be included to assess the results. Those samples scoring greater than or equal to 0.50 picomoles gMP incorporated above the normal controls will be called positive.

Appendix 5

CLINICAL DRUG EVENTS

GUIDELINES FOR DETERMINING RELATIONSHIP TO TEST DRUG

REMOTE (must have first two)

In general, this category can be considered applicable to those adverse experiences which, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the test drug. An adverse experience may be considered remote if or when, for example:

1. It does not follow a reasonable temporal sequence for administration of the drug.
2. It could readily have been produced by the patient's clinical state, environmental or toxic factor, or other modes of therapy administered to the patient.
3. It does not follow a known response pattern to the suspected drug.
4. It does not reappear or worsen when the drug is readministered.

POSSIBLE (must have first two)

This category applies to those adverse experiences in which, after careful medical consideration at the time they are evaluated, the connection with the test drug administration appears unlikely but cannot be ruled out with certainty. An adverse experience may be considered possible when --

1. It follows a reasonable temporal sequence from administration of the drug.
2. It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
3. It disappears or decreases on cessation or reduction in dose.*
4. It follows a known pattern of response to the suspected drug.

II. Improvements in the Assay

The reference lab will assess the ability of replacing the normal culture T-cells added at day 7 with an equal amount of one or the other of two cell lines, the T-cell line HUT-78 or the B-cell line FCRC-15. Both lines are capable of productive infection of HTLV III. While both lines undergo some cell death, not all cells in the culture will die during the initial infection and will ultimately result in immortalized HTLV III positive cell line. The advantage to such a system would be a more guaranteed expansion of the infection, the lack of TCGF requirement for expanding the target cells, and the availability of a stable, constant cell target throughout the clinical trial.

We also seek to develop a quantitative HTLV III detection assay using either highly absorbed (normal T-cells or HUT 78) high titer anti-HTLV III human sera or anti-HTLV III monoclonal antibodies in a double antibody immunofluorescent assay. Fresh peripheral blood mononuclear cells from the patient will be cultured as before in PHA and TCGF for 7 days and stimulated with iododeoxyuridine (2 ug/ml) and 10^{-6} M dexamethasone for 48 hours, fixed in 70% ethanol and incubated sequentially with the anti-HTLV III sera and then FITC-conjugated goat anti-human or mouse IgG and analyzed on the cell sorter. Appropriate HTLV III infected and uninfected cells would be used as controls. The advantage to such a system would probably be increased sensitivity over reverse transcriptase and improved quantification of total number of cells infected per 10^6 peripheral blood mononuclear cells during the course of the clinical trial.

PROBABLE (must have first three)

This category applies to those adverse experiences which after careful medical consideration at the time they are evaluated, are felt with a high degree of certainty to be related to the test drug. An adverse experience may be considered probable if, for example:

1. It follows a reasonable temporal sequence from administration of the drug.
2. It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
3. It disappears or decreases on cessation or reduction in dose.*
4. It follows a known pattern of response to the suspected drug.

*There are important exceptions when an adverse experience does not disappear upon discontinuation of the drug, yet drug relatedness clearly exists; e.g., 1) bone marrow depression; 2) fixed drug eruptions; and 3) tardive dyskinesias.

*file foscarnet
drugs*

MINUTES FROM MEETING ON AIDS AND FOSCARNET
PHOENIX, ARIZONA, DECEMBER 9, 1985

Participants: Donald Armstrong, New York, NY
Alvin E. Friedman-Kien, New York, NY
Michael S. Gottlieb, Los Angeles, CA
Evan M. Hersh, Houston, TX
H. Clifford Lane, Bethesda, MD
Paul Volberding, San Francisco, CA
Martin S. Hirsch, Boston, MA (prevented from attending
by an illness)

Stig Agurell, Astra Läkemedel, Sweden
Stefan Behrnetz, Astra Läkemedel, Sweden
Alf Larsson, Astra Läkemedel, Sweden
Bengt S. Nilsson, Astra Läkemedel, Sweden
Bo Öberg, Astra Läkemedel, Sweden

Tania A. Assaykeen, Astra Clinical Research Associates,
Hopkinton, MA

OBJECTIVES

The objectives of this meeting were:

- to discuss methodological issues in studies of antiviral agents in HTLV-III infected patients
- to discuss antiviral agents in general, and foscarnet in particular with regard to their usefulness in HTLV-III infected patients
- to discuss strategies for study programs in HTLV-III infections in the U.S.

METHODOLOGIC ISSUES

Patient selection

Patients included in studies should be early in their disease (corresponding to ARC or possibly early Kaposi's sarcoma patients), with essentially preserved immune functions. The patient group should be narrowly defined, and positive virus isolation mandatory. It is important to select patients who can be followed for prolonged periods. However, from an ethical point of view, it may be problematic to exclude patients with more advanced disease. On the other hand, including completely asymptomatic patients may also be problematic, due to potential drug toxicity.

Although in principle double-blind, placebo controlled studies are desirable, such studies may be problematic due to the seriousness of the disease, especially if i.v. treatment is involved. Open controlled studies may be a realistic alternative, as well as cross-over studies, where patients serve as their own controls.

Effective treatments against HTLV-III infections will in the end probably consist of combinations of several drugs. However, at the present stage it is preferable to include only patients who do not require any other drug treatment during a study.

Virus culture techniques

The available techniques have several drawbacks, being very laborious and time-consuming and lacking possibilities for quantitation of the amounts of virus. No satisfactory method for antigen detection and quantitation seems to exist for the moment, probably due to the lack of good monoclonal antibodies, and to the low amounts of circulating antigen. The use of in situ hybridization is also problematic, due to the low numbers of infected cells - probably as few as 1:100 000 T4 cells could be infected.

Thus, at present virus detection techniques are rather primitive, laborious and time-consuming and of uncertain precision. In addition, there probably exists a considerable inter- and intraindividual variation in virus excretion. Since virus detection techniques are crucial to any drug study program, these facts point to the need for a central reference laboratory in any study program.

Other technical factors were also discussed, e.g. possible influence of drug in test samples and contamination of cultures by non-HTLV-III enzymes.

Although investigation of blood lymphocytes is the basic technique, it is also important to study, if possible, the existence of free virus in the blood, and virus content in CSF and semen.

Immunologic variables

A relatively small number of variables can be used as key efficacy parameters, the most important being the number of T4 cells and delayed type skin reactivity to a standard battery of antigens. There is no evidence for booster effects of skin testing in this patient category, although this has not been systematically investigated.

Clinical symptoms

It is important to study the existence of a variety of symptoms (e.g. pyrexia, weight loss, G-I symptoms, KS lesions, opportunistic infections) but it is crucial to use standardized methods for assessing the frequency/severity of symptoms. CNS symptoms are very common, ranging from subtle disturbances in cognitive function to frank dementia. Special psychologic/psychiatric rating scales can be used to assess those symptoms. Such scales can not routinely be included in studies and may require special studies.

ANTIVIRAL AGENTS

Foscarnet

The participants of the meeting had received a package of information about foscarnet, which was supplemented by brief presentations at the meeting. The following facts were pointed out as important:

- foscarnet inhibits the HTLV-III RT, and HTLV-III multiplication in vitro
- the whole herpes virus group is sensitive to foscarnet
- lymphocytes from patients with LAS showed increased T-cell colony formation in vitro in presence of foscarnet, compared to control cultures without foscarnet
- based on in vitro data on the sensitivity of CMV, a plasma concentration of 150 µg/ml is being used for treating severe CMV infections with foscarnet. The available data suggest that HTLV-III may be more sensitive, but it seems reasonable to start a study program in HTLV-III infections at 150 µg/ml, and then work downwards
- drug penetration to the brain may be of great importance in treating HTLV-III infections. Preliminary data on foscarnet suggest that CSF levels of 20-40% of the plasma levels are obtained
- adverse reactions observed with foscarnet include thrombophlebitis, headache, lowered haemoglobin (without concomitant influence on WBC or platelets) and increased serum creatinine. The creatinine increases have mainly been moderate, but some cases of marked elevations have been seen. Available data suggest full reversibility of the changes.

One case of severe, reversible CNS symptoms in conjunction with extreme plasma levels has occurred

- determinations of plasma concentrations are useful, but not necessary for handling the treatment. At present, only the Astra labs in Sweden have the method in use, but efforts are ongoing to introduce the method in the U.S.
- oral uptake of foscarnet varies strongly between species (extremely low in the mouse, extremely high in the rabbit). A first bioavailability study in man will be performed Spring 1986 in Sweden.

Suramin

Most of the experience gathered suggests that when administered at dose levels inhibiting virus replication, suramin is associated with significant tolerance problems, e.g. fever, malaise, skin rashes, fatigue, renal and neurotoxic effects. Suramin seems unlikely to penetrate the blood-brain barrier.

HPA-23

An MCT study is ongoing in the U.S., no data are available at present.

3' - Azidothymidine

This is judged as one of the most promising drugs and several studies are ongoing. Preliminary results in man show an increase in the total T cell numbers and improvement in skin tests. It is conceivable that the drug may in part act as an immunomodulator.

MISCELLANEOUS

Studies of bone-marrow cells indicate that stem cells may not have receptors for HTLV-III.

By using in situ hybridization techniques it has been possible to detect integrated HTLV-III in the genome of T4 cells only.

The cellular location of the CNS infection is not known with certainty, although most data would suggest the glia cells as the best candidates.

Bone-marrow transplantation has as yet not been successful in restoring the immune function in AIDS. Possibly, this kind of manipulation under the cover of antiviral protection could be more successful.

Drug penetration into semen may be an important issue, which initially should be addressed in experimental animal studies.

STRATEGIES

Opinions at the meeting seemed to indicate that it would be possible to create cooperation between centres in a drug evaluation program.

Astra expressed the view that the optimum way of evaluating a drug would be to create a systematic research program, addressing a number of key issues. However, Astra is not in a position to take on organizational and financial responsibility for such a major program in the U.S. Astra has therefore been invited to the NIH/NCI Aids Drug Selection Committee to discuss a possible foscarnet program in the U.S.

An additional possibility is for Astra to apply for an orphan drug status for foscarnet.

COMPASSIONATE USE

Some companies have disapproved of compassionate use of the drugs in AIDS, for different reasons. In case of an NIH IND for foscarnet, this kind of questions may be handled by NIH, rather than by Astra. All the participants agreed that compassionate use should be avoided as much as possible.

January 21, 1986



BACKGROUND

September 19, 1986

Azidothymidine

Fourteen months after the National Cancer Institute began administering an experimental drug to 25 patients with AIDS and AIDS-related complex, 21 are still alive, Drs. Samuel Broder and Robert Yarchoan of the National Cancer Institute said. It now appears that the drug, called azidothymidine (also known as AZT, "Compound S", or 3'-azido-3'-deoxythymidine), may stabilize the disease in some of these patients.

Of the 10 AIDS patients who had Pneumocystis carinii pneumonia (an unusual form of pneumonia characteristic of AIDS patients), 9 are still alive. The expected median survival of AIDS patients who have had Pneumocystis carinii pneumonia is 35 weeks.

Several of the AIDS patients treated during the NCI Phase I trial had neurological symptoms induced by the AIDS virus. These symptoms improved in certain cases, suggesting that AZT may partially reverse the neurological symptoms associated with AIDS under some circumstances.

AZT is a member of a broad spectrum of antiviral drugs called nucleoside analogs. It was first synthesized by Jerome P. Horwitz of the Detroit Institute of Cancer Research in 1964. NCI scientists were the first to show that the compound had antiviral activity against the AIDS virus in the test tube and the first to use it for the treatment of AIDS.

The experimental drug is manufactured by the Burroughs Wellcome Company of Research Triangle Park, North Carolina, which referred the drug to NCI for

human testing after the company found that it had activity against mouse retroviruses.

Last March, NCI and collaborating scientists reported in Lancet (March 15, 1986 issue) that AZT, when tested on the first 19 patients in the study, brought about increases over the short term in the number and function of T cells. T cells, an important arm of the immune system are characteristically depleted in AIDS patients. They also reported that at moderate doses (250 mg, every 4 hours for 2-6 months) AZT prevented the AIDS virus from multiplying. The report was presented by scientists from the NCI, Duke University Medical Center, and the Burroughs Wellcome Research Laboratories. Based on the encouraging results of this study, a Phase II study to compare patients treated with AZT with untreated patients was started in February 1986 at multiple centers.

AZT is a derivative of thymidine, one of the normal components of DNA (the molecule of life), which is needed by the host cell and the virus to make chemicals necessary for replication. When AZT enters a cell infected by HTLV-III (the virus that causes AIDS), the drug floods the cell with false DNA building blocks so the virus cannot make copies of itself. Once this happens, viral infection and replication is halted, thereby protecting target cells.

At the time of the initial AZT report in Lancet on the first 19 patients, Dr. Yarchoan said, "The most significant aspect about this study is that it shows that the immune system of an AIDS patient can at least partially reconstitute itself if the patients are given a drug that blocks the replication of the virus." He cautioned, however, "...that although patients receiving AZT showed some improvements, they still have AIDS. We do not know if the drug will be useful for patients in the long run. We have no evidence that AZT is a cure for AIDS." Dr. Broder added that the ability to give this drug over a

long period of time will depend on an understanding of how the drug is metabolized within cells and how it disturbs normal cell metabolic pathways.

Fifteen of the original 19 patients had increases in the number of their circulating helper-inducer T cells. Skin test reactivity to antigens was also restored in six of the patients, suggesting that the T cells were working better. It is not known how long lasting these changes will be. In some patients, fevers decreased or ceased, fungal infections of the nail bed cleared up without antifungal therapy, and patients experienced improved appetite and weight gain, the doctors said.

In addition, the drug effectively crossed the brain-blood barrier. This may be a crucial step in preventing encephalopathy, a brain disorder caused by HTLV-III in AIDS patients that results in irreversible brain damage, they said.

Furthermore, the drug can be prescribed orally.

In terms of toxicities, 9 of the 19 patients complained of slight headaches, one of mild stomach discomfort, and several patients at higher dosages had bone marrow toxicities, Dr. Broder said. At high doses, it is likely that bone marrow suppression will be a limiting factor for the drug.

Scientists began treating the 19 AIDS patients in July 1985. Eleven of the patients were treated at NIH, while the remaining eight were treated at the Duke University Medical Center. The study was a collaborative effort between NCI, Duke University Medical Center, and Burroughs Wellcome Research Laboratories. Investigators at the University of Miami also played a role.

In February 1985, AZT was shown to have activity against HTLV-III in laboratory studies by NCI scientists Drs. Hiroaki Mitsuya and Broder. Prior to that, AZT was found to have activity in an important animal virus screening program by Burroughs Wellcome Research Laboratories.

AIDS is caused by a retrovirus named HTLV-III, proven by Dr. Robert C. Gallo and his co-workers at NCI to be the cause of the disease.

Retroviruses, including HTLV-III, require an enzyme, reverse transcriptase (or RNA-dependent DNA polymerase), which enables genetic information to insert itself into the genetic information of the cell it infects.

In October 1985, Drs. Mitsuya and Broder, in collaboration with scientists at Burroughs Wellcome Research Laboratories, published laboratory findings showing that AZT inhibits the replication of HTLV-III, most likely by interfering with reverse transcriptase (Proceedings of the National Academy of Sciences, October 1985). In other laboratory studies at NCI, AZT reduced the ability of several animal viruses to replicate in vitro and in vivo.

To date, AZT does not appear to have antiviral activity against most viruses other than retroviruses, although the compound has shown antibacterial activity against certain gram negative bacteria.

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For more information, contact the AZT Information Line at 1-800-843-9388 or write the AZT Treatment IND Coordinating Center at Box 6042, Rockville, MD 20850.

HUMAN SUBJECT PROTECTION COMMITTEE

Approval Notice

HSPC # 85-09-377

PRINCIPAL INVESTIGATOR OF MAIN GRANT _____

TITLE OF MAIN GRANT _____

DEPARTMENT _____ DIVISION _____

PRINCIPAL INVESTIGATOR OF PROJECT Michael S. Gottlieb, M.D.TITLE OF PROJECT A Protocol for the Treatment of AIDS Patients Who Are Infected with HTLV-III
with 3'-Azido-3' -Deoxythymidine (BW A509U)DEPARTMENT Medicine DIVISION Clinical Immunology/AllergyFUNDING AGENCY None CONTRACT OR GRANT NO. _____DATES FOR WHICH REVIEWED: FROM October 3, 1985 TO October 2, 1986DATE FOR RE-SUBMISSION August 2, 1986 DATE APPROVED October 3, 1985

The Human Subject Protection Committee has reviewed the proposed use of human subjects in the project identified above and has determined that:

The rights and welfare of the subjects are adequately protected; the risks are outweighed by potential benefits; the informed consent of subjects will be obtained by methods that are adequate and appropriate.

(WRITTEN X ; ORAL _____ ; WAIVED _____.)

Research involves use of: Minors _____ Fetuses _____ Abortuses _____ Prisoners _____

Pregnant Women _____ Mentally Retarded _____ Mentally Disabled _____

The Committee has recommended and/or determined that significant changes have been made in the approved project over that submitted to the granting agency: yes ☐ no ☐. If "yes", it is the principal investigator's responsibility to forward the revised material to the granting agency through the Office of Contract and Grant Administration.

CODICIL:

Signature: Dorothy Rosenthal
Chairman, Human Subject Protection Committee

- ☐ Human subjects will be at risk
☐ Human subjects will not be at risk

Original to: Principal Investigator

cc to: Director, Office of Contract and Grant Administration

See reverse