
How Does Project Inform Communicate Its Message?

We distribute information to patients and physicians through (1) a national toll-free hotline and mailing service, (2) regularly scheduled town meetings in San Francisco, and (3) involvement in the public media (the Donahue Show, 20/20, network and local news programs, local and national print media).

Your Help Can Make a Difference

Volunteer time or provide services or equipment. We need:

- ☐ Hotline operators
- ☐ Clerical assistance
- ☐ Research assistance
- ☐ Copy writing
- ☐ Statistical experience
- ☐ Dbase III data input
- ☐ Microsoft Word experience
- ☐ Fund raising skills

- ☐ IBM compatible computers

Make a contribution, bequest, or give a gift in someone's name. All donations are tax deductible.

Or use the service for yourself or a friend.

Contact Project Inform:

By mail:

PROJECT INFORM
25 Taylor Street, Suite 618
San Francisco, CA 94102

By phone:

National 1-800-822-7422
California 1-800-334-7422
Local 415-928-0293

What is Project Inform?

Project Inform is a non-profit foundation formed to meet a need for expanded AIDS/ARC treatment information. The Project was founded in San Francisco in 1985 as a service to the local community. In subsequent years, media attention and escalating demand have caused us to extend our services to meet the needs of patients and physicians across the nation.

Project Inform

What Does Project Inform Do?

Project Inform's evolving mission is threefold:

- to inform people at risk of HIV infection of reasonable strategies for early diagnosis and treatment
- to give patients and physicians the means to make informed choices about an expanded range of treatment options, including promising treatments which may be overlooked or stalled in the federal licensing process
- to help those in need gain access to the treatments they chose without being victimized by unscrupulous profiteers or the endless delays of bureaucracy.

Why is All This Necessary?

Our role is made necessary by the rapid pace of the epidemic, which makes it impossible for most patients or physicians to be current on all treatment options. Since few treatments are recognized by the FDA, the physician's normal sources of information are restricted from providing data. Federal approval may be years away for most treatments. We believe that, in the meantime, patients faced with grave choices have an absolute right to any information which has a reasonable hope of helping them.

At the same time, our community needs to be protected from potential harm in the promotion of ineffective or harmful treatments. The desperation inherent in the AIDS market presents opportunities for profiteering and fraud.

How Does Project Inform Fulfill Its Mission?

Project Inform collects and assesses research on promising treatments. We distribute information only on treatments which meet our criteria of (1) established safety, (2) a reasonable expectation of efficacy, and (3) general availability. The information provided summarizes current research findings, reports by users, known side effects, overall risks and benefits, and how to purchase and correctly use the treatments. In addition, we conduct periodic user surveys to build a base of practical knowledge about the effectiveness and safety of treatment options. We report results back to our constituents and the community at large.

To insure accuracy, we follow current journal articles and medical conferences. Whenever possible, we discuss clinical findings with primary sources—the investigators who conduct the research. Similarly, we maintain contact with private physicians, major urban treatment centers, and representatives of regulatory agencies. While the medical establishment doesn't always concur with our conclusions, we invite its input into our decision-making process. We urge patients to enter into a healing partnership with their physicians which explores all reasonable options.

JUL 27 1987

PROJECT INFORM
25 TAYLOR ST. #618
SAN FRANCISCO, CA. 94102

TREATMENT OF ARC PATIENTS WITH DTC (IMUTHIOL®) A MULTICENTRIC, RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED TRIAL

Members of the AIDS-IMUTHIOL FRENCH STUDY GROUP.

Center n° 1.

Hôpital Hautepierre, Strasbourg.

J.-M. Lang,
A. Falkenrodt.

Center n° 2.

Hôpital E. Meriot, Lyon.

J.-L. Touraine,
J.-M. Livrozet, M.-P. Richard,
F. Touraine.

Center n° 3.

Hôpital Bretonneau, Tours.

P. Choutet,
L. Hervieu, F. Barin,
A. Goudeau, M. Renoux,
P. Bardot, G. Renoux.

Center n° 4.

Hôpital St-Vincent-de-Paul, Paris.

M. Kirstetter, A. Pompidou,
M.-C. Delsaux, L. Telvi,
C. Platel.

Center n° 5.

Hôpital des Charpennes, Lyon.

C. Trepo,
C. Retamez, J.-P. Heyraud.

Trial coordination.

Institut Mérieux, Lyon.

J. Caroux*, M. Musset,
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Département Immunologie, Institut Mérieux, B.P. 7046, 69348 Lyon Cedex 07, FRANCE.

In the U.S.A. : enquiries : A. Lamotte, P. Cohen, Mérieux Inc., 7855 N.W. 12th Street, Suite 114, Miami, FLORIDA 33126.

INTRODUCTION

Rationale for clinical trials in ARC patients :

1) Immunopharmacological effects of DTC :

DTC (Diethylthiocarbamate, Imuthiol®, Mr = 171.27)

- is a thymomimetic drug^{1,2}, inducing T cell maturation and enhancing T cell functions,
- is not mitogenic for T cells and thereby would not offer new targets to be damaged by HIV,
- restores T cell functions and delayed type cutaneous hypersensitivity in immunodeficient hosts at a dosage of 5-20 mg once a week.

2) In vitro antiviral activity of DTC :

- DTC has been reported to partially inhibit reverse transcriptase activity and expression of p15 and p25 induced by HIV infection *in vitro*³,
 - DTC is a metal chelator, which are known to exhibit general antiviral activity⁴.
- 3) Furthermore :
- DTC can be administered orally,
 - DTC has no side effects except for antabuse-like activity.

METHODS

PATIENT POPULATION (n = 90).

ARC with > 2 symptoms, or LAS.

Sex : 12 ♀ 68 ♂

Age : 21-54 (mean value : 32).

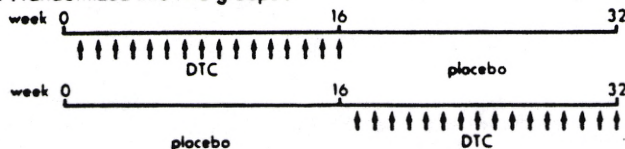
TREATMENT.

Method : randomized, double blind, placebo controlled.

Dosage : DTC 10 mg/kg once a week, or placebo.

Route : oral (125 mg DTC capsules).

Scheme : randomized into two groups :



CLINICAL AND BIOLOGICAL EVALUATION.

Every two months : clinical status, ARC symptoms, tolerance, immunology, hematology.

EVALUABLE PATIENTS (Study not totally completed).

Weeks	0-16	16-32
Evaluable patients	80	72

STATISTICAL ANALYSIS.

Covariance analysis was used for quantitative variables, Fisher's exact test was used for qualitative variables.

RESULTS

I. DTC vs Placebo (4 months treatment).

● Decrease in ARC symptoms ($p = 0.01$).

Number of ARC symptoms	Before treatment	After 4 months
DTC (n = 40)	2.5	1.7
Placebo (n = 40)	2.3	2.1

● Improvement in overall clinical status* ($p = 0.0001$).

	Improved	Stable	Worse
DTC (n = 39)	18	20	1
Placebo (n = 40)	2	35	3

* Appreciated from combined evaluation of ARC symptoms, incidence of intercurrent infections, KS, and CNS neuropathy.

● Lower incidence of serious events : ($p = 0.01$).

Event	DTC (n = 40)	Placebo (n = 40)
O.I. (definition of AIDS)	0	3
Kaposi	0	1
Lymphoma	0	0
Neuropathy	0	0
Death	0	1
Total	0	5*

(3 OI in 2 different patients).

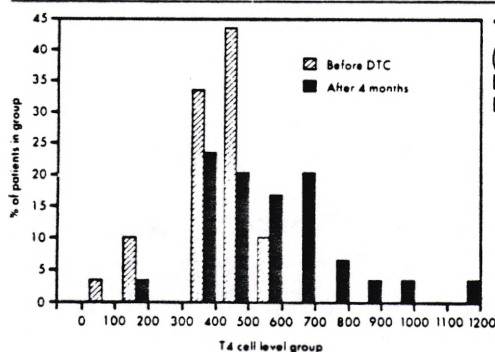
* 3 patients.

● Disappearance of splenomegaly ($p = 0.02$).

	Number of patients with splenomegaly	
	Before treatment	After 4 months
DTC (n = 39)	5	2 (3 disappeared)
Placebo (n = 39)	8	10 (none disappeared) (two appeared)

● Recruitment of T4 lymphocytes ($p = 0.032$).

	DTC	Placebo
mean values at entry	393 $\pm$ 129 (/mm ³)	398 $\pm$ 137
mean increase after 4 months	+ 169 $\pm$ 269	+ 38 $\pm$ 181
number of patients with increase greater than + 300	7	1



● Other.

- Decrease in lymph node involvement ($p = 0.026$) not associated with disease progression.
- No major changes in serum immunoglobulin levels.

CONCLUSIONS

- When compared to placebo, DTC treatment of ARC patients over a 4 months period induced :
 - clinical improvement,
 - recruitment of additional T4 cells,
 - a trend towards decreased progression to AIDS.
- On account of clinical benefits observed, patients participating in this 8 months study are still treated with DTC (open treatment).
- No unanticipated nor serious adverse effects were seen.
- After discontinuation of DTC treatment (double blind, 4 months follow up with placebo) clinical benefit induced by DTC was progressively lost. T4 cell numbers, after rising under DTC, had a tendency to return to pre-treatment values.

REFERENCES.

- Renoux G. and Renoux M. Thymus-like activities of sulphur derivatives on T cell differentiation. *J. Exp. Med.* 145:466, 1977.
- Renoux G., Renoux M., Guillaumin J. and Gouzien C. Differentiation and regulation of lymphocyte populations: evidence for a role of thymus-like activities.

- Pompidou A., Zagury D., Gallo R.C. et al. In vitro inhibition of LAV/HTLV-III infected lymphocytes by dithiocarbamate and inosine pranobex. *Lancet* ii:1425, 1985.
- D.W. Hutchinson.

- Brock N., Milgord P., Pohl, Ormstad K. and Orrenius S. Pharmacokinetics and mechanism of action of detoxifying low molecular weights thiol. *J. Cancer Res. Clin. Oncol.* 108 87, 1984

● Tolerance.

- No hematologic toxicity.

	DTC		Placebo	
	before	after 4 months	before	after 4 months
erythrocytes	4.97	5.00	4.68	4.58 ($\times 10^6/\text{mm}^3$)
leucocytes	5.22	5.35	4.90	4.27 ($\times 10^3/\text{mm}^3$)
platelets	201	185	202	190 ($\times 10^3/\text{mm}^3$)

At 4 months : in all patients, erythrocytes were $> 3 \times 10^6/\text{mm}^3$, leucocytes $> 2000/\text{mm}^3$, platelets $> 80 \times 10^3/\text{mm}^3$.

- Side effects.

Complaint	DTC (n = 38)	Placebo (n = 37)
stomach pain	8	4
nausea	8	2
metallic taste	7	2
malaise	3	3

(No treatment interruptions due to side effects.)

II. DTC (4 months) followed by Placebo (4 months). Effect of treatment interruption.

Loss of clinical benefit seen during DTC treatment with :

- increase in ARC symptoms (after decrease under DTC therapy),
- decline in overall clinical status* (after improvement under DTC therapy),

months	treatment	improved	stable	worse
0 - 4	DTC (n = 39)	18	20	1
4 - 8	Placebo (n = 29)	2	17	10**

followed by :

* Appreciated from combined evaluation of ARC symptoms, incidence of intercurrent infections, KS, and CNS neuropathy.

** Loss of clinical benefit seen during 0 - 4 month period with DTC.

- loss of beneficial effects on splenomegaly : 3 out of 5 had disappeared under DTC therapy, 3 additional ones appeared when placebo replaced DTC. Furthermore, in the group which had initially received placebo (no disappearance, 2 additional splenomegalies), 4 out of 10 splenomegalies disappeared when placebo was replaced by DTC.
- decrease in T4 cells (after increase under DTC therapy). T4 cell numbers had increased by + 169 after 4 months DTC therapy. When DTC was replaced by placebo, mean T4 cell decrease observed was - 118 (+ 216) after 4 months placebo.

III. Long term follow up (> 2 years) (open study).

- 4 ARC patients evaluable : 3 years (3 patients) or 2 years (1 patient) :
 - fatigue and general symptoms vanished within six months, together with 50% reduction in the size of lymphadenopathies,
 - 3 patients tested for DCH were anergic before treatment : after 2-3 years, DCH scores were normal.
 - T4 cell numbers increased clearly in all patients.

patient n°	age	DO	T4 cell number/mm ³			
			6 months	1 year	2 years	3 years
1	55	141	429	468	335	308
2	26	102	672	684	417	471
3	25	416	1047	815	558	566
4	21	471	388	531	788	-

- No biological toxicity was noted.

Although these results are encouraging, we are aware that the size of the population studied and length of double-blind evaluation are not sufficient to conclude that DTC treatment does effectively reduce progression from ARC to AIDS. Ongoing studies are designed to address this critical issue.

● Perspectives :

- Present trials in the U.S.A., France and Germany (FRG) address the following :
 - effect of DTC treatment on progression from ARC to AIDS (longer treatment, larger patient population),
 - effect of DTC treatment on patient survival in AIDS,
 - optimisation of DTC dosage,
 - combination of DTC treatment with antiviral drugs.

PROJECT INFORM

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13 January 1987

FOR IMMEDIATE RELEASE

Contact: Tom Jefferson
(415)928-0293

PROJECT INFORM WILL HOLD PUBLIC MEETING

PROJECT INFORM announced that it will host another in its series of public forums at the Metropolitan Community Church, 150 Eureka Street, San Francisco on Monday, January 26th from 7:30 p.m. to 9:00 p.m.

Martin Delaney and Joseph Brewer, founders of PROJECT INFORM, will present an update of the latest information about Ribavirin, one of the leading anti-viral drugs used in treatment of AIDS/ARC, as well as Isoprinosine, Naltrexone, DNCB & D-Penicillamine (all immunebooster drugs under clinical trials at this time and available to the public).

Ribavirin has been the focus of recent news on the AIDS treatment front with announcement of portions of the FDA approved clinical trials being made public early in January. More data is expected to be released before the public forum.

Participants in the PROJECT INFORM research survey study on Ribavirin and/or Isoprinosine are urged to bring their completed forms to the meeting if they have not already returned those forms to PROJECT INFORM offices.

The public forum will be held:

Monday, January 26th at 7:30 p.m.
METROPOLITAN COMMUNITY CHURCH
150 Eureka Street
San Francisco

Bay Area PI List
Bay Area AIDS INFO

PROJECT INFORM

25 Taylor St. Suite 618
San Francisco, CA. 94102

National: 1-800-822-7422
California: 1-800-334-7422
Local: 415-928-0293

20 June 1987

FOR IMMEDIATE RELEASE

Contact: Tom Jefferson
(415)928-2237

PROJECT INFORM TOWN MEETING #8

PROJECT INFORM announced that it will hold another in its series of Town Meetings at the Metropolitan Community Church, 150 Eureka Street, San Francisco on Tuesday, July 14th starting at 7:30 p.m.

The public forum topic will be "HIV SEROPOSITIVITY - HOW EARLY SHOULD EARLY TREATMENT BEGIN?"

Dr. Paul O'Malley will explain the new statistics on conversion to AIDS/ARC - the bad news recently published at the International Conference on AIDS in Washington, D.C.

Joesph Brewer and Martin Delaney, of PROJECT INFORM, will discuss HIV medications and current treatment strategy for seropositive people and early ARC.

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Bay Area PI Press Lit
Bay Area AIDS INFO

PROJECT INFORM

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21 July 1987

FOR IMMEDIATE RELEASE

Contact: Tom Jefferson
(415)928-0293

PROJECT INFORM announced the receipt of a grant from the Design and Interior Furnishings Foundation for AIDS (DIFFA). The grant, totaling \$8,000.00 is supported by both the Northern California Chapter in San Francisco (\$3,000) and the national office in New York City (\$5,000).

The grant will support the operation of the PROJECT INFORM toll-free HOTLINES, which provide information on available experimental treatments for AIDS, ARC and HIV seropositivity.

"The DIFFA grant makes it possible for us to continue to provide this much needed service," stated PROJECT INFORM leaders Joe Brewer and Martin Delaney. "Since our work was recognized on such programs as ABC's 20/20, DONAHUE, & NIGHTLINE and in magazines such as NEWSWEEK, TIME, AMERICAN HEALTH MAGAZINE, our small staff has been overwhelmed.

- more -

The DIFFA grants were facilitated by Andrew Belschner, Funding Committee Chairman of the Northern California Chapter in San Francisco and Russ Radley, National Executive Director New York. Well-known New York activist and GMHC founder Larry Kramer also urged DIFFA's support for PROJECT INFORM. DIFFA has previously provided funds to help feed people with AIDS, for psychological support services and for emergency funds. 85% of moneys raised locally by DIFFA stays in the local community.

This generous funding by DIFFA is most timely and will directly benefit the community. As the AIDS crisis becomes ever more demanding, the work of PROJECT INFORM has been strained to it's limits. The toll-free HOTLINES have been averaging 4,000 to 5,000 calls per months from AIDS affected individuals, health care professionals and other AIDS service organizations. Over 1,500 information packets are mailed each month. PROJECT INFORM'S long held contention that "early intervention" can slow progression of the disease is now receiving wide support in the medical community. "Unfortunately, only one treatment (Retrovir-AZT) has been approved for limited distribution, and it is not well suited for everyone. Other safe treatments are available; those in need have a right to know all their options and to be protected from possible exploitation," stressed Brewer and Delaney.

Members of the local DIFFA chapter have also been assisting PROJECT INFORM obtain a new telephone system that will alleviate overloading of the HOTLINES. That donation from a private communications company is scheduled for installation shortly.

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Daring To Stay Alive

Project Inform Offers Hope in HIV Infection

by Paul Reed

P A R T I : T A K E T H E T E S T

Editor's Note: This is the first of a two-part feature covering the activities and message of Project Inform, the San Francisco-based organization which functions as an information clearinghouse on AIDS testing and treatment.

Amidst the widespread debate about the use of AIDS antibody testing, one national organization is articulating both the value and necessity of voluntary, anonymous testing as a frontline approach to fighting the disease. Project Inform, based in San Francisco, argues strongly that the medical realities of AIDS necessitate a medical response. The key bit of knowledge is one's antibody status as infected or not infected by the AIDS virus.

In recent months, Project Inform has been holding "town meetings" about AIDS treatment. The events have drawn standing-room-only crowds and influenced many people to discover not only their antibody status but to take immediate action to begin treatment against HIV infection.

"The popular idea that the AIDS antibody test doesn't tell you anything—and that there's nothing you can do about it anyway—is quite simply wrong," says Joe Brewer, a gay San Francisco psychotherapist and co-director of Project Inform. "A positive antibody test can be seen as a diagnosis of a major infection by a life-threatening agent."

This message is one that is just now coming of age throughout the nation, in large part because of Project Inform's national reach. Project Inform is the only AIDS organization that is vocal about the necessity for voluntary testing. Other established AIDS-service organizations focus on patient services and education, whereas Project Inform is focused on treatment research—providing necessary information about available treatment options—and on urging immune status monitoring.

Their's has been a controversial position, because political and psychological problems have clouded the issue of testing. But that is beginning to change, as

more and more people realize that they want to take immediate steps to avoid illness in the future by taking advantage of the treatment options that are now available (to be covered next week, in Part II of this series).

SILENT INFECTION

"Arguments against testing are either political or psychological responses to a medical problem," says Project Inform in their recent newsletter, *PI Perspective*. "These should be answered in the political and psychological realms. What's too often overlooked is the need to make a medical response to the medical problem. How many more must die or cross the line to full-blown AIDS while we argue about the politics and stress of testing?"

Project Inform directors Brewer and Martin Delaney stress that recent epidemiologic data clearly show that if left untreated, "silent" (asymptomatic) HIV infection leads to AIDS or ARC symptoms for nearly 80 percent of those infected after seven years.

There is growing evidence, then, that there is very little possibility of dormant HIV infection and that the length of time an individual has been infected is critical. This past summer, the

San Francisco Men's Hepatitis Study released the results of a years-long study of infected individuals which showed that by the seventh year after infection, 78 percent of those individuals with HIV develop symptoms of AIDS or ARC.

While many people have tried to argue with the data from every possible angle—pointing to lifestyle, fast-lane living, and so on as possible co-factors—the fact remains that all these other variables were "factored out" of the study. Yet the rate of progression toward illness remained uniform.

"The number who became ill in the first five years of infection increases slowly, but after that, the rate rises rapidly," says Project Inform in its newsletter. "The study shows that this alarming rate of disease is equally true for people classified as being in the 'fast lane' or the 'slow lane.'"

Project Inform points out this study has been presented at two international conferences, has been subjected to extensive peer review, and has been corroborated by other studies. "These are the best facts available to a gay man today on which to base his health choices," Delaney states. "To ignore this is to deny it—burying your head in the sand."

Brewer points out that although this data has been known for several months, massive denial has prevented individuals from fully realizing the implications of this data for themselves and for their potential conditions. "The reasons for getting yourself tested are now very clear—you have to know to begin to protect yourself."

For this reason, Project Inform has become emphatic in its position on the absolute necessity for voluntary antibody testing, and the sooner the better. They stress that the widespread availability of several anti-HIV treatments has rendered the argument in favor of "not knowing" as dangerously out of date.

"In light of the recent data, the AIDS antibody test now does have a prognostic value," states Brewer. "As infection continues, you progress generally towards illness."

TIME ONLY VARIABLE

"The only real variable here is time," explains Delaney. "This study let us know what happens over a long period of time. Regarding possible co-factors, sex practices, prior health—the study found no correspondence between these and the progression towards illness. Time is the only variable."

Both Brewer and Delaney point out that this study shows what *has* happened, but it need not be necessarily predictive. "People react as if the only possible responses to this alarming data are denial or despair," Brewer says, "but this study is based only on people who got no medical intervention or treatment therapy—not from their doctors, and not self-treatment. The recent availability of several substances to treat HIV infection may have an immediate and beneficial effect on that soaring rate of progression into AIDS or ARC."

What, then can an individual do?

"There are things you can do to fight infection by the AIDS virus," explains Delaney, "but before you start treatment, of course you have to know where you stand. Are you infected? If so, in what condition is your immune system?"

Project Inform suggests that individuals find out exactly where they stand in relation to this infection. "First, find out where you stand right now," advises Brewer. "The antibody test gives you and your doctor critical medical information."

"Testing opens the doors," says Delaney. "Without testing, you can't know whether or not to start the process of evaluating your immune system and choosing a treatment."

Both Brewer and Delaney are well aware of the great resistance that individuals have to taking the AIDS antibody test. But both agree that ambivalence and resistance to testing are results of fear brought about by political and psychological problems.

MEDICAL VALUE OF TEST

Delaney stresses that although the political and psychological problems surrounding testing are serious issues, they should be addressed in their own ways. "Never let a psychological barrier prevent you from doing what's necessary for your health—nor a political barrier. The political and psychological concerns are very real, but not insurmountable, AIDS is."

Brewer points out that "if you have the virus in your body, there's going to be one terrible experience sometime in your life—either being told you're antibody positive, when you can still do something about it, or when you're diagnosed with an opportunistic infection, when it may be too late to do something about it."

Project Inform advises that individuals get tested voluntarily and confidentially. Says Delaney of the political resistance to testing, "The gay community has endangered itself more by overlooking the medical value of the test. Voluntary testing obviates the need for involuntary testing. Refusal to test feeds the notion that the community is irresponsibly spreading AIDS. The way the laws are going, we ought to do it now before we can't be tested confidentially or voluntarily."

Brewer cautions, however, of the psychological resistance to testing, advising that individuals be prepared for their test results. "Do be careful about to whom you release the results of your test," he warns. "And do be prepared for the psychological impact."

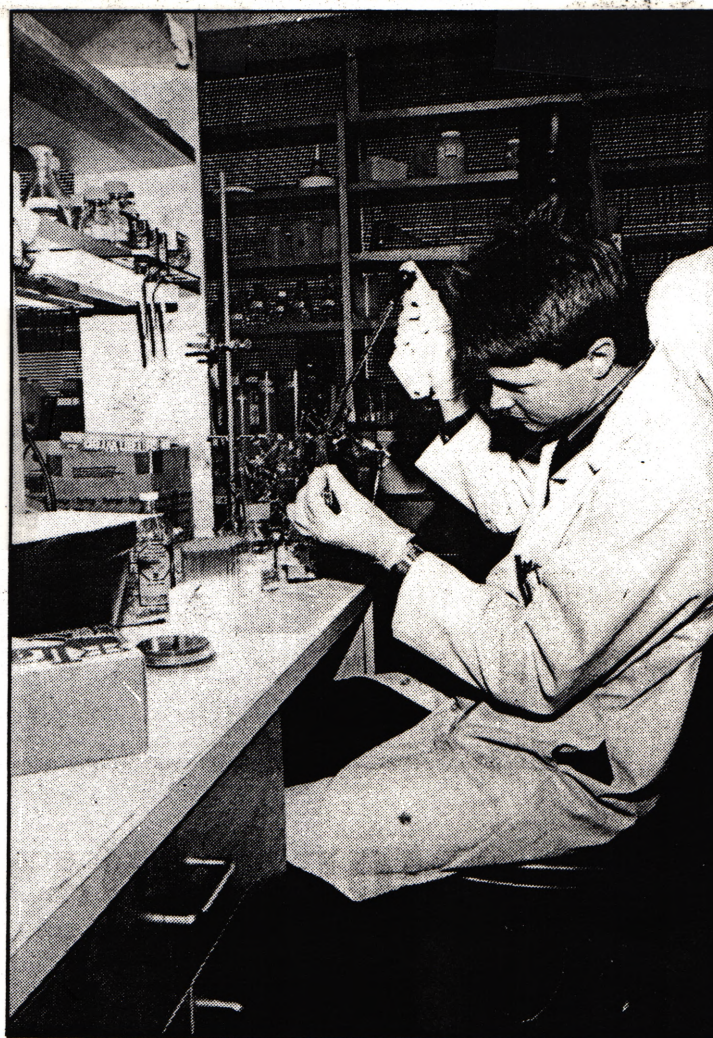
For individuals who test negative, the relief from worry will provide great energy—energy that is often directed towards helping the community in its struggle.

For those who test positive, they will have to face just what that means. According to Project Inform, a positive antibody test means that it is time to take immediate action to fight the disease process in one's body. In addition to learning whether or not one is infected, then, Project Inform counsels that the clinical laboratory test for T4 helper cells is essential in determining one's health status.

"The best measure of the disorder of the immune system is the T-cell count," counsels Brewer. "There is a demonstrated correlation between decline in T4-helper cells and development of symptoms. As the T4-cells decline, your ability to fight off disease diminishes and symptoms may begin to appear."

Once an individual has learned the condition of his immune system, he faces the critical decisions about what form of treatment to adopt. There are many available treatments, and sorting one's way through both the meaning of one's T-cell count and treatment options is a decision process that Project Inform is ready to help with. ●

Next week: Project Inform's views on how to interpret the T-cell count, the available treatment options, and how to choose.



It pays to stay informed about AIDS

(Photo: Photo Graphics/Darlene)

MORE INFORMATION

Project Inform is an organization that provides information about treatment approaches for AIDS, ARC, and HIV infection. Information packets are available for the asking. You can reach Project Inform by phoning: (415) 928-0293 (local); California toll free (800) 334-7422; and national toll free (800) 822-7422. Or write: 25 Taylor St., Suite 618, San Francisco, CA 94102.

The project functions on volunteer energy (neither of the two directors—Joe Brewer or Martin Delaney—draw salaries). The information hotline also needs daytime volunteers. ●

PROJECT INFORM

AIDS Update

25 Taylor St. Suite 618
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3 August 1987

FOR IMMEDIATE RELEASE

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FDA TELLS PROJECT INFORM RIBAVIRIN AND OTHER AIDS DRUGS "NOT DEAD IN WATER"

Martin Delaney, Co-Founder of PROJECT INFORM (a San Francisco based AIDS drug information organization) met in an unprecedented gathering of Food & Drug Administration and National Institute of Health officials in Washington, D.C. last week. While in Washington, Delaney also debated FDA Commissioner Frank Young on the ABC NIGHTLINE program.

The conference had been requested by PROJECT INFORM months before and Commissioner Young extended the opportunity to include other FDA and NIH officials. The three (3) hour meeting covered these major concerns: (1) the controversial handling by FDA/NIH of testing and licensing reviews of the drug ribavirin, (2) community perceptions of unfairness in the government's response to non-government sponsored AIDS treatment drugs, and (3) the lack of coordination in the federal government's approach to AIDS treatment efforts.

Delaney described the meeting as "extremely candid and productive."

-more-

FDA TELLS PROJECT INFORM RIBAVIRIN AND OTHER AIDS DRUGS "NOT DEAD IN WATER"

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FDA officials clarified important issues that have been distorted in press coverage of the ribavirin controversy. "The inside story, as presented by FDA," Delaney said, "isn't as negative or hopeless as presented in the press or among some AIDS researchers who had only second-hand knowledge of the reviewed data. I am disturbed that highly regarded professionals who conducted the clinical trials have been maligned and unfairly accused by people who did not have the facts."

The FDA remained very interested in the on-going & future ribavirin trials and assured PROJECT INFORM that the drug was by no means "dead in the water." FDA welcomed community research and case reports from private physicians. Delaney urged officials to look at the drug's efficacy on scientific basis only - not on suspicions about the manufacturer or past difficulties with ICN Pharmaceuticals, Inc.

Delaney said he felt Commissioner Young was coming to understand the AIDS community's complaints about lack of coordination on the federal level. Dr. Young pledged to seek a solution, saying he felt FDA could assist inexperienced companies to quickly steer their submissions through the approval process.

-more-

FDA TELLS PROJECT INFORM RIBAVIRIN AND OTHERS AIDS DRUGS "NOT DEAD IN WATER"

Page 3 - 3 Aug 1986

"It is easy to make promises - we will give them every opportunity to straighten out the mess in Washington - but I'll hold my applause until I see results," Delaney asserted. One encouraging sign came when I suggested that the Presidential AIDS Commission should have been designed to solve these problems, and the groans from those assembled indicated that many shared our concerns over that ill-conceived commission," he concluded.

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Editor's note: specific comments on the ribavirin discussion are available by calling PROJECT INFORM.

PROJECT INFORM ANNOUNCES THREE PUBLIC FORUMS

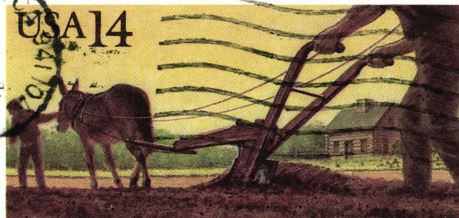
WEDNESDAYS, FEBRUARY 10TH & MARCH 9TH
(For those who have never before attended)

AND

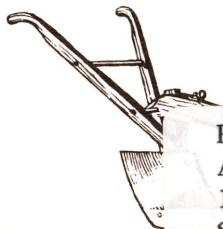
MONDAY, FEBRUARY 29TH
(Focus: To Be Announced)

ALL THREE: 7:30 P.M.
150 EUREKA STREET, SAN FRANCISCO
METROPOLITAN COMMUNITY CHURCH

PROJECT INFORM
25 TAYLOR ST. #618
SAN FRANCISCO, CA. 94102



Self-scouring steel plow, 1837



Pat Franks
AIDS Resource Program, U.C.S.F.
1326 Thrid Ave.
San Francisco CA 94143-0936

11 September 1987

Dear PROJECT INFORM Correspondent:

PROJECT INFORM PUBLIC FORUM #9

MONDAY, SEPTEMBER 28th at 7:30 P.M.

150 EUREKA STREET, SAN FRANCISCO
METROPOLITAN COMMUNITY CHURCH

PROJECT INFORM
25 TAYLOR ST. #618
SAN FRANCISCO, CA. 94102



National Guard Heritage, 1636-1986

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FOR IMMEDIATE RELEASE

Contact: PI Hotline

DATE: October 1, 1987

PROJECT INFORM RELEASES THE REPORT OF ITS SURVEY OF AIDS/ARC PATIENTS SELF-MEDICATING TREATMENTS IMPORTED FROM MEXICO.

Project Inform has released its report on people purchasing and using Ribavirin and Isoprinosine, a popular combination therapy that has been in use since 1984. Project leaders Joe Brewer and Martin Delaney cautioned the public to recognize the limited conclusions which can be drawn from this type of survey. "Since this type of survey does not meet standard research assumptions of random selection, random grouping of participants, and homogeneity of the sample group, it is incorrect to generalize from the data presented," Brewer said. Delaney added "It's best to think of this report solely as a description of the experiences of the people who participated, not as a general statement about the safety or effectiveness of these drugs." After expressing these cautions, they went on to say they believed the survey was important because it is the only information available regarding patients' treatment experience with the combined use of self-obtained Ribavirin and Isoprinosine and may provide useful input for future research.

The survey followed a total of 119 men, using the combination of the two drugs or using Ribavirin alone. Participants included a wide mix of people with full-blown AIDS, ARC, LAS, and others without symptoms who had tested positive to HIV. Use of the drugs was divided between those who used them on an every-day basis and others who followed an intermittent or "pulse dosing" approach. Dosages, particularly of Ribavirin, ranged widely, with a substantial percentage using amounts higher than those tested in the manufacturer's controversial clinical studies. Many patients used doses of 1000 mg or higher, with some as high as 2400 mg., versus a maximum of 800 mg. in the official studies. The survey tracked 36 individual symptoms, standard blood and T-cell tests, and participants' subjective assessment of side effects and their overall health and experience using the drugs.

The survey report concluded that, overall, participants experienced a decline in reported symptoms, except for participants with AIDS on low doses of drug. A number of symptoms showed statistically significant improvements and an advantage was noted for patients using the higher doses.

Participants reported favorably on their experience, with 51% saying their health improved overall, despite the normally

regressive nature of the disease; 65.6% claimed that their overall rate of deterioration from HIV "slowed, stopped, or reversed" while on treatment. At the last reporting period of the survey, 67% reported they still were using Ribavirin. The most common reason cited for discontinuing was the cost or difficulty of obtaining the drug. A larger number reported discontinuing the use of Isoprinosine, citing uncertainties about its effectiveness as the most common reason. Project Inform felt it would be very difficult to determine which drug was providing perceived benefits, and wondered whether unfavorable opinions expressed by some researchers about Isoprinosine might have affected participants' views. Shortly after conclusion of the survey, Ribavirin also became the subject of unfavorable commentary due to disputes between its manufacturer and the FDA, probably leading to increased drop-out among Ribavirin users.

The side effect most commonly noted was anemia, reported by 37% of participants. Analysis of lab data supplied by a subgroup of participants, however, showed the degree of anemia was small, with a mean drop in hemoglobin of 9.9% and mean drop of hematocrit of 11.3% after 3 or more months of treatment. Of interest was the finding that the use of higher doses of Ribavirin in the survey was not associated with increased anemia. The next most common side effect reported was a drop in white blood cell counts.

In its discussion of the results, Project Inform concluded that although the survey participants reported a positive experience no matter how the question was asked, more research is required before generalizations can be made about the use of these drugs. Others using them may or may not have similar experiences. Project leaders, however, feel that the survey clearly points to the need for continuing research. Future research might explore the effects of higher doses and the use of intermittent or pulse dosing. At the release of the survey, Project leaders were pleased to note that new studies of both drugs were already underway, testing higher doses of Ribavirin and larger groups with Isoprinosine. "It's about time," Delaney said, "that the FDA stopped its stalling tactics and put more effort into helping determine whether these drugs can help. Controversial FDA actions on both drugs is in the best interests of neither science nor the lives of HIV infected people." Delaney pointed out that the FDA's analysis of the recent study of Ribavirin with LAS patients has now been disputed by four world class statistical experts, as well as the 4 independent researchers who conducted the study. He said he believed there was a growing trend among NIH researchers to reconsider that study and the drug, although few seem willing to directly confront the FDA over it.

Copies of the complete study are available through the Project Inform hotline. The report will also be supplied to the National Institutes of Health and the FDA, which requested this in Project Inform's meeting with them in Washington on July 28th, 1987.

FEDERALLY UNAPPROVED MEDICATIONS
FOR TREATMENT OF AIDS
AND
AIDS RELATED CONDITIONS

HOW TO GET THEM

HOW TO BRING THEM HOME

HOW TO USE THEM

VERSION 4.1
November 1986

Prepared from anecdotal, unofficial sources.

TF+

THIS DOCUMENT IS DISTRIBUTED AT COST

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I. THE GENERAL SITUATION:

Before deciding to run over the border to seek "unapproved" medications, it's important to consider all the alternatives. If you've already done so, you might want to skip to page 6. If not, take a few minutes to consider the following points.

If You Have Been Diagnosed with AIDS:

If you have been diagnosed as having AIDS, you needn't assume you are beyond hope and head for the bridge. Though the death rate is substantial, many people are coping with the disease. At the very least, they are prolonging their useful lives, and in many instances appear to be waging successful battles to stay alive and functional.

To date, no medical treatments have been completely successful in eliminating the virus or the damage it causes. Many approaches have been helpful in treating some of its effects and a few experimental treatments seem to stop the reproduction of the virus. There is no guarantee, however, that simply entrusting yourself to your doctor's care will make any of these treatments available to you. Some people have done quite well in their doctor's care, while others have found it necessary to break away from the traditional medical system. Many people believe both approaches can work, as well as a combination of them.

The first hurdle is to take responsibility for your own health rather than surrender it to hospitals, researchers, or personal despair. This is not to minimize the importance of working carefully with your doctor. There are real limits, though, as to what your doctor can do for you and he or she should be the first to applaud you for accepting your responsibility in the healing process.

The people who live longest seem to wage a personal campaign for survival both within and outside of the traditional medical community. Before considering either conventional or unconventional therapies, learn everything you can about the disease and your personal situation. If you are an AIDS patient, press your doctor for the following information:

What standard "approved" treatments are being used?

- what are the benefits, drawbacks, and risks of each?
- what results are claimed for these approaches?
- what does the most current research say about them?
- what criteria does the doctor suggest for choosing among different treatments?

What clinical studies are underway now or in the near future which relate to your particular condition?

(examples: AZT, Ribavirin, Alpha Interferon, etc.)

- what are the risks and possible benefits of these approaches?
- where else have they been used, and what were the results?
- which approaches seem most promising, and why?
- how do the risks and benefits of such programs compare with the risks and benefits of doing nothing?
- how can you get into such programs?
- how does your doctor feel about your entering such programs? (your doctor's opinion is one of several you should consider)
- how can your doctor help you get in?
- if your doctor isn't interested or knowledgeable, who can he or she refer you to who might have more information?

What remedies are available in or outside of the United States, or which can be brought in? (examples: prescription drugs, drugs brought in from Mexico or other foreign countries)

- what is your doctor's opinion of such approaches, and how was it formed?
- does your doctor have patients who have tried such approaches? If so, what were the results?
- who can your doctor refer you to who might be more knowledgeable about these approaches?
- will your doctor be willing to monitor your condition while using such approaches? If not, who can you be referred to who will?

What non-standard, non "approved," non "medical" approaches have been tried? (Examples: vitamin therapy, macrobiotics, visualization, eastern medicine)

- what are the results, benefits, risks?
- if the doctor isn't knowledgeable, who can he or she refer you?
- if the doctor is skeptical of other approaches, why and what evidence contributes to that opinion?
- how can you make an informed decision about trying alternate approaches?

The most important message is to ASK QUESTIONS and keep on doing so until you get answers. No one, not even the best informed doctors, have all the answers and you must share the responsibility for gathering and evaluating information.

If you wish to get into an experimental program, it helps to make yourself well known directly to the researchers. Find out what programs are underway, what is being planned. AMFAR (New York) can supply a list of all current clinical trials in the U.S. Contact the researchers or their staff, repeatedly. Help them see that you are sincere and will follow their protocol (rules) with diligence. Convince them of your will to live. Researchers are most interested in patients who will benefit from their treatments, thus making their research productive. Look and act like you'll put up a good fight. Be aware, however, that all such programs have entry requirements you must meet.

There are many fighters in our community who have effectively prolonged, perhaps saved their own lives. They didn't do it by sitting passively and awaiting a medical miracle. There are choices available to you, but you can't expect every doctor to keep every patient informed about every option. Do your own digging around, become your own medical detective. Meet with others who share your problem, learn from their experiences and be ready to share yours. Don't accept anyone's suggestions until they make sense to you, until you understand what you're doing and why. In a few words:

DON'T:

- *Sit back, wait, and wonder*
- *Continue the use or abuse of drugs and alcohol*
- *Burn the candle at both ends*
- *Expect your doctor to cure you or assume that his or her opinion is shared by all other doctors*
- *Despair*

DO:

- *Get on the phone, learn about your options*
- *Ask questions until you're satisfied*
- *Read all you can*
- *Take advantage of all the services available*
- *Meet others who share your problem*
- *Act responsibly toward yourself and others*

If you don't have the information you need, or your doctor is not fully informed on the latest treatments, you might wish to contact the "AIDS Foundation" in your town (or its equivalent), AMFAR, or PROJECT INFORM in San Francisco, which maintains a large library of AIDS related research materials.

If You Have an Aids Related Condition (ARC):

The most common AIDS RELATED CONDITION is called LYMPHADENOPATHY, a long term, general swelling of lymph nodes at many places in the body. Some other common symptoms of an AIDS RELATED CONDITIONS include various skin infections, oral yeast infection (thrush), persistent diarrhea, night sweats, persistent unexplained fevers, neurological

problems, and changes in white blood cell count and T-cell ratios.

If you have been diagnosed as having an AIDS RELATED CONDITION, you needn't despair of developing the full AIDS syndrome, nor should you casually assume that you won't.

**AN AIDS RELATED CONDITION IS
NEITHER A FREE RIDE NOR A
DEATH SENTENCE.**

Many people with AIDS RELATED CONDITIONS do not appear to go on to develop AIDS. Some early statistics suggest that only 10% to 30% do, but those statistics are based on a very limited number of people and may or may not be accurate. One recent European study suggests as many as 90% of people infected with the AIDS virus will eventually develop some degree of immuno-deficiency, though not all will be classified as AIDS. No evidence yet indicates that the condition goes away completely.

Having an AIDS RELATED CONDITION very likely means that you have been exposed to the AIDS virus. Most researchers feel that you are carrying the virus and are capable of spreading it to others. It might mean that you are waging a battle with the virus, one which you haven't lost yet. It might mean that your system is strong enough at the moment, but still in danger. Some people report having had LYMPHADENOPATHY for years and then later developing more serious symptoms or AIDS. Others simply continue to have LYMPHADENOPATHY without other complications.

Some who report sudden changes from LYMPHADENOPATHY to more serious problems associate the change with periods of great stress, poor nutrition, or substance abuse. Some researchers fear that continued exposure to the virus may increase the chances of ARC progressing to fully diagnosed AIDS.

Although it's easy to worry excessively when you have an AIDS RELATED CONDITION, it is something you should take seriously. You should be examined regularly by your doctor and quickly report any changes. Good nutrition, safe sex practices, and moderation in the use of alcohol and other substances are all thought to be very important when you have any AIDS RELATED CONDITIONS.

Perhaps the most important message for anyone who has an AIDS RELATED CONDITION is that you may be in a crucial period of your life. How you care for yourself, your nutrition, what substances you use or don't use, how you feel about yourself, and what (if any) treatments you take all may make a difference. You are really in a position to create your own future or surrender it. In a few words;

DON'T:

- *Sit back, wait, and wonder*
- *Continue the abuse of alcohol or other drugs*
- *Burn the candle at both ends*
- *Expect your doctor to cure you or assume that his or her opinion is shared by all other doctors*
- *Despair*
- *Casually assume you'll be OK or that AIDS has already passed you by.*

DO:

- *Get on the phone, learn about your options*
- *Ask questions until you're satisfied*
- *Learn all you can about your condition*
- *Take advantage of the services available*
- *Meet others who share your problem*
- *Act responsibly toward yourself and others*

If You Test "Positive" But Have No Symptoms:

People who test positive on the HTLV-III antibody test have been exposed to the AIDS virus and their immune systems have reacted by producing antibodies to fight the infection. A positive test result does not necessarily mean that you will develop an illness related to your exposure. Early studies suggested that only a small percentage of people who are antibody positive would become ill, but as additional experience with the disease has been gained, that estimate has repeatedly been revised upward. A recent European study suggests that nearly everyone who is antibody positive will, in the absence of effective treatment, eventually develop a serious immunodeficiency disease (ARC or AIDS). Other researchers believe that some antibody-positive people may be able to throw the virus off almost immediately, or successfully hold the virus in check indefinitely, or even eventually eliminate it. They believe that such people may never show any effects of their exposure to the virus. It is generally assumed, however, that people who are antibody positive are carriers of the virus and are capable of transmitting it to others.

Many researchers believe that exposure to co-factors such as stress, substance abuse, other diseases, etc. plays an important role in determining which antibody-positive people will develop ARC or AIDS and which will not. To the extent that this is true, you can reduce the risk of becoming ill by eliminating such co-factors from your life.

A growing number of researchers believe that the best chances of success in treating an AIDS- virus infection will occur if treatment is begun at the earliest possible moment. This viewpoint is very controversial in the United States and will remain so until some treatment option is proven to be both safe and effective. Until then, many physicians warn their patients that they are better off doing nothing than experimenting with unproven remedies. Many others, however, are already advising their patients to use the anti-viral remedies

available beyond the U.S. border. In fact, quite a number of physicians are using these drugs themselves. Whatever opinion your own doctor offers on this point, you can be certain that there are others, equally qualified, who recommend the opposite.

In some other countries, it is the practice to treat antibody-positive people with anti-viral and/or immune-boosting drugs even if they do not yet have symptoms.

As an antibody-positive person you should at least maintain a healthful lifestyle and keep yourself informed of all the options available to you. Monitor your condition carefully and be prepared to act on any changes which occur. Also be prepared to encounter conflicting medical advice. If you aren't getting it, you probably haven't searched very far.

II. "UNAPPROVED" MEDICATIONS

Although your doctor may be able to provide the latest approved treatments, he or she cannot legally provide access to "officially" unapproved (not "illegal") substances which many people have found helpful. Some of these can be easily purchased across the Mexican border. The following information can help you decide if you want to take this step and, if so, how to do it.

The drugs involved are not the "quack" remedies often associated with border towns. They are widely available throughout much of the world, they have been tested extensively (if not exactly for this purpose), and come from reputable manufacturers headquartered in the United States. Although their usefulness in treating AIDS or ARC is unproven, they have a known track record in producing useful effects on the immune system or against viral diseases.

Your doctor may be uncomfortable with the "self prescription" of unproven drugs. Honest concern and medical tradition make it difficult ethically and legally for physicians to recommend any unapproved drug. Some doctors may have heard discouraging news from early trials of these or similar drugs. If your doctor is not in agreement, you should take his or her advice under consideration - but you needn't let it be the final word. There are many competent physicians throughout the country who are very supportive of the use of these drugs. Listen to all the information sources and make your own decision.

If you choose to use them, it is strongly recommended that you **enlist your doctor's aid in monitoring your condition while using the drugs.** If your doctor is unwilling to monitor your condition after you choose to use these drugs, find a doctor who will. There are many, many doctors already doing so. Local AIDS

foundations or PROJECT INFORM in San Francisco can refer you to doctors who will help.

III. THE MOST COMMONLY USED DRUGS

1. RIBAVIRIN

An "anti-viral" substance widely available in other countries, RIBAVIRIN is used for a variety of viral conditions, including herpes, CMV, flu, and colds. It is currently under intense study for its effectiveness in dealing with AIDS and AIDS RELATED CONDITIONS.

Side Effects: RIBAVIRIN is believed to have only modest side effects which are well known. The most common reported by researchers is some degree of anemia, which is often a problem for AIDS patients with or without this drug. While potentially dangerous if unmonitored, this effect is known to be closely related to the dosage used. Care in choosing the right dosage and frequent monitoring can be very successful in preventing anemia. Some patients note that while anemia might be a problem, it is far less serious than death, the certain side effect of untreated AIDS. When anemia occurs, it is usually treated by dose reduction, or in extreme cases, with a blood transfusion. Iron supplements are not effective.

Form: RIBAVIRIN, its chemical name, is sold in Mexico under the brand name VILONA in three forms:

- in small blue and white boxes containing twelve 200 mg. tablets;
- in a liquid form in small bottles;
- in an injectable form.

While greatest absorption occurs using the injectable form, this should not be attempted without the direct supervision of a physician. If the injectable form is used, the correct dosage is MUCH lower than that described here. If your doctor chooses to administer the injectable form, he or she should check both with on-going research programs or the manufacturer to determine the proper dose. Dosages mentioned here are for the oral forms only. Most Mexican pharmacies are reluctant to sell the injectable form.

Price: RIBAVIRIN/VILONA is fairly expensive. The prices for a box of twelve capsules has ranged from \$7.00 to \$31.00 per box over the last year, dependent on the Dollar/Peso exchange rate. Maximum retail prices are fixed by Mexican government, though the exchange rate differs daily and from one store to the next. Some stores are willing to offer discounts from the maximum legal price. Periodically, the maximum selling price is adjusted upward to account for Mexico's wildly increasing inflation rate.

2. ISOPRINOSINE

This drug is sold in 70 countries around the world and is best known for its apparent ability to stimulate certain functions of the immune system. It is currently the subject of research with AIDS and ARC patients. Some studies have indicated (but not proved) that it can improve the status of patients with AIDS RELATED CONDITIONS. Many people think it is most likely to be of use not on its own but when used in combination with an "anti-viral" substance such as RIBAVIRIN. Due to conflicts between the FDA and the drugs U.S. manufacturer, and inconclusive test results, ISOPRINOSINE is unpopular with many U.S. researchers. Researchers in European countries, however, seem to have a much higher regard for it.

Side Effects: ISOPRINOSINE is known to be a very benign drug with minimal side effects. It is commonly used in other countries for such viral diseases as herpes, colds and flu.

Form: It is sold in small pink and white boxes under the brand name ISOPRINOSINE or PRANOSINE from the Sanfer Company, and, recently, in blue and white boxes under the brand name ISOPRINOSINE from the Roussel Company. From either distributor, the boxes contain twenty 500 mg. tablets. The PRANOSINE version is considerably less expensive.

Price: Selling prices in Mexico have increased substantially in 1986, going from a previous low of \$1.80 per box to around \$4.50 currently (\$2.50 for PRANOSINE). The price varies daily with the exchange rate.

Combinations

Most people believe these drugs are more effective when used together than either is alone. AIDS and ARC are thought to include at least two problems: the virus itself, and the damage it does to the immune system. Researchers predict that an effective therapy must knock out the virus and work to restore the immune system.

RIBAVIRIN appears to be capable of suppressing the virus, at least temporarily. ISOPRINOSINE has been shown to stimulate some of the functions of the immune system (primarily T-Cell production). A number of unofficial sources (some dating back as far as 1982) have claimed that the two drugs work well in combination against AIDS. RIBAVIRIN alone may be

able to suppress the virus, but unless the immune system is restored, opportunistic infections may recur.

Another immune stimulant, INTERFERON, has recently been licensed for some uses in the U.S. Many researchers suspect that it is a much better immune booster than ISOPRINOSINE, though it also has much more serious side effects. Since INTERFERON can now be legally obtained, it is likely that some people will begin using it experimentally in combination with RIBAVIRIN. To do so will require a great deal of cooperation from your physician. At the moment, little is known about appropriate dosages.

IV. RESULTS PEOPLE HAVE REPORTED

When discussing results obtained with experimental drugs, NOTHING IS CERTAIN and there are no guarantees. One person's results may not be repeatable for another or may differ based on "what else" they're doing, such stress reduction, nutrition, or use of other substances. Side effects suffered by one person may not occur for another. It is even possible that the benefits attributed to these drugs may really be brought about by the increased attention to overall health and nutrition which often accompanies their use. Some AIDS and ARC patients get better for periods of time without any type of therapy. It's possible that the positive effects reported after taking these drugs might just as well have occurred without them.

With that said, however, it must be reported that many people who are taking these drugs claim important benefits.

Among those who have used these drugs in combination with other supportive efforts at nutrition, stress reduction, and substance control, many have reported major improvements in one or more of the following areas:

- fewer opportunistic infections
- some reduction in size or apparent elimination of long swollen lymph nodes
- better control of thrush (yeast infections)
- increased energy levels and improved psychological outlook
- return to more normal weight
- reduction or elimination of night sweats
- improvement in T-Cell ratios and the T4 count

Many of these results seem most likely to occur from long-term usage. Short-term improvements in T-cell ratios, for example, should not be expected.

Physicians may reasonably question the accuracy of these reports or may be unwilling to attribute the results to over-the-counter drugs they cannot provide. We have no argument with any medical specialists on these matters and only wish to report what people say and how they feel they achieved the results. Some are extremely satisfied with the results and we know of many, many people using them who are apparently now in the best health they've had for years, despite AIDS or AIDS RELATED CONDITIONS. The difference in some people is startling. Whether the improvement was caused by the drugs remains a matter of opinion.

The best results appear to be obtained by people with AIDS RELATED CONDITIONS, although some fully AIDS diagnosed, very ill patients also claim important improvements. The degree of improvement often seems related to how early in the course of the disease the drugs were used. The importance of an overall health plan cannot be stressed enough. No drug on its own is likely to produce perfect results for such a serious illness.

Whatever dosage is used, these or any drugs have the best chance of success when combined with a program of sound nutrition, proper sleep and exercise, stress reduction, and self-control of substance use. Taking these drugs while continuing to burn the midnight oil, living on junk food, or abusing alcohol or other drugs, is simply throwing your money away. Taking these drugs as the latest treatment "fad," without proper monitoring and a long-term strategy, is also likely to be a waste of money.

V. WHAT DOES CURRENT RESEARCH SHOW?

It is well known that medical researchers are testing both these drugs. As is the case with all AIDS research to date, some early reports have been encouraging, while others have not. No researchers to date have tested the combined effects of these two drugs as an anti-viral agent and an immune booster in a controlled study. Until such testing occurs, research data only provides answers to a different set of questions - not to the question of combined therapy.

Research with RIBAVIRIN has grown substantially during 1985 and 1986, with some 18 study groups begun or planned. Many researchers claim to be "cautiously optimistic" about its use, particular against ARC. It has been shown, in the lab, to suppress reproduction of the AIDS virus. It has been shown, in human subjects, to suppress a range of other viruses. It has also been shown to be one of the few drugs capable of crossing the "blood-brain" barrier. Thus RIBAVIRIN may be capable of suppressing the virus in the brain and spinal fluids where the virus is known to do significant damage.

Some research groups around the country, including Harvard Medical School, have reported patients on RIBAVIRIN changing from "positive" to "negative" on important "viral culture" tests. This implies a major decrease in the level of HTLV III (AIDS) viral activity, if not its complete suppression, at the time of the test. In addition, some degree of clinical improvement has been confirmed in human subjects. RIBAVIRIN is one of only two drugs which have demonstrated this type of effectiveness in actual human use. The other AZT, is not addressed here because it is still only available in clinical trials (to an increasing number of people).

Some researchers worry about possible unknown side effects of RIBAVIRIN. A conservative approach is standard practice in the medical profession. Other feel, however, that there is always some risk of this, and that in general both of these drugs and their side effects are quite well known. Far more is known, for example, about RIBAVIRIN than about SURAMIN, which researchers seemed confident in administering. How does the risk of side effects compare to the risk of doing nothing? How does this risk compare to the long accepted risks taken by our community with the use of anonymous white powders and other recreational drugs for a single night's high?

Some studies of ISOPRINOSINE cast doubt on its effectiveness when used alone. Other studies have been much more positive. In England and the U.S., ISOPRINOSINE was shown by two research groups to be effective in delaying the transition of ARC patients to full-blown AIDS. In New Zealand, and other countries ISOPRINOSINE is widely used to treat ARC patients and even antibody-positive individuals who have no other symptoms. Sweden and Australia have initiated (in 1986) massive tests of ISOPRINOSINE involving nearly 1/3 of those countries' antibody positive people.

VI. BUYING IN MEXICO

Buying these drugs in Mexico is now quite simple and completely legal. Despite fears about mistreatment south of the border, most who have taken the trip report nothing but cooperation and good will from the Mexican people.

Tijuana can be reached by car or by bus. If you choose to drive, take INTERSTATE 5 going south from San Diego (about a 20 minute ride). The highway leads directly into Tijuana. If you wish to walk across the border there are parking lots on the US side adjacent to the border crossing point. If you fly into San Diego, there is a trolley which runs from downtown San Diego to the San Ysidro border crossing. There is also bus service between San Diego and Tijuana.

If you leave your car in the US and walk across the border you may save some time by avoiding the long lines of traffic leading to the US Customs inspection point upon returning. It is about one mile from the border crossing to downtown Tijuana. You can take a Mexican taxi from the border to downtown if you prefer not to walk. You won't have any trouble finding your way - just follow the crowds.

If you plan to drive into Mexico, stay on the freeway. You will pass a small Mexican inspection point at the border. U.S. tourists are routinely waved through without question. If questioned, just describe yourself as a tourist. Continuing on that same road, follow the signs toward "Centre" - the downtown of Tijuana. Don't get upset if you're not sure where you're going. Just stay on the road heading toward the "Centre" or ask for directions there. You are likely to end up on a wide one way street (3rd Ave.) lined with open shops. After a few blocks, you should look for a major cross street labelled "REVOLUCION" - one of the main drags (groan...). When you find it, turn left onto the street. Go another block or so, looking for the intersection of REVOLUCION and 5TH ST. - this will leave you right in the middle of town, in a safe location within a block of the central police station. (It's not critical to reach this exact spot - it's only a reference point.)

Once you are in the center of the tourist area, simply look for large store signs indicating "FARMACIA." (Note: by far the least expensive way to purchase RIBAVIRIN is through the "buying co-ops described later; when purchasing RIBAVIRIN that way, there is no need to deal directly with the Farmacias). There are dozens of them. Before bothering to park, look in the window of the store. You'll want to stop at a large, well stocked FARMACIA. Some of the smaller stores have a lot of empty shelf space and aren't likely to have much of the drug you need. There are many large FARMACIAS which are well supplied. The bigger stores also accept credit cards, though some will require that credit card purchases take place before 4 pm (to allow calling to check card validity). Drug stores are usually open at least until 6 pm, some until 8.

Among others, the REGIS, OLYMPIA, VIDAS, and the PARIS FARMACIA have been consistently helpful. Your best bet will often be with the larger stores, since they tend to carry a larger inventory.

Any of these stores will take plain old American cash, in fact, they love it (you may, however, get a better currency exchange rate by going to a bank there first). Most Farmacias have someone on staff who speaks English. Go to the drug counter and simply tell them what you want. Due to its high price, some stores may be unable to fill a large order for VILONA. ISOPRINOSINE is easily found in large quantities. Some Farmacias may suggest a substitute called PRA-

NOSINE as a replacement for ISOPRINOSINE, since they are the same drug. There is also a substitute for VILONA, from the distributor called GROSSMAN. Don't take any other substitutes - get the drug you came for or go to another store. If you arrive on a day when the main stores are in short supply, try the stores a few blocks farther away from the center of town.

You needn't fear walking around in the central district of Tijuana. Despite obvious poverty, it is little different from American cities. Once you get beyond the central area, however, things might get a little rougher - just as they would in LA or San Francisco. Any experienced urbanite will quickly recognize the safe areas and the not-so-safe areas.

Be careful about parking. Most central area streets are highly regulated. Individual stores "own" the parking space in front of them and reserve it for their customers. You are likely to be hassled for parking violations, not by the police but by store personnel.

If you drive into Mexico be aware that US insurance is invalid in Mexico. You must purchase a Mexican insurance policy before crossing the border and carry proof of insurance with you. Such insurance is sold at well marked stands and store fronts near the border. If you have an accident in Mexico without insurance you will go to jail until all claims are settled. The Tijuana Policia have been known to stop cars with US plates to check for proof of insurance coverage (sometimes looking for a pay-off). Most rent-a-car companies forbid bringing San Diego based cars into Mexico. Many tourists do it anyway. Be aware though that if a problem arises, the rental company's insurance is unlikely to help out. Despite rumors, driving in Tijuana appears no more dangerous than in any other large city, though drivers may be a bit less predictable.

VII. RETURNING TO THE USA

As most international travelers will tell you, the most tiresome aspect of any journey is facing U.S. customs checkpoints. Anticipate a long wait in line, especially if you're in a car. Be careful to read ALL of the following information before your trip. A few key points first:

- Don't be stupid - avoid carrying marijuana, other drugs, or drug paraphernalia
- Don't smoke your last joint just before reaching the border, leaving the smell all over yourself and your vehicle
- Dress all-American casual, Sears Roebuck style - some Customs agents will feel right at home
- Wear your least noticeable earrings, or none at all. Leather gear can also be left at home or at least kept under your clothing.
- Look as ordinary as possible; consider it a new type of drag.

This is no time to make a statement about anything. You're there to bring the goods home, nothing else. Anything which might interfere with that or possibly stir up the juices of the good ol' boys at customs jeopardizes your mission.

A variety of approaches have been successfully used to bring the drugs back in. Here are a few:

STRATEGY #1. THE STRAIGHT AND NARROW:

The safest method is to stay within the law and prominently display a "personal use quantity" (currently defined as 300 or so tablets of ISOPRINOSINE [15 boxes] or VILONA [25 boxes]) on the front seat of your vehicle or in a shopping bag. Attempting to hide it creates a different legal situation. When you finally meet the customs agent (expect to wait from 10 to 60 minutes), he'll ask why you came to Mexico, how long you were there, and what you bought. Your answer:

"I bought a personal supply of an anti-viral drug from a Pharmacy. It's called ISOPRINOSINE (or VILONA)."

Show him a sample box of pills from your shopping bag, or show him the bag itself. Be prepared to tell him the actual quantity, but don't offer this information unless asked. If an agent asks what the drug is for, it is safe to answer "AIDS" since nearly all agents are now familiar with the drugs and their use. Most agents will simply wave you on across the border.

Importing these drugs for your own use is LEGAL. Despite inconsistency before September of 1985, the border patrol has now publicly stated a policy permit-

ting people to bring in these "personal use" quantities. Unfortunately, the amount allowed in legally for personal use is only enough to supply one person for a little more than one month. That makes it somewhat impractical and very expensive to obey the letter of the law.

A few alternatives:

- if you're not willing to argue with the agents about quantities, stick to the limit and make several trips back and forth over the border in a single day. Though this is time consuming, it works well.
- If you're stopped or harassed in any way, **DON'T SURRENDER THE DRUGS.** You may be sent to a secondary inspection area or to a supervisor.

A slightly more bold alternative is described in **STRATEGY #2.**

STRATEGY #2. THE SMUGGLER SAMARITAN

While we in no way condone breaking the law, the current definition of "personal use quantities" creates a dilemma for many people. The trip is costly and must be repeated monthly to continue treatment. Therefore, some people choose to answer to a higher authority and attempt to bring in larger, yet reasonable quantities. Though this is a technical violation of the law, moral, ethical, and financial justification for such action is widely claimed. The strategy outlined below reports the practices used by people who cannot afford the luxury of monthly trips, or who are motivated by compassion for sick friends and lovers.

Tactics reportedly used for bringing in larger supplies:

- Hide the drugs elsewhere in the car
- Buy some blankets or trinkets and act silly like a regular straight tourist as a diversion.
- Carry a camera, wear green polyester golf slacks, clip-on sunglasses, and a pressed short sleeve shirt with pens in the pocket.
- Bring a blouse and skirt-wearing woman or a child, best of all a pregnant woman
- Remove the drugs from their boxes so they'll take up less space and be easier to conceal.
- Increase the number of pills in each box
- Take the pills out of their boxes — they take up less room that way and are easily concealed.

They say this works fine if you can keep your cool, lie with a straight face, don't feel like you're breaking any cosmic laws, and don't tremble or sweat a lot. Customs agents, though, are very good at spotting people who

act like they're hiding something. Know yourself and act accordingly.

While you do expose yourself to additional legal risks this way if caught, the most likely outcome is confiscation of the drugs. Stronger penalties are technically possible but unlikely since the drugs are not narcotics. Some who have been stopped and detained using this method report that no charges were filed. The border patrol admits that no has been charged with any violations for importing any quantity of these drugs. There's no guaranty that that will always be the case.

STRATEGY #3. THE INNOCENT DUPE

Some people report doing both of the above and claim it is a fairly safe strategy. They:

- A. Buy a larger supply of the drugs. Hide the majority of the supply in small stashes throughout the car and the trunk. Taking the pills out of their boxes makes them much easier to conceal:

<i>under floormats</i>	<i>in your clothing</i>
<i>in the ashtray</i>	<i>inside & under spare tire</i>
<i>in blankets</i>	<i>in other tourist wares</i>
<i>under the seats</i>	<i>in center consoles</i>
<i>inside the dash</i>	<i>buried in luggage</i>
<i>under tools</i>	<i>in the trunk, etc.).</i>

- B. **ALSO** keep a full legal supply openly displayed on the front seat.

When they reach the customs agent, they declare the drugs on the front seat openly as described in strategy #1 above. The agent then either waves them through or he doesn't. If he doesn't, he sends them to the "SECONDARY INSPECTION AREA" (which is **NO BIG DEAL — DON'T PANIC**), where they're asked the same questions and might be required to fill out a Declaration form. The same rules will apply at the secondary inspection, so the same lines work fine there. They say it's very, very likely that he won't suspect what's being hidden (the larger stash) elsewhere. The drugs displayed on the front seat supposedly act as a very effective diversion.

A Big Word of Caution:

DON'T even think of using this trip (or these methods) to bring anything illegal through. It leaves you open to serious criminal charges (in addition to not getting the drugs you need). If people abuse this process, it may result in a reversal of the fairly sympathetic treatment we've been given at the border.

VIII. DOSAGE - USING THE DRUGS

You won't be getting a label with your pills. You'll need to know about both dosage (how much to take) and duration (how long to go on taking it).

The proper dosage of most drugs varies with body weight. The dosages suggested here are based on their use by the average sized, health and fitness conscious slim but tight all American queer, body weight about 150 lbs.

Most people who use these drugs believe you should be taking a cycle of both drugs. How much of each is described below, as well a strategy for their combined use. Read all of the suggestions here before deciding on a personal strategy.

RIBAVIRIN (VILONA):

Dosage: RIBAVIRIN (VILONA) Reported dosages for this drug vary widely, both from "official" and "unofficial" sources. Your doctor may not be too helpful on this since there is little experience with this drug in the USA. New studies underway may help clarify proper dosage. As with any drug, some individuals may be more susceptible to side effects than others so what is an acceptable dose for one may not be OK for another. Careful monitoring by your doctor, especially in the first month or two of use, will help you avoid side effects.

Typical reported dosage varies from three to nine 200 mg. tablets per day, both with and without scheduled interruptions in the use of the drug. Some individuals have reported taking nine or more capsules every day for extended periods of time without significant side effects. Others have reported side effects on as few as three capsules per day. Anemia resulting from the destruction of mature red blood cells appears to be the most significant common side effect of RIBAVIRIN use. This anemia is reversible by stopping the drug or lowering the dose as are other reported side effects. If a person seriously overdoses himself without proper monitoring, a blood transfusion may be required to rapidly replace the damaged red cells. Some degree of anemia is common among AIDS and ARC patients with or without RIBAVIRIN. If you are anemic before beginning RIBAVIRIN treatment, you should be especially careful about choosing your dosage. Anemia can be detected early by means of a simple blood test known as a "complete blood count" or "CBC". It costs less than \$10 at most labs.

The dosages reported here are based on RIBAVIRIN/VILONA sold in 200 mg. tablets - not injectable RIBAVIRIN. If using the liquid form of VILONA, each bottle is approximately equivalent to 12 tablets or one full box. Using the spoon provided with the liquid form, two spoonfuls is the equivalent of 1 capsule.

CAUTION: in medicine, more isn't always better (nor is less) - something we should have learned from our "recreational" drug experiences. Choose a reasonable dosage which takes your condition into account.

The "Loading Dose" Approach

Most medical researchers seem to feel that the best strategy for using RIBAVIRIN is to begin by taking a relatively large "loading" dose to quickly build up the level of the drug in your blood. The loading dose is continued for three to five days and then is followed by a smaller daily "maintenance" dose which just balances losses of the drug by metabolism and excretion. The FDA-approved clinical trials of RIBAVIRIN have adopted this strategy.

People have reported taking loading doses of 6 to 12 capsules (1200 to 2400 mg) per day for 3 to 7 days followed by maintenance doses of from 3 to 9 capsules (600 to 1800 mg) per day for extended periods. FDA sponsored trials currently use a loading dose of twelve capsules daily (2400 mg.) for the first five days, then either 3 or 4 capsules (600 or 800 mg) daily thereafter.

Recent research at Harvard Medical School, UC San Diego, Cornell Medical Center, the UC Medical Center and other locations on small numbers of people suggest the following tentative conclusions: At doses of 600 mg/day (3 capsules/day) very little side effect is likely but, at least for short-term therapy, relatively little therapeutic effect occurs. At 800 mg/day (4 capsules) side effects are still relatively insignificant in most individuals and some inhibition of the AIDS virus can be demonstrated. At 1200 mg/day (6 capsules) measurable reduction in viral activity and improvement in immune function can be observed in many patients. This dosage can be expected to produce a mild anemia in many individuals which, for a few, can become serious enough to require reduction of the dosage. There are many reports of individuals converting to "negative" on viral culture tests at this level. Above 1200 mg/day the incidence and severity of side effects increases until at 2400 mg/day (12 capsules), most people can expect to develop significant anemia within two weeks. For most people, a constant dose of 2400 mg/day will lead to serious anemia.

Informal observations by groups of RIBAVIRIN users and physicians who monitor them are consistent with the formal research findings. We are aware of patients who take 1800 mg/day (9 capsules) for many months without significant side effects, while there have been a few reporting problems at a dosage of 600 mg/day (3 capsules).

Duration: RIBAVIRIN does not kill the virus like penicillin kills bacteria for example. Like other anti-viral agents, RIBAVIRIN is thought to only inhibit the virus' ability to reproduce. The theory behind using such anti-viral agents is that by slowing or stopping the

replication of the virus, the body is given time to build up its own defenses so it can control or eliminate the remaining virus. Some viruses are known to hide in a dormant state within the body for long periods of time only to be triggered into activity again by future events. The AIDS virus is thought to be capable of hiding in this way. With such viruses, treatment with an anti-viral agent must be continued for a very long time, perhaps for life.

Many researchers believe that it will be necessary to use an anti-viral agent such as RIBAVIRIN indefinitely. Results of early studies mentioned above indicate that when treatment was stopped, signs of viral activity reappeared in the patients, sometimes immediately, sometimes after a few months. Other researchers are hopeful that, at least in some individuals, the body's own defense mechanisms will eventually be capable of cleaning up the remaining virus or at least holding it in check so that drug treatment can be stopped. The truth is that it is too soon to know how long treatment must be continued. A few days or weeks of treatment is certainly not enough and may just be a waste of money. To get lasting results it seems that at least several months of RIBAVIRIN treatment must be considered.

With any drug there is always the possibility that new side effects will appear after long-term use. RIBAVIRIN has been used extensively in humans for short-term therapy but so far there is virtually no long-term human experience. Animal studies suggest that it is safe for long-term use but, to be sure, the final test must be in humans. We are aware of a few individuals who have taken RIBAVIRIN for 1-1/2 years without significant side effects.

With this in mind, many patients have decided to continue taking RIBAVIRIN indefinitely. Or at least until something better comes along or unless some harmful effect is demonstrated.

ISOPRINOSINE:

Dosage: For someone of the median weight, the manufacturer has repeatedly and publicly recommended six 500 mg. tablets every 24 hours (3000 mg. per day). Some patients are taking twice the standard dosage with no reported side effects. The pills should not be taken all at once, but spread out over at least 3 periods during the day. Most people report no side effects whatever using the standard dosage.

Duration: While some clinical trials have tested using the drug for 30 day periods, people not part of official studies report achieving the best results using ISOPRINOSINE daily for 2 or more months. Some have used it non-stop for a year or more. Most people take at least three months of treatment and often continue at least some dosage indefinitely for maintenance purposes. Throughout this time, your doctor can perform blood and urine tests to determine

the presence of any side effects, the most likely of which is an insignificant increase in the level of uric acid. It's important to remember, however, that *not everything that happens to you while taking a drug is a side effect of that drug.*

Some researchers feel it is risky to boost the immune system with ISOPRINOSINE while infected with the AIDS virus. There is an untested concern that such stimulation might build a better breeding ground for the AIDS virus. If this makes sense to you, you might consider suppressing the virus first with RIBAVIRIN. It should also be pointed out, however, that other researchers have publicly disputed this theory.

Some people believe that it is best to begin taking an anti-viral agent such as RIBAVIRIN 1 to 2 weeks before taking ISOPRINOSINE. It is thought that by first loading the body with an anti-viral agent, the new T-cells will be less likely to become infected.

Other Strategies

Many patients use an older "intermittent" dosing strategy for both RIBAVIRIN and ISOPRINOSINE. Under this protocol patients typically take the drugs every day for some period such as 5 or 10 days. They then stop taking the drugs for 5 days. This cycle is then repeated throughout the treatment period. Usually the dosage during the "on" days is greater than it would be under the continuous dosing strategy.

People using the intermittent protocol report good results but there is no hard evidence that it is better or worse than the continuous dosing strategies mentioned above. Some claim that side effects are less of a problem using the intermittent program. But others claim that there is no theoretical basis for this and that there is no good experimental evidence to show that it is true. Some say that there is a possibility that the virus could begin replicating during the "off" days but others say RIBAVIRIN is stored long enough in the body to prevent that.

Some medical researchers worry that use of an intermittent protocol is more likely to cause mutation of the virus to a drug-resistant form. While there is no hard evidence that this happens, it remains a theoretical possibility.

A Starting Point

Many people want to know "Where should I start?" The most accurate answer is of course "That depends." The following protocol is one which many patients have found satisfactory. For most people who are not taking other drugs and who do not have existing problems with anemia, it represents a reasonable starting point. Some patients using this protocol may find it necessary to reduce the maintenance dose of RIB-

AVIRIN upon the appearance of unacceptable side effects (anemia).

Remember that with any drug there are always a few individuals who have unusual reactions and there may be special circumstances for you which make this protocol unsuitable. Consult with your physician before YOU decide to use this or any other treatment protocol and while you are taking the drugs. Be prepared to reduce your dosage if unacceptable side effects appear.

Loading dose: Take 1800 mg/day (9 capsules/day) of RIBAVIRIN for 5 days.

Maintenance dose: Beginning on the 6th day, take 1200 mg/day (6 capsules/day) of RIBAVIRIN.

Immune boosting: After being on the RIBAVIRIN for 14 days, start taking 3000 mg/day (6 tablets/day) of ISOPRINOSINE.

Monitoring: Have your physician monitor for side effects, especially anemia. This should include at least weekly complete blood counts (CBC) for the first month or until your condition is stable. After you are satisfied that your reaction to the drugs has stabilized, you may want to reduce the frequency of monitoring but it should continue at some level for as long as you continue to take the drugs.

Duration: Continue treatment until you have some definite reason to stop. Some reasons to discontinue treatment might be: availability of a better treatment; appearance of an unacceptable side effect; or the need to take some other drug with which there might be some unacceptable reaction. Questions about possible interactions with other drugs can be answered by calling PROJECT INFORM in San Francisco.

Adjustments: Adjust your dosage as required to accommodate your body's reaction to the drug and your philosophical assessment of the relative risks and benefits of treatment vs. side effects. Remember that these drugs are unproven for the treatment of AIDS and ARC and that more is being learned about them every day. Keep yourself informed of current developments and adjust your treatment accordingly.

Combinations With Other Drugs:

A significant number of patients are taking another anti-viral agent, ACYCLOVIR, to control certain Herpes-type virus infections including Herpes simplex, Herpes zoster, and Epstein-Barr Virus. Many physicians feel that control of such secondary infections is important to minimize the progressive destruction caused by the AIDS virus. Because most of the population is infected with at least one of these viruses and because dormant Herpes-type virus infections tend to become reactivated in individuals with compromised immune systems, many AIDS and ARC patients have

chosen to use Acyclovir on a prophylactic basis. We know of no reports of adverse interactions between RIBAVIRIN, ISOPRINOSINE and ACYCLOVIR.

What if You're Not Mr. Average Slim and Trim?

If your weight differs by more than 20 lbs. from the 150 lbs. median weight used in the above recommendations, it might make sense to calculate an adjusted dosage based on body weight. Here's how.

- first, choose a prudent dosage from the range given for Mr. Average
- calculate (use a calculator) your body weight as a percentage of the median weight (150 lbs.), using the following formula:

Step one:

YOUR WEIGHT (divided by) THE MEDIAN WEIGHT = ? [a number]

Step two:

Multiply [that number] times THE STANDARD # OF PILLS PER DAY = ADJUSTED # OF PILLS PER DAY

Example 1: if you weigh 200 lbs., divide 200 by 150, resulting in 1.33 (which means your weight is 133% of the median weight). Assuming the dose for Mr. Average is 6 pills per day, multiply 1.33 times 6, which equals about 8 pills per day.

Example 2: if you weigh 120 lbs., divide 120 by 150, resulting in .80 (or 80% of the median weight). Multiply .80 times the standard dose (.80 times 6), which equals 5 pills per day.

IX: PRECAUTIONS

Since this is still not a proven medical success, a few cautions are in order:

- Don't start the protocol if you're under treatment with other drugs prescribed for Pneumocystis or other AIDS related illnesses. The possible interactions between these and other drugs in your system are completely unknown. It would be prudent to wait until your condition stabilizes and other drugs are withdrawn. Similarly, it may be imprudent to use this protocol instead of recommended, approved treatments for such infections.
- Discuss your own dosage and duration with your doctor, taking into account this protocol, researchers' concerns for and against boosting the immune sys-

tem with ISOPRINOSINE before suppressing the virus, and any suggestions you can get from researchers, doctors, or people using these drugs (a major effort is underway to educate primary care physicians about these drugs).

- This approach, like all others being tried in the lab up to this time, is unlikely to fully eliminate the AIDS virus for everyone. Set reasonable expectations and you're less likely to be let down by the results. Quality of life and a stabilized condition are very valuable benefits, whether or not the virus is destroyed.
- Even if the virus is completely eliminated, patients whose immune system has been severely damaged will still remain susceptible to infections until the immune system is repaired. There is some evidence that, to the extent that it does occur, rebuilding of the immune system may be a slow process. This means that even though the virus may be suppressed by RIBAVIRIN, some patients may be unlucky enough to contract a serious infection before the immune system is restored. Controlling the virus is only a necessary first step in treating this disease.
- When there's a genuine, comprehensive and reliable cure (even if this is it), you won't have to learn about it from sources such as this.

What About Rumored Dangers of Immune Boosting for AIDS Patients?

A few researchers have expressed a fear that boosting the immune systems of diagnosed AIDS patients with ISOPRINOSINE may be harmful. They note a theoretical concern that, because the drug may stimulate production of T-Cells, (which in turn are the very cells in which the AIDS virus reproduces itself) it may actually hasten the reproduction of the virus. They feel, therefore, that if an AIDS patient chooses to use ISOPRINOSINE at all, it should only be done after a regimen of an anti-viral drug, such as RIBAVIRIN.

When evaluating this concern, it's important to remember that the T-cells in question are also very important in fighting off opportunistic infections associated with AIDS. Failure to stimulate their production may also have a serious negative effect.

Other researchers dispute this theory, contending that if ISOPRINOSINE did cause this effect, related factors would be detectable in the blood tests, most notably a decline in the total T-cell count as the virus takes over these cells. This, they say, simply does not occur and they conclude that the theory is incorrect. In fact, their research concludes that the T-cells stimulated by ISOPRINOSINE are particularly resistant to the virus.

X. OTHER REASONS THIS MAY WORK

Aside from the fact that you can get them (unlike other drugs in research studies), is there any compelling reason to use these drugs?

Some evidence seems to suggest that the AIDS virus is potentiated or activated in the presence of other viral infections, such as hepatitis, herpes, colds, flu, etc. Some researchers have speculated that the AIDS virus can only do its dirty work when other types of viral infection are present as co-factors.

RIBAVIRIN and ISOPRINOSINE may at least be suppressing general types of viral activity. While RIBAVIRIN'S effectiveness as an anti-viral agent against the AIDS virus is still being studied, there is wide agreement that both these drugs have an impact on common viral infections - some or all of which may be co-factors to the reproduction of the AIDS virus. If researchers can confirm that good general health and freedom from common viral infections help discourage the AIDS virus, this may validate why these drugs seem to produce positive results.

Until then, take a balanced outlook. Claiming too much for them may only increase the resistance by the traditional medical community. But don't ignore the possible benefits they offer. Many people who use them feel they owe their life to them. Finally, don't discount the important healing power of the "hope" generated by this alternative.

The medical community needs to test some combination of these drugs and/or look for benefits to AIDS patients brought about by avoiding general types of viral infections. If a study is conducted which asks the right questions, we might get some reliable answers. In the meantime, if you are a "user," you are encouraged to report your results to your doctor, and to PROJECT INFORM.

PROJECT INFORM
25 Taylor St. Suite 618
San Francisco, Ca. 94102

PROJECT INFORM also supplies information on NALTREXONE (immune booster), DNCB (immune booster), and d-Penicillamine (anti-viral).

(Organizations listed or mentioned within are in no way responsible for this document of its content).

XI. IN CONCLUSION

Nothing said here is medically proven. The approaches described here have been used by enough people that we feel confident no one will do themselves harm and might do a lot of good. At the least, these drugs may buy time until more effective treatments become available. There is hope that these drugs can fight this plague when used as part of a responsible personal health plan.

The FDA's actions continue to make it awkward for people to obtain these drugs. Their own red tape has all but strangled the "compassionate use protocols" bragged about in their public statements.

Your doctor may or may not like the idea of your prescribing drugs on your own. These concerns are understandable, predictable, and should be respected. But they're not necessarily correct and needn't be the last word on the subject until the research offers something more hopeful or disproves this approach. Until we are offered a better solution than "wait and see," it is not imprudent to seek the possible benefits of these drugs. It could be argued that it's imprudent not to.

PROJECT INFORM

25 Taylor St. Suite 618
San Francisco, CA. 94102

National: 1-800-822-7422
California: 1-800-334-7422
Local: 415-928-0293

NOTES ON CROSSING THE BORDER

Most people have no difficulty importing personal quantities of ribavirin and Isoprinosine and are surprised at how easy it is. However, the treatment of individuals crossing the border at Tijuana continues to be uneven. In part this stems from a refusal of the FDA to clearly define its policy on these drugs.

The FDA has publicly stated a policy of non-enforcement of its importation regulations for personal-use quantities of ribavirin and Isoprinosine. Calls to various FDA offices have produced various statements of this policy. Frequently callers are told that they will be allowed to import a 3-month supply of each drug for their personal use only. When pressed for how much drug that represents, the FDA compliance officers say "that depends on the dose being used" and refuse to elaborate further. Other callers are only told that the FDA has adopted a policy of non-enforcement for personal-use quantities. Questions as to the meaning of "personal-use quantities" are unanswered. The FDA refuses to provide written acknowledgment of its policy (whatever it is).

For its part, Customs at the Tijuana border has adopted a formal policy of allowing people to import 300 capsules or tablets of each drug per month. There is a letter dated in 1985 from the local director, Mr. Rappaport, to the agents stating this policy. Individual agents seem to have their own agenda. Many wave people declaring these drugs right through without question. Some routinely send people to secondary inspection where additional questions may be asked and inspections performed. Usually, it seems that people carrying reasonable quantities of the drugs are allowed to pass. Sometimes Customs insists on a strict limit of 300 capsules or tablets of each drug. There are a few agents who give the impression of being downright hostile to people importing these drugs, but most are at least polite and many are sympathetic.

Occasionally, when an agent elects to hassle someone, the individual is asked to produce a statement or prescription from a physician. Sometimes a prescription from a Mexican physician is accepted and sometimes the agent will insist on it being from a US physician. PROJECT INFORM has been repeatedly assured by Mr. Gerry Martin, Director of the US Customs San Ysidro Office (Tijuana crossing), that it is NOT the policy of US Customs to require prescriptions or physician's statements. If you should be so unlucky as to run into this situation, ask to speak to the highest level supervisor on duty. Also get the badge number and any other identification from each agent or supervisor you talk to. If talking to the supervisor doesn't help, the simplest solution is often to simply return to Mexico with the goods, wait a few hours and try again with a different agent. Report such incidents promptly to PROJECT INFORM.

If you fail to declare what you are importing, it is pretty clear that you could be charged with smuggling. Under those conditions, Customs has rather broad authority to seize the goods and whatever other property, such as your car, was used to assist in the operation. They also could prosecute you for a criminal offense. In practice, we know of no case where anyone has been actually arrested but we have heard of a few cases in which the smuggled drugs were seized. More commonly, the person is questioned, told to return the excess drugs to Mexico and then released.

If you declare more than the agent chooses to allow (i.e. 300 pills), you may be told that you cannot import that quantity and be forced to return the excess to Mexico. On rare occasions agents have attempted to confiscate the excess quantity. Apparently they have no authority to do this, since at that point, you have done nothing more than ask permission to import more than the agent will allow.

As a practical matter, most people are allowed to import reasonable quantities (often somewhat more than 300 pills) with very little hassle. Most customs agents are reasonably human and it appears that the agency is not anxious to fight a public battle on this issue.

We have distilled the following points from the comments of many individuals who have experience in importing these medications. We make no recommendation as to their validity but offer them for your consideration:

**** Be polite and straightforward.**

**** Do not volunteer more information than is requested.** For example: when asked what, if anything, you are importing, say "I am bringing in a personal supply of medication for treating AIDS." Let the agent ask about quantity - often he won't.

**** Don't panic - no matter what.** Moral right is on your side and most agents would prefer to spend their time catching criminals than hassling sick people. Even in the worst of situations, a compromise can probably be found.

**** If challenged as to quantity, say "I called the FDA and was told I could import a 3-month supply."** A statement from your doctor documenting your daily dosage may be helpful. (Most doctors won't write a prescription but many are willing to state how much drug you are taking on your own.) Prescriptions or doctor's statements are NOT officially required.

**** Look sick.** (Some have suggested that coughing on the agent helps!)

**** Appeal to the agent's sense of sympathy.** Discuss how hard it is for you to make the trip - how this medication is your only hope for survival.

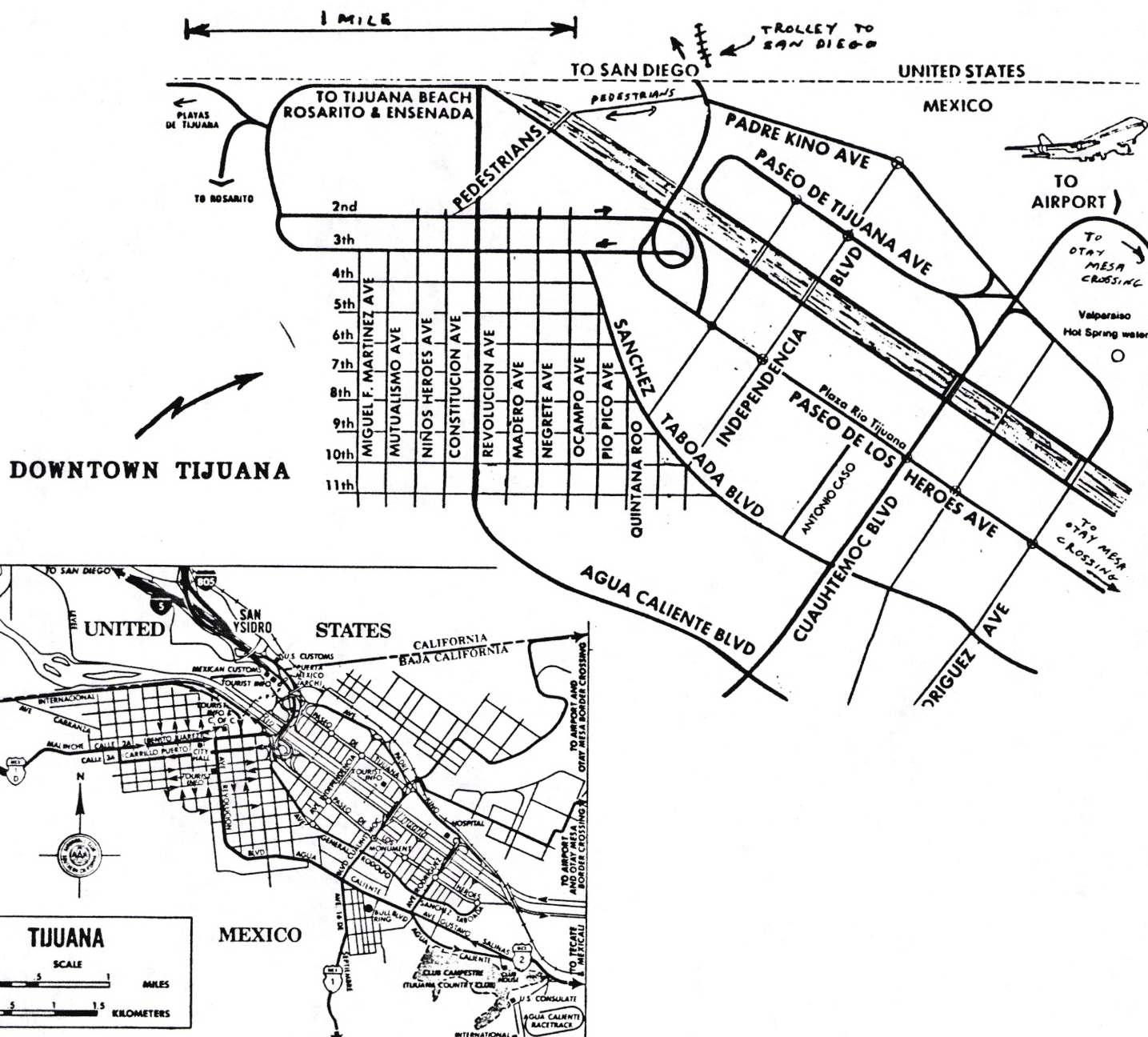
**** Avoid directly challenging the agent's authority.** Customs people have a lot of power and can use it in arbitrary ways. No matter what the law says, in the short run you are likely to lose a shootout.

**** Don't give up too easily.** Keep talking until you get at least part of what you want or it becomes clear that further talk will hurt your position. If you are not satisfied, ask to talk to a supervisor.

**** If you are importing more than 25 boxes per person, go through customs with at least one other person.** If Customs limits you to 25 boxes per person, one person can stay behind with the excess while the others cross with their allotments. Most people then simply recross the border and pick up the remainder. (Getting the same agent on the second trip should be avoided.)

**** Report any difficulties or unusual experiences, along with the agent's identification, promptly to PROJECT INFORM at 800-822-7422 (in Calif. 800-334-7422).**

**** If you need immediate assistance contact the San Diego Aids Project.**



TRANSPORTATION:

1. A trolley line runs from downtown San Diego to the border crossing in San Ysidro. The ride takes 45 min. - 1 hour (about 20 miles).
2. If you cross the border on foot, you can walk to the tourist district of Tijuana or take a Mexican taxi for about \$5.00.
3. Returning to the US on foot is often faster because the auto lines sometimes are more than 1 hour long.
4. Do not leave valuables in sight in a car parked on the US side of the border.
5. If you want to drive into Mexico be sure you purchase Mexican insurance before crossing the border. It is available at numerous stands in San Ysidro. Cost is about \$10/day. Many rental car companies prohibit taking their cars into Mexico.
6. If driving in Tijuana, be careful. The Tijuana police often seek bribes from US tourists, especially those driving rental cars.

PHARMACIES KNOWN TO OFFER DISCOUNTS:

1. Farmacia Olympia
5th & Ninos Heroes (NW corner)
Phone: 85-25-45
2. Farmacia Regis
5th & Constitucion (SE corner)
Phone: 85-13-49
3. Farmacia Nachos
5th between Revolucion & Madera
4. Shop around. There are many other pharmacies in the area if you have time to compare prices.

PROJECT INFORM

25 Taylor St. Suite 618
San Francisco, CA. 94102

National: 1-800-822-7422
California: 1-800-334-7422
Local: 415-928-0293

Drug/Agent Name: NALTREXONE

Chemical Name: Trexan

General Description:

Naltrexone is licensed for medical use in the U.S. as a narcotic antagonist and treatment for heroin addiction. Naltrexone has also been used as a treatment for obesity.

The clinical testing of Naltrexone in AIDS and AIDS Related Complex is based on recent evidence that suggests that endorphins serve as essential chemical messengers between the immune systems and central nervous system. Further, it is hypothesized that the prolonged presence of elevated levels of serum interferon in patients with AIDS/ARC may down-regulate opiate receptors.

Naltrexone is intended to stimulate an increase in opiate receptors in lymphocyte stem cells and an increase in circulating endorphins and enkephalins.

Toxicity and side effects, at doses averaging 50 mg/day as a narcotic antagonist, include mild depression, dysphoria, irritability, and restlessness. At the 200-300 mg. dose used in the treatment of obesity, hepatotoxicity is seen. In AIDS

Some materials included in this information developed by AmFAR (American Foundation for AIDS Research)

and ARC, the dose tested is 1.75 mg/day and no side effects are expected.

Manufacturer/developer: Dupont
Wilmington, Delaware

Indication: CDC-defined AIDS
AIDS Related Complex

Study Protocol: A double-blind, placebo controlled study with patients randomly assigned to active treatment or placebo.

Investigator: Bernard Bihari MD
Downstate Medical Center
Department of Psychiatry
450 Clarkson Avenue
Brooklyn, NY 11203
718 270 1094
212 929 4196

Inclusion Criteria: CDC-AIDS
ARC
HIV ab+

Exclusion Criteria: Women of child bearing age.
Patients currently using any narcotic (including morphine, demerol, lomotil, darwon, talwin, and any other drug with opiate agonist activity.)
Narcotic use is an exclusionary factor since narcotics would block the mechanism of action of the naltrexone.

////////

Investigator: Lawrence A. Higgins, MD, MPH
412 Avenue of the Americas 3rd Floor
New York, NY 10011
212 598 9445

Indication: ARC or AIDS

Study Protocol: To study the effect on CD-4 helper cells and symptoms of ARC and ARC (in patients who are self-administering ribavirin)

Inclusion Criteria: ARC/AIDS

Exclusion Criteria: Negative HIV Ab.

Dosage: 1.75 mg

Route/s of Administration: PO

Frequency: 6 days/week

Treatment Duration: 6 months

Number of Subjects: 40

Duration of Trial, Including Follow Up: 6 months

Estimated Start Date: March 1986

NALTREXONE

Directions for Pharmacy Preparation and Use

The drug is prepared by the pharmacist using 50mg tablets of Trexan (by Dupont). Grind and dissolve the tablet in 50ml of syrup (i.e. 1mg/1ml). The patient should then be given a bottle of the mixture and a 3 or 5 ml syringe marked at 2.5ml.

To take the medication, the patient should shake the bottle well, draw 2.5ml with the syringe, squirt it into water, shake and drink.

It is legal for a physician in private practice to prescribe this treatment.

This information was provided by Dr. Bernard Bihari, who may be contacted for further information, at:

Bernard Bihari, M.D.
Downstate Medical Center
450 Clarkson Ave.
Brooklyn, New York 11203
718-270-1094

POSTER 597

Low Dose Naltrexone in the Treatment of the Immune Deficiency in AIDS and ARC

BERNARD BIEHL, F DEUKY, V RAGONE, M ORBE, W FOESTE, J THOMAS, E KIRK, E KLEIN, E KOKAYI

Downstate Medical Center, Brooklyn, New York, USA

Evidence accumulating in recent years strongly suggests that the endorphinergic system plays a central role in homeostatic regulation of the immune system and that endorphins and opiate receptors are essential links between the immune system and the CNS. There are as well, reasons to believe that AIDS may be accompanied by a deficiency in endorphins and in opiate receptors on cells of the immune system, secondary in part to continuously elevated levels of alpha-interferon, which as a potent opiate agonist is likely to down-regulate the endorphinergic system. Such down regulation, if present, may contribute to the pathophysiology of AIDS.

Naltrexone, an oral opiate antagonist used in the treatment of narcotic addicts, (at doses of 50 mg/day) produces an increase in opiate receptors and pituitary beta-endorphin production when given in single doses to laboratory animals. This study involves an attempt to up-regulate the endorphinergic system in order to improve immune function by the use of very small doses of naltrexone (1.75 mg/day), large enough to stimulate production of both receptors and beta-endorphin, and small enough to be metabolized in 2 or 3 hours, permitting the patients' immune system to benefit from the endorphinergic up-regulation the rest of the day.

We are treating 60 patients in a double blind protocol and following a number of clinical and laboratory parameters as indicators of efficacy and in an effort to answer some of the questions raised above about pathophysiology. The study will be completed in April or May, 1986 and the results will be presented at the conference.

PROJECT INFORM

25 Taylor St. Suite 618
San Francisco, CA. 94102

National: 1-800-822-7422
California: 1-800-334-7422
Local: 415-928-0293

D-PENA CILLAMINE DPA

DPA is a commercially available drug which has been used in patients with inflammatory and metabolic disorders, including Wilson's Disease, chronic active hepatitis, primary biliary cirrhosis and rheumatoid arthritis.

DPA has been shown to inhibit replication of HIV virus in vitro and it is postulated that DPA inhibits HIV by cross-linking disulfide groups and inactivating essential viral proteins.

Current information is limited, but it is thought that the use of DPA in conjunction with other anti-virals and immunopotentiators can produce culture negativity.

Dosage regimes have been 250 mg/day for up to six (6) months and sometimes (if no viral suppression was noted at the lower dose) up to:

250 mg bid for 1 week
250 mg qid for 1 week
500 mg qid for 2 weeks
then recycle monthly for additional 3 months.

Manufacturer

Developer:

Carter/Wallace & Degussa Pharmaceuticals
Rt. 46 at Hollister
Teeterboro, NJ 07608
(201) 288 6500

Some material included in this information developed by AmFAR (American Foundation for AIDS Research)

Estimated Start Date: TBA

References:

Schulof RS et al. Treatment of HTLV-III/LAV Infected Patients with D-Penicillamine. Drug Research, October 1986 In Press.

Chandra P, Sarin PS, Selective Inhibition of Replication of the AIDS Associated virus HTLV-III/LAV by synthetic D-Penicillamine. Arnheim Forsch Drug Research. 36:184-186, 1986.

Jaffe I, Penicillamine, Arthritis, McCarthy DJ, ed. Lea and Febringer, Phila. 1983 pp 502-511.

#

Drug/Agent Name: D-PENICILLAMINE
(DPA)

Chemical Name: TBA

General Description:

D-penicillamine (DPA) is a commercially available drug which has been used in patients with inflammatory and metabolic disorders, including Wilson's Disease, chronic active hepatitis, primary biliary cirrhosis, cystinuria and rheumatoid arthritis.

DPA has been shown to inhibit the replication of HIV in vitro. The mechanism by which DPA inhibits replication of HIV has not been defined. However, among the biochemical properties ascribed to DPA are its activity as a metal chelating agent and its ability to interact with proteins and peptides by the formation of mixed disulfides. It has been postulated that DPA inhibits HIV by cross-linking disulfide groups and inactivating essential viral proteins, especially

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25 TAYLOR ST #618
SAN FRANCISCO, CA 94102

cysteine-rich proteins such as the nucleic acid binding protein. DPA has a high affinity for tissue proteins and exhibits a broad tissue distribution including spleen, liver, kidney and brain.

A phase I pilot trial to assess tolerance and antiviral activity of DPA was performed in 13 HIV-infected male homosexuals with PGL and depressed T-helper cell levels. Treatment time varied from 2 to 6 weeks. Results indicated that orally administered DPA inhibited HIV, as measured by reverse transcriptase in co-cultivation of PBLs and expression of the viral proteins p15 and p24. All patients treated for at least 2 weeks exhibited evidence of HIV inhibition. Maximal suppression of HIV required at least 4 weeks of daily administration and complete inhibition was seen in 60% of patient treated for six weeks. 3 of 6 patients treated for 6 weeks remained culture negative for at least 6 weeks after stopping drug. Treatment with DPA was also associated with a decrease in lymph node size.

Side effects and/or toxicity associated with DPA administration in the pilot study were a mild generalized lymphopenia (approximately 20% drop in absolute lymphocyte counts) and a transient depression of T-cell function in lymphoproliferative assays.

Manufacturer/Developer:	Carter/Wallace & Degussa Pharmaceuticals Rt. 46 at Hollister Teeterboro, NJ 07608 201 288 6500
Project Supervisor:	John Respodek, MD
FDA License Status:	NDA for inflammatory disorders
Indication:	PGL or ARC with HIV viremia and immune dysfunction
Study Protocol:	An open, Phase I study to assess tolerance and antiviral effect.
Investigator(s):	Richard Schulof, MD Gary L. Simon, MD David M. Parenti, MD Rochelle G. Scheib, MD George Washington Univ. Med Ctr. 502 Burns Bldg. 2150 Pennsylvania Ave NW Washington DC 20037 202 676 4716

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Inclusion Criteria:

Positive HIV serology
PGL or ARC
Positive HIV culture (RT and
presense of p15, p24)
T4/T8 ratio < 1.0
T4 number < 500 but > 100 cmm
Mixed lymphocyte response:
LAS 20-75% normal
ARC 10-75% normal

Exclusion Criteria:

Frank AIDS
Active infections
Immunomodulatory or antiviral
therapy within past 4 weeks
Hemoglobin < 11.0 gm/dl
WBC < 2500 cmm
Platelets < 120,000 cmm
Creatinine > 2.0 mg/dl
SGOT, SGPT, Alkaline phosphatase
> 3x normal

**Route/s of
Administration:**

Oral

Dosage #1:

250 mg

Frequency:

Bid

Treatment Duration:

up to 6 months

Dosage #2:

250 mg

Frequency:

Bid for 1 week
Qid for 3 weeks
off therapy for 4 weeks
then recycle
Up to 6 months

Treatment Duration:

Dosage/Frequency #3:

(beginning at week 12 if no viral
suppression at lower dose)
250 mg bid for 1 week
250 mg qid for 1 week
500 mg qid for 2 weeks
then recycle monthly for
additional 3 months

Number of subjects:

Up to 30

**Duration of trial,
including follow-up:**

TBA

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SAN FRANCISCO, CA 94102

From the Departments of Medicine¹ and Biochemistry², The George Washington University Medical Center, Washington, DC (USA), Maryland Medical Laboratory³, Baltimore, MD (USA), the Laboratory of Tumor Cell Biology⁴, National Cancer Institute, Bethesda, MD (USA) and the Laboratory of Molecular Biology⁵, Frankfurt University Medical School, Frankfurt/Main (Federal Republic of Germany)

Treatment of HTLV-III/LAV-infected Patients with D-Penicillamine

By R. S. Schulof^{1,2}, R. G. Scheib¹, D. M. Parenti¹, G. L. Simon¹, R. A. DiGioia¹, H. M. Paxton¹, M. B. Sztein¹, P. Chandra³, J. W. Courtless¹, Y. T. Taguchi⁴, D. K. Sun⁴, A. L. Goldstein⁵, and P. S. Sarin⁴

Summary: 13 asymptomatic, HTLV-III/LAV-infected male homosexuals with generalized lymphadenopathy were treated with oral D-penicillamine. All patients had depressed T4/T8 ratios and 12 had impaired T-cell function. An escalating dose schedule was employed over 2–6 weeks with doses from 0.5 to 2 g/day. Generalized skin rashes developed in 4 patients which required discontinuation of therapy in one patient. Two patients developed mild transient elevations of hepatocellular enzymes. Reversible decreases in lymph node size, absolute lymphocyte counts, and T-cell lymphoproliferative responses were observed in the majority of pa-

tients without change in baseline T4/T8 ratios. All 10 patients treated for at least 2 weeks exhibited evidence for suppression of HTLV-III/LAV replication; complete inhibition of virus expression was seen in 60% of patients treated for 6 weeks. Three of the patients treated for 6 weeks remained culture negative for at least 6 weeks after stopping the drug. D-Penicillamine appears to be an effective drug for suppressing HTLV-III/LAV expression in vivo. Its potential role in the treatment of patients with the acquired immune deficiency syndrome (AIDS) and AIDS-related complex (ARC) will require further evaluation.

Zusammenfassung: Behandlung von HTLV-III/LAV-infizierten Patienten mit D-Penicillamin

13 asymptomatische, HTLV-III/LAV-infizierte männliche Homosexuelle mit generalisierter Lymphadenopathie wurden oral mit D-Penicillamin behandelt. Zu Beginn der Therapie wurde bei allen Patienten ein vermindertes T4/T8-Verhältnis festgestellt, und 12 der Patienten hatten eine gestörte T-Zell-Funktion. Die Patienten wurden 2–6 Wochen mit steigenden Dosen von 0,5–2 g/d D-Penicillamin behandelt. Ein generalisierter Hautausschlag wurde bei vier der Patienten beobachtet; bei einem dieser Patienten wurde die weitere Behandlung mit D-Penicillamin abgebrochen. Zwei der Patienten entwickelten eine vorübergehende, leichte Erhöhung der hepatozellulären Enzyme. Bei der Mehrzahl der Patienten wurde eine reversible Abnahme der Lymphknoten-

größe, der absoluten Lymphozytenzahl und der lymphoproliferativen Aktivität der T-Zellen beobachtet bei unverändertem Baseline-Wert von T4/T8. Die Replikation von HTLV-III/LAV wurde bei allen 10 Patienten, die mindestens zwei Wochen behandelt wurden, gehemmt. Eine totale Hemmung der Virusexpression wurde bei 60% der Patienten nach einer 6wöchigen Behandlung festgestellt. Drei der Patienten die 6 Wochen lang behandelt wurden, blieben nach Abbruch der Medikation mindestens 6 Wochen virusfrei.

D-Penicillamin scheint die In-vivo-Replikation von HTLV-III/LAV wirksam zu hemmen. Eine potentielle Anwendung der Substanz bei der Behandlung der erworbenen Immunschwäche (AIDS) und des AIDS-verwandten Komplexes (ARC) bedarf einer weiteren Abklärung.

Key words: Acquired immune deficiency syndrome-associated virus · HTLV-III/LAV, inhibition of replication · D-Penicillamine, clinical studies, effect on lymph node size

1. Introduction

The identification of HTLV-III/LAV as the etiologic agent [1] of the acquired immune deficiency syndrome (AIDS) and its prodromal syndromes has prompted the evaluation of drugs that inhibit virus replication in vitro and in vivo. Recently, it has been reported that the replication of HTLV-III/LAV can be inhibited in vitro by D-penicillamine [2] (DPA), a structural analogue of cysteine. DPA was shown to exhibit a concentration dependent suppressive effect on HTLV-III/LAV expression and the concentration which totally inhibited viral growth (40 µg/ml) was less than 10% of the cellular toxic dose.

Synthetic DPA is employed clinically in the treatment of a number of diseases including Wilson's Disease, chronic active hepatitis, primary biliary cirrhosis, cystinuria, and rheumatoid arthritis [3]. The recent promising in vitro results have led us to evaluate the usefulness of DPA for the treatment of HTLV-III/LAV-infected patients.

2. Methods

2.1. Patients

13 patients were treated with DPA. All patients were asymptomatic, HTLV-III/LAV culture positive male homosexuals with generalized lymphadenopathy and ranged in age from 24–47 years. None of the patients had a prior history of frank AIDS. All patients, on 2 separate pre-study screenings, exhibited: 1. depressed T4/T8 ratios (< 1.0), 2. depressed absolute helper T-cell levels (< 400/mm³), and 3. positive cultures for HTLV-III/LAV. 12 of the 13 patients exhibited depressed T-cell function in lymphoproliferative assays (MLR, RPI < 0.8, see below). All patients gave written informed consent.

2.2. Study design

Synthetic DPA tablets (a product of Degussa AG, Frankfurt/Main, FR Germany) were supplied by Carter-Wallace, Inc., Cranbury, NJ (USA). Initially, 5 patients received daily oral DPA as follows: 250 mg p.o. b.i.d. for 1 week, 250 mg p.o. q.i.d. for 1 week, then 500 mg p.o. q.i.d. Five additional patients began treatment 2 weeks after the first group with a different dose escalation schedule that omitted the 500 mg/day dose based on the tolerance of the first group. Treatment was scheduled to continue for up to 3 months. Immune profiles and HTLV-III/LAV cultures were repeated every 2 weeks while receiving DPA, and 2, 4, and 6 weeks after discontinuing the drug. Routine physical examinations, and hematologic, biochemical, and urine studies were repeated weekly during the study.

2.3. Immune profiles

Immune profiles included an assessment of T-cell subset percentages (T4, helper-inducer, and T8, cytotoxic-suppressor) and absolute numbers, and the T4/T8 ratio using appropriate monoclonal antibodies (Ortho Laboratories, Raritan, NJ, USA), and flow cytometry. T-cell function was assessed using lymphoproliferative responses of peripheral blood mononuclear cells to alloantigens (mixed lympho-

cyte response, MLR), and mitogens (phytohemagglutinin, PHA 2 µg/ml, Burroughs Wellcome, Greenville, NC, USA) as previously described [4] and to soluble antigens (tetanus, 0.1–20 µg/ml, Mass. Public Health Biologicals, Boston, MA, USA). Mitogen and antigen assays were carried out for 4 and 6 days, respectively. As a quality control, all lymphoproliferative data were normalized and depicted as relative proliferative indices (RPI) [5] based on a comparison to the mean response of 3 healthy heterosexual normal donors (tetanus boosted) repeated serially each time the patient was studied. A RPI of < 0.8 is considered abnormal.

2.4. HTLV-III/LAV cultures

Mononuclear cells were stimulated with 0.1% phytohemagglutinin (PHA) and co-cultured with H9 cells to detect HTLV-III/LAV as previously described [6]. Cultured cells were examined for HTLV-III/LAV expression with monoclonal antibodies to p15 and p24 core proteins by immunofluorescence and assayed for the presence of reverse transcriptase activity [6]. All results reflect viral cultures that were continued for a total of 4 weeks.

3. Results

3.1. Patient accrual

Five patients were started on DPA as described in Methods. After it was established that the drug was well-tolerated for 2 weeks, an additional five patients received 250 mg p.o. q.i.d. for 2 weeks, then 500 mg p.o. q.i.d. Three of the latter 5 patients discontinued therapy within 2 weeks (one for personal reasons, a second because pneumocystis carinii pneumonia was diagnosed on the day treatment began, and a third because of a drug-induced skin rash). An additional 3 patients were started on DPA 2 weeks later. Six weeks after the first 5 patients had begun treatment it was determined that DPA had caused a decrease in T-cell lymphoproliferative responses (MLR, tetanus, see below) and therapy was stopped prematurely in all patients. Thus, the total duration of treatment for the first 5, second 2, and last 3 patients, was 6, 4, and 2 weeks, respectively.

3.2. Side effects

DPA was well tolerated in all but one patient whose treatment was discontinued after a week because of a diffuse maculopapular rash which did not respond to anti-histamines. Three other patients developed mild, transient generalized skin rashes over the first few weeks. Two patients developed mild elevations of hepatocellular enzymes (SGOT, SGPT) which were transient. One patient who had received DPA for 6 weeks developed oral candidiasis, peripheral eosinophilia, elevated hepatocellular enzymes, and a bacterial pneumonia one week after discontinuing therapy. The patient improved following treatment with oral clotrimazole and intravenous cefamandole. No other infections were encountered.

tered throughout the 12 week follow-up period. No other hematologic, biochemical or urinary abnormalities were noted. Antinuclear antibody tests were negative in all patients after treatment.

3.3. Clinical effects

All patients had measurable generalized lymphadenopathy prior to treatment with indicator lymph nodes at least 1 cm in diameter in at least 2 extra-inguinal sites (Table 1). Seven of the patients completed at least 4 weeks of treatment with DPA. Of these 7 patients, 3 (nos. 3, 4, 6) with bulky lymphadenopathy exhibited 33–60% decreases in maximal lymph node diameters after 4 weeks of treatment. Each of the remaining 4 patients who had smaller lymph nodes (maximal diameter 1–2 cm) exhibited a decrease in overall lymph node size after treatment (decreased sum of squares) but the change was less pronounced (0–25% decrease in maximal diameter). All patients exhibited a stable performance status throughout the study. Of the 7 patients who completed 4 weeks of treatment, 6 had lymph node size re-measured 6 weeks after discontinuing therapy (Table 1). In 5 of these 6 patients, lymph nodes increased after therapy to baseline or near baseline size.

3.4. Effect on HTLV-III/LAV infection

HTLV-III/LAV replication was suppressed in all 10 patients who were treated for at least 2 weeks with DPA (Table 2). Of the 5 patients who received DPA for 6 weeks, 3 exhibited complete suppression of viral replication in each of the 3 assays employed at the completion of therapy, whereas 2 others exhibited 70–90% inhibition. One of these latter patients became culture negative 2 weeks after the drug was discontinued. Of the 5 patients who completed 2–4 weeks of therapy, 4 exhibited at least 85% inhibition of virus expression at the time of last culture. As seen in Table 2, mean HTLV-III/LAV expression for all patients decreased gradually with duration of DPA administration with a nadir in p15 and p24 expression after 4 weeks of therapy. Three pa-

tients (nos. 2, 3, 4) who received DPA for 6 weeks, and who became viral culture negative remained essentially culture negative (at least 90% inhibition of viral replication in each of the 3 assays) for at least 6 weeks after stopping the drug. In contrast, one of the patients treated for 4 weeks (no 7) and none of the patients treated for 2 weeks remained culture negative by 6 weeks after stopping the drug.

3.5. Effects on T-cell numbers and function

Immunologic effects of DPA were similar for all 10 patients. Results of serial immune studies for the first 5 patients, each of whom completed 6 weeks of therapy, are shown in Fig. 1. Most of these patients (4 of 5) experienced a mild reversible lymphopenia resulting in a transient decrease in absolute numbers of circulating T4 lymphocytes by approximately 20% but with a concomitant decrease in T8 cells so that there was no change in the baseline T4/T8 ratio. The patient who had the most marked decrease in lymph node size (no. 4) exhibited as transient lymphocytosis of both T4 and T8 cells. All 5 patients exhibited a gradual decrease in T-cell lymphoproliferative responses to alloantigens (MLR-RPI) while on therapy. Prior to treatment only 2 of the 5 patients mounted detectable lymphoproliferative responses to tetanus antigen (tetanus-RPI = 0.97 and 0.45) and in both cases this response decreased during therapy (to 0.28 and 0.05, respectively). No consistent changes were seen in PHA-RPI. Following the discontinuation of therapy there was gradual restoration of all lymphoproliferative responses to baseline or near baseline levels over 2–6 weeks (Fig. 1).

4. Discussion

In this study we have shown that orally administered DPA is well tolerated by asymptomatic, HTLV-III/LAV-infected patients with generalized lymphadenopathy and that it decreased lymph node size and suppressed viral replication in all treated patients. An escalating dose schedule and maximal dose of 2 g/day was employed based on the experience

Table 1: Effect of DPA on lymph node size.

Patient	No. of indicator lymph nodes	Largest lymph node			Sum of squares ^{a)}		
		Pre-Rx	on DPA ^{b)}	Post-Rx ^{c)}	Pre-Rx	on DPA ^{b)}	Post-Rx ^{c)}
1.	2	1.5 × 1.5 ^{c)}	1.5 × 1.0 (0%) ^{d)}	2 × 1	3.25	1.5	7.0
2.	4	1.5 × 0.5	1 × 0.5 (–33%)	2 × 1	1.75	1.25	4.75
3.	3	1.5 × 2.5	1 × 1 (–60%)	1 × 2	6.7	1.75	4.25
4.	4	2.5 × 3	1.5 × 1.5 (–50%)	2 × 3	25.3	5.25	13.0
5.	2	1 × 2	1.5 × 1 (–25%)	1.5 × 1	2.5	2.0	1.5
6.	2	1.5 × 3	2 × 2 (–33%)	ND ^{e)}	6.0	3.0	ND
7.	2	2 × 1	2 × 1 (0%)	2 × 1	3.0	2.25	3.0
Mean values	2.4	1.6 × 1.9	1.3 × 1.1 (–29%)	1.8 × 1.6	7.0	2.2	5.6

a) $\sum (\text{Diameter}_1 \times \text{diameter}_2) \dots n$.

b) After 4 weeks treatment with DPA.

c) Bipерpendicular diameters of largest lymph node (cm).

d) Percent change in maximal diameter from pre-treatment indicated in parentheses.

e) Six weeks after discontinuation of DPA.

f) ND = not done.

Table 2: Effect of DPA on HTLV-III/LAV replication.

Patient	Weeks received DPA	Reverse transcriptase ^{a)}							p15 ^{a)}							p24 ^{a)}						
		Weeks on treatment				Weeks post treatment			Weeks on treatment				Weeks post treatment			Weeks on treatment				Weeks post treatment		
		0	2	4	6	2	4	6	0	2	4	6	2	4	6	0	2	4	6	2	4	6
1.	6	100	100	53	27	100	100	100	100	67	55	22	50	33	33	100	100	28	21	75	50	25
2.	6	100	63	0	0	0	0	0	100	33	0	0	0	0	0	100	33	0	0	10	0	0
3.	6	100	100	100	30	0	10	0	100	66	33	10	0	0	0	100	100	30	16	0	0	0
4.	6	100	100	30	0	0	0	0	100	100	0	0	0	0	0	100	100	0	0	0	0	0
5.	6	100	58	21	0	100	100	100	100	40	0	0	60	28	40	100	17	0	0	70	33	33
6.	4	100	70	10	–	60	–	–	100	60	0	–	100	–	–	100	67	0	–	100	–	–
7.	4	100	33	10	–	25	15	0	100	50	10	–	30	0	0	100	60	0	–	0	0	0
8.	2	100	57	–	–	50	60	25	100	50	–	–	75	20	25	100	50	–	–	75	30	30
9.	2	100	0	–	–	35	40	35	100	0	–	–	25	25	50	100	0	–	–	30	25	45
10.	2	100	10	–	–	100	100	–	100	13	–	–	50	50	–	100	15	–	–	75	75	–
Mean values		100	59	32	11				100	48	14	6				100	54	8	7			

a) Expressed as % positive control after 4 weeks in culture [6].

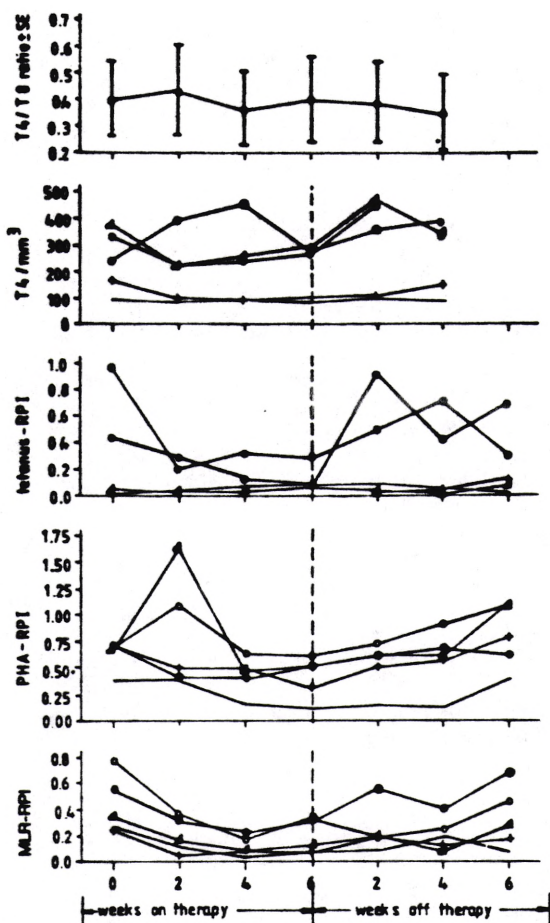


Fig. 1: Serial immunologic parameters for 5 patients who received DPA for 6 weeks. Mean values $\pm$ SE are depicted for T4/T8 ($n = 5$ patients). For all other parameters each patient is identified separately: patient no. 1 (—); patient no. 2 (○—○); patient no. 3 (Δ—Δ); patient no. 4 (●—●); patient no. 5 (+—+).

in the treatment of patients with rheumatoid arthritis [3]. With the doses and schedules employed, suppression of HTLV-III/LAV was observed as early as 2 weeks after initiating therapy. HTLV-III/LAV expression was completely inhibited in 3 of the 5 patients (60%) who completed 6 weeks of treatment. The viral suppressive effects of DPA occurred gradually with maximal suppression only after 4–6 weeks of continuous treatment. The anti-viral activity appeared to be prolonged since 3 of 5 patients who received therapy for 6 weeks remained HTLV-III/LAV culture negative for at least 6 weeks after stopping the drug. Furthermore, the anti-viral activity of DPA was not simply related to its inhibitory effects on T-cell numbers or function, since viral cultures remained negative in 3 patients after their immune status had returned to baseline.

The mechanism by which DPA inhibits replication of HTLV-III/LAV has not as yet been defined. Among the biochemical properties ascribed to DPA are its activity as a chelating agent, and its ability to interact with proteins and peptides by the formation of mixed disulfides [3,7]. It has been postulated that DPA inhibits replication of HTLV-III/LAV by cross-linking disulfide groups and inactivating essential viral proteins, especially cysteine-rich proteins such as the nucleic acid binding protein [2]. We did not measure plasma DPA levels in this study since such quantitations are difficult due to the lability of the drug and because serum levels do not reflect its cumulative tissue uptake [7]. It is noteworthy, however, that DPA has a high affinity for tissue proteins [7] and exhibits a broad tissue distribution including spleen, liver, kidney, and brain, a sanctuary for HTLV-III/LAV [8].

In the last 5 patients, DPA treatment was discontinued after 2–4 weeks because data became available from the first 5

patients indicating that T-cell function in MLR was decreasing on therapy. In our experience a marked depression of MLR-RPI (<0.15) has been associated with an increased risk for developing opportunistic infections [4]. Of the 13 patients treated with DPA, only 1 developed an infection while on study. This patient had completed six weeks of therapy with DPA, and had an excellent clinical response with regression of lymphadenopathy and suppression of virus. He developed oral candidiasis and a bacterial pneumonia the week after therapy with DPA was discontinued. The patient's MLR-RPI had decreased from a baseline of 0.35 to 0.12 at the completion of therapy and improved to near baseline levels (0.27) 6 weeks after stopping the drug. No other infections were noted throughout the study period. With a minimal post-study follow-up time of 6 months, none of the treated patients have developed frank AIDS. However, 1 patient (no. 5) who had complete inhibition of viral replication at 6 weeks, but in whom viremia recurred within 2 weeks after discontinuing treatment, has subsequently developed fevers and night sweats.

In summary, we have shown that DPA suppresses replication of HTLV-III/LAV in asymptomatic patients with generalized lymphadenopathy. The only major side effects observed in this short term study were the development of skin rashes, and transient depressions of helper T-cell numbers and of T-cell functions in lymphoproliferation assays. The clinical relevance of the immunologic findings is presently unknown since none of the treated patients has developed clinical signs of immunosuppression, such as an opportunistic infection or an AIDS-related malignancy. It will be important to extend our observations and assess the anti-viral activity of DPA in symptomatic patients with ARC or AIDS. However, because DPA depresses T-cell lymphoproliferative responses it should be administered with caution to patients who exhibit impaired T-cell function prior to treatment. Nevertheless, the promising results from this pilot study form the basis for further trials with DPA as treatment for HTLV-III/LAV infection. Several different treatment approaches are currently being explored including low dose daily administration and intermittent treatment schedules.

5. References

- [1] Sarin, P. S., Gallo, R. C., *Cancer Rev.* 1, 1 (1986) – [2] Chandra, P., Sarin, P. S., *Arzneim.-Forsch./Drug Res.* 36 (I), 184 (1986) – [3] Jaffe, I. A., in: *Penicillamine in Arthritis*, O. Ariel, J. McCarty, pp. 502–511, Lea & Febiger, Philadelphia (1985) – [4] Schulof, R. S., Simon, G. L., Szein, M. B., *J. Biol. Resp. Med.*, in press (1986) – [5] Dean, J. H., Connor, R., Herberman, R. B., *Int. J. Cancer* 20, 359 (1977) – [6] Sarin, P. S., Taguchi, Y., Sun, D., *Biochem. Pharmacol.* 34, 4075 (1985) – [7] Chandra, P., Koch, A., in: J. C. P. Weber, A. S. St. J. Dixon, R. Williams (eds.), *Recent Advances with D-penicillamine*, pp. 15–23, Royal Society of Medicine Symposium, London (1974); Verlag G. Braun, Karlsruhe (1975) – [8] Ho, D. D., Rota, T. R., Schooley, R. T., *N. Engl. J. Med.* 313, 1493 (1985)

Acknowledgements

The authors acknowledge Winston Kelly, the study coordinator; the technical assistance of Dao Mai, and Arthur Thornton; Leonidas Leonaridis for performing data computerization; and the nursing assistance of Margaret Lloyd, Mary Anne Nelson, Angela Chan, and Helen Howze. We are grateful to Carolyn Dunham and Margaret Snyder for preparation of the manuscript.

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Stimulation of T-cellular immunity by cutaneous application of dinitrochlorobenzene

To the Editor:

I have collected a series of twenty-six cases from my practice. These cases suggest that topical administration of 1-chloro-2,4-dinitrochlorobenzene (DNCB) to per-

Volume 14
Number 6
June, 1986

Journal of the
American Academy of
Dermatology

Table 1. Alterations of lymphocytic parameters by topical application of dinitrochlorobenzene

		WBC*	Lymphocytes	B cells	OKT11	OKT4	OKT8	OKT4/OKT8
Normal patients (n = 8)	Before	7,984	2,528	237	1,885	960	841	1.32
	After	7,850	2,823	329	2,002	1,087	877	1.42
	Change (%)	-2	12	39	6	13	4	8
"Moderately" suppressed (n = 12)	Before	3,862	1,788	356	1,152	390	799	0.60
	After	3,190	1,849	259	1,402	518	838	0.76
	Change (%)	-11	3	-27	22	33	5	27
AIDS patients (n = 6)	Before	4,308	1,426	185	1,055	175	871	0.21
	After	3,928	1,210	185	886	230	605	0.47
	Change (%)	-9	-15	0	-16	31	-31	124

*All cell counts are given as cells/mm³.

sons of varying immunologic status induces changes in numbers of circulating T and B lymphocytes and T-lymphocyte subsets, as well as improved transformability of these lymphocytes in vitro by exogenous mitogens. The evidence gained correlates with clinical evidence of enhanced T-cellular function. Normalization of other laboratory abnormalities associated with the acquired immunodeficiency syndrome (AIDS), including anemia, thrombocytopenia, and hypergammaglobulinemia, was noted during the course of the DNCB applications and suggests that topically administered DNCB also promotes reconstitution of T-cell immunoregulatory functions in immunosuppressed patients.

Laboratory studies were obtained at intervals both before and after weekly application of 2% DNCB in acetone to the ventral surface of the upper extremities until erythema, edema, and pruritus could be induced by a 1% DNCB solution within 24 to 72 hours after its application to the quarter-sized site. Immediately following administration of the DNCB solution, the site was covered with gauze and paper tape; the patient was instructed to remove the dressing and cleanse the site the following morning. The number of applications administered prior to the appearance of delayed hypersensitivity was roughly proportional to the severity of the immune deficiency, if present.

Alterations of lymphocyte parameters, as well as other AIDS-associated laboratory abnormalities, were frequently found even prior to the development of cutaneous hypersensitivity in immunosuppressed patients, although eventually all patients were successfully sensitized as judged by clinical examination of the application sites. Normal patients (i.e., with initial OKT4/OKT8 values >1.0) and "moderately" suppressed patients (i.e., with initial OKT4/OKT8 values <1.0 but

without diagnoses of Kaposi's sarcoma or opportunistic infections) had increases in total T-cell counts, as well as both OKT4 and OKT8 subsets, resulting in an increased OKT4/OKT8 ratio. The AIDS patient group (i.e., with diagnoses of Kaposi's sarcoma and/or *Pneumocystis carinii* pneumonia who were not receiving any other treatment concurrently) had decreased total T-cell and OKT8 counts but increased OKT4 counts, resulting in approximate doubling of the initial OKT4/OKT8 ratio (Table 1).

Patients with anemia and/or thrombocytopenia underwent increases in red blood cell numbers, hemoglobin, hematocrit, and platelet counts while erythrocyte sedimentation rates and IgG and IgA levels decreased. The immunosuppressed group also demonstrated improved transformability of lymphocytes in vitro to phytohemagglutinin, pokeweed, and concanavalin A mitogens while the *Staphylococcus aureus* mitogen test usually remained below normal values. Patients with Kaposi's sarcoma underwent changes in their mucocutaneous lesions, consisting of reductions in lesional size, number, and thickness, as well as decreased discoloration when DNCB was applied to foci of involved skin. These changes included DNCB-treated as well as untreated lesions and were generally preceded by perilesional erythema, edema, and pruritus. Diminution of the violaceous discoloration began on interfollicular skin, leaving persistent perifollicular violaceous erythema. This anecdotal collection of cases suggests that cutaneous administration of DNCB may prove to be of therapeutic benefit in the amelioration of the immunologic defect in AIDS, primarily or adjunctively.

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[OVER]

PROJECT INFORM
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APR 1 1987

HOW TO OBTAIN DNCEB

The following chemical companies produce DNCEB (dinitrochlorobenzene). One can find out who the local distributor/retailer is by phoning the chemical companies, asking for the division handling DNCEB (dinitrochlorobenzene), and then inquiring for their local sales agent. Since DNCEB is not a prescribed drug nor (as yet) a controlled substance, the only obstacle we have encountered in obtaining it is having a retail (tax) number. Any doctor, psychologist, or for that matter, florist will have a retail (tax) number. The average cost for DNCEB is about \$30.00 for a bottle of 100 grams of crystals. Grade I is immunology quality (99% pure with 1% "inert" ingredients); Grade II is photographic quality (96% pure with 4% "inert" ingredients). Either grade will cause skin reactions.

- 1- SIGMA CHEMICAL
St. Louis, Missouri
(call directory assistance for #)
- 2- J.T. BAKER COMPANY
Phillipsburg, New Jersey
(call directory assistance for #)
- 3- SERGENT-WELCH
Skokie, Illinois
(call directory assistance for #)
- 4- EASTMAN-KODAK
Rochester, New York
1-800-225-5352

(Also there are companies overseas that produce DNCEB—such as AGFA CHEMICAL in West Germany.)

D N C B I I WHY, HOW, and WHEN!

Congratulations on your decision to take charge of your life and your health. Although the medical community is just beginning to recognize this treatment, it is mostly "patient experimental" at this time. The effect of DNCB on "normalizing" the blood counts and helping KS lesions to go into remission have been remarkable. At this time, however, this treatment should not be considered a "cure", but a treatment that will help your own immune system to rebuild itself to the point where it can control the virus on its own. The treatment may not work on everyone, but we know of no one that has experienced any health threatening side-effects from the use of DNCB, so you have little to lose, and a lot to possibly gain.

It is recommended that you discuss your use of this treatment with your physician so that he is aware of it. If possible, get a complete blood workup including helper/suppressor ratios as this is about the only medically acceptable way to measure the effectiveness of the treatment. The blood workup should be taken just before starting the protocol, and then every two/three months thereafter as a measurement. Ask your doctor for a copy of the results, as we would like to compile the results of our experiences in order to interest the medical community to pursue further studies.

Now that you're ready to start, what do you do, and what do you look for? Assuming you have 2% acetone solution and the Vaseline Intensive Care Lotion formula (see recipe) at your disposal, you are ready to "paint". Both formulas should be kept in airtight containers, the acetone in glass and refrigerated (4-6 months shelf life) and the Vaseline Lotion formula can be kept in a plastic container (shelf life indefinite—do not refrigerate).

* Select a spot on the ventral (underside) surface of the arm between the shoulder and elbow and, using an applicator like a Q-tip, apply a coat of the DNCB acetone solution to an area about the size of a quarter. Cover with a gauze bandage, leave on for two to three hours initially, then wash area with mild soap and rinse well.

* At the application site, within 24 to 72 hours, you should eventually become reactive. When you are fully reactive, the site will be pink or red like a sunburn, somewhat puffy looking, and possible itch. This may take a few months, so don't worry if little happens the first month or so. Even if you do not visibly react, you are modulating your immune system and eventually your T-cells will respond. You may feel a slight tingling or burning sensation for 15 to 30 minutes after an application, which is normal. However, if you experience definite pain, wash off immediately.

* After your initial applications, it might be necessary to adjust the time or the concentration of your application. If you get no reaction at the site, double the time on your next application. If you get a very strong reaction or blister, cut back on the application time or the concentration, or both.

* Alternate arms weekly always using different application sites. It is unnecessary to paint more than once a week after you become reactive, but the painting should be continued regularly for the most effective immune modulation.

Remember that it is thought that the continuous skin reaction is causing the immune benefit—not the DNCB directly—but the body's induced immune response to the DNCB skin applications.

KS APPLICATION SPECIAL NOTES

If you have Kaposi sarcoma and will be applying the Vaseline Lotion formula to your lesion sites, here are a few special notes for you. In a way, you're lucky because you will be able to see results to measure your success. In most cases the lesions will simply decrease in size and depth, and start to change color from the red/purple to brown, and then fade away to a freckle. However some people have also reported that some lesions that are basically on the skin surface have become like a scab and literally peeled off. That's exciting!

* Do the patch application each week and, in addition, start applying to your lesions beginning with the ones you hate the most. The lotion should be applied to the lesions only, you don't need to cover a larger area outside of the lesions themselves. Leave the lotion on for a couple of hours and then wash off. If you have a lot of lesions, you might want to set up a rotating schedule rather than hit them all at once.

REAPPLY THE LOTION TO THE LESIONS ONLY AS OFTEN AS NECESSARY TO MAINTAIN A SLIGHT REACTIVE AREA AROUND THE LESION SITE! The time between applications will vary from person to person and also from lesion to lesion. Some people may require almost daily applications. As you become more reactive, it may also be necessary to cut back the amount of time you leave the lotion on the lesions. Your goal at a lesion site is to promote a constant but mild reactive condition, without causing the lesions to blister or develop a dermatitis condition.

* Some studies have indicated that untreated lesions can respond nearly as well as treated ones, so if you have any open lesions, do not apply the lotion to them! Let your improved immune system fight them from within.

* If you have any lesions that are not normally covered by clothing and are socially visible, bear in mind that a small area around the lesion will become reactive also, i.e. red and puffy. This will make them much more noticeable. So if you have any on your face, hands, etc., you might want to think before you paint them and concentrate on the ones on your legs, arms, and trunk instead.

The results from previous DNCB users that have KS indicate that there is usually no dramatic increase in blood tested T-helper cells until the KS is in "clearance" or remission. The doctors feel that this is because the T-cells are concentrated at the lesion sites and don't become "free-floating" in the blood until the cancer is conquered.

Hopefully this information will answer most of your questions, but if you have any more just call your DNCB contact from the attached networking list. They will do their best to answer or find out for you. Good luck and Good Health!

(Our thanks to Dennis and the DNCB "Free Clinic" folks in Minneapolis for drafting the original of these directions.)

REVISED RECIPE FOR MAKING DNCB VASELINE INTENSIVE CARE SOLUTION
(AS ORIGINATED AT ST. VINCENT'S HOSPITAL IN NEW YORK CITY)

Utensils Needed:

- Pair of plastic gloves and asthma-type mask to avoid breathing in crystal particles during measuring
- A scale capable of measuring out grams (type often used by "drug dealers" and available at most "headshops")
- A glass beaker (for mixing in)
- A stirrer (such as a glass wizzlestick)

Supplies Needed:

- 2.4 grams DNCB crystals (preferably Grade I, 99% pure)
- 1/4 cup #ethanol alcohol
- One 10 oz bottle VASELINE INTENSIVE CARE lotion
- Glass or chemical-resistant plastic bottles for storage and distribution (whatever size suitable)

Directions:

First in glass beaker dissolve the DNCB crystals in the *ethanol. Stir until all crystals are thoroughly dissolved (which takes a long time unless the ethanol is room temperature or warmer). Then take four teaspoons of this 2% percent ethanol solution and add to the 10 oz VASELINE INTENSIVE CARE lotion and stir well. Pour into containers for distribution and storage. The result is a 2/15ths of 1% final solution. (Store remaining 2% DNCB in ethanol in tightly closed bottle in the refrigerator; the prepared VASELINE lotion does not need to be refrigerated.)

This recipe obviously makes enough solution to treat a good number of people with AIDS and ARC for quite some time. Dr. John W. Angers of the Human Immunology Foundation at St. Vincent's Hospital in New York City developed this formula and reports good results with it. Dr. Mills has confirmed these results after testing and conferring with Dr. Angers. Patients reportedly only have to leave the VASELINE solution on their arms (or lesion sites) for several hours under a bandage to achieve the same skin reactivity as with the acetone solutions left on overnight.

*To make a 2% acetone solution for arm patches simply use the same basic recipe exchanging the ethanol for an equal amount of reagent acetone. (However, only the ethanol solution should be mixed with the Vaseline lotion and both basic solutions, ethanol and acetone, must be kept refrigerated.)

#One group of patients in Santa Barbara reports success using Smirnoff's vodka! (Smirnoff's is about 50% ethanol or "grain alcohol".)

Dated: November 17, 1986

(OVER)

DNCB DIRECTIONS FOR USE (12/12/86)

DNCB in acetone or ethanol solution must be kept refrigerated (but do not freeze). It will keep potency for approximately three months in an airtight refrigerated container. (Acetone must be kept in glass and NOT plastic bottles.) DNCB in Vaseline Intensive Care lotion-based formula does not need to be refrigerated, but should be kept in an air-tight container and stored away from excessive heat and strong light.

1. Apply to ventral (underside) surface of arm, between shoulder and elbow, using Q-tip swab dipped in DNCB solution. Paint only a quarter-sized skin area.
- 2a. (2% or 1% acetone solutions.) Cover area with 2-3 inch gauze pad. Leave on overnight or just as long as necessary to obtain good reaction without blistering. (If you blister dilute the solution with more acetone.)
- 2b. (2/15s of 1% in Vaseline Intensive Care lotion-based solution.) Cover area with 2-3 inch gauze pad. Leave on two hours or just as long as necessary to obtain good reactions without blistering. (If you blister dilute the lotion with more Vaseline.)
3. Remove gauze pad and wash area with soap and water.
4. Alternate arms at least weekly. It is unnecessary to paint more often than once or twice weekly unless you have KS. (See KS instructions below.)

You will want to see an "allergic" reaction (pink or red in color) in the area painted. It may take several weeks (or even months) to achieve, but do not be discouraged. Eventually, everyone has reacted. Painting should continue on at least a weekly basis for the most effective immune-modulation. Think of the weekly or twice weekly painting with DNCB as comparable to, say, maintenance insulin shots for diabetes: neither treatment is a cure, but rather a control of the ongoing disease process.

If you have K.S.:

Lesions should be painted daily (starting immediately, even before arm patch reactions are noted) with 2/15s of 1% Vaseline Intensive Care lotion-based formula until "clearance" (i.e. visible remission) is achieved. If there are many lesions, a rotating schedule of painting should be performed instead of painting every single lesion every day: lesions on one leg one day; other leg the next; chest the following; then the back; then again on the first leg, and so on. After all the lesions have "cleared", return to just the arm patch (at least weekly) immune-modulation paintings as described above (either acetone or lotion formulas).

Remember that it is thought that the continuous skin reaction is causing the immune benefit—not the DNCB directly—but the body's induced T-cell response to the DNCB skin applications.

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JUN 26 1987

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Rev. 6/15/87

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PROJECT INFORM
25 TAYLOR ST. #618
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JUN 26 1987

PI perspective

PROJECT INFORM
San Francisco, California

MAJOR FDA PROPOSAL ON EXPERIMENTAL DRUGS

Gay Activist Groups Divided in Response

In what appears to be a major shift in policy, FDA commissioner Frank E. Young proposed a change in regulations which would allow greatly increased access to experimental treatments for patients with life threatening illnesses. The new policy, submitted for public comment on March 16, 1987, would permit drug companies to sell certain experimental medicines to two classes of patients. Slightly different regulations would address (1) patients with "immediately life-threatening diseases" (including "advanced cases of AIDS"), and (2) "serious illnesses" (examples quoted in the proposal are Alzheimer's disease and multiple sclerosis; many assume that ARC would also qualify).

Two motives of the proposal, in the words of the FDA, are "to provide promising new drugs to patients with serious diseases... for which there are no alternative therapies, and "to provide sufficient incentive for the rapid development of drug and biological agents." The FDA feels it is acting with an "abundance of caution" and has invited public comment.

Many gay groups, including Project Inform, support this policy as an important response to our needs and the most immediate means of making treatment available to all in need. Presently, only a very small number of AIDS and ARC patients have had access to experimental treatments, while all others have been asked to "wait and see." Thousands have expressed their willingness to accept some degree of risk and uncertainty from treatment options as an alternative to the certainties of AIDS. Other gay groups, such as the National Gay and Lesbian Task Force (NGLTF), have come out in opposition to the proposal, believing it will invite profiteering by drug companies and slow the research process.

Project Inform encourages dissenting organizations to carefully consider their positions. If the proposal is flawed in detail, let's fix the problems. But to reject it outright would be a disservice to AIDS and cancer patients everywhere who have begged for access to experimental treatments. The proposal can only increase our options.

Since this proposal has long reaching implications, and since it has met with conflicting responses within the gay community, a lengthy analysis follows. The reader is invited to study the matter in detail and form his or her own opinion. Whatever conclusions are reached, we encourage you to express your views directly to the FDA in Washington and to any gay groups you feel are not adequately representing your views.

(continued)

PI perspective is a new publication of Project Inform. It will replace the sporadic "special issue" mailings we have sent in the past and will provide information on key issues we think you'll be interested in. For our first issue, we have borrowed heavily from the look of the D.A.I.R. Update, which some of our people also write for.

In this issue:

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Major FDA Proposal (continued)

What Does the Proposal Say?

Specifically, the plan would permit the sale of experimental treatments to seriously ill or life threatened patients under the following conditions: when

- "no satisfactory alternative drug or therapy is available to treat the disease"
- "the drug is under investigation in a controlled clinical trial under an IND (Investigational New Drug application) in effect for the trial"
- "the sponsor of the controlled clinical trial is pursuing marketing approval (full FDA approval) of the investigational drug with due diligence"

Two additional criteria apply separately to the two levels of illness addressed:

For "serious diseases:"

- the commissioner may deny a request for treatment use (of the drug) if he or she finds that there is insufficient evidence of safety and effectiveness to support such use"

For immediately life-threatening disease:

- "the commissioner may deny a request for treatment use if he or she finds that, on the basis of clinical data or other reliable scientific evidence in the IND file, the drug clearly does not provide a therapeutic benefit; or the drug would expose the patients... to an unreasonable and significant additional risk of illness or injury."

The proposal describes two contexts in which the sale of experimental drugs would be permitted: (1) during controlled clinical trials, and (2) under a treatment IND (one of the last stages in the testing of a drug before full approval). To sell a drug during the clinical trial period, a drug company would be required to obtain prior approval by the FDA, which would be granted "only upon a showing that sale is needed for the sponsor to undertake or continue the clinical trial." For drugs under a treatment IND, the drug company would automatically have the right to sell the drug as long as it complies with certain designated safeguard against commercialization and notifies the FDA.

Finally, and perhaps most importantly, the proposal contains a provision allowing the FDA "to withdraw authorization for sale if the price charged is manifestly unfair or if the conditions underlying the initial authorization for sale are no longer satisfied."

Project Inform General Comments:

As written, the proposal reaffirms the FDA's total authority to decide what drugs are released. The lack of specific written criteria defining adequate safety and efficacy says that nothing other than the Commissioner's opinion is necessary to block the sale of a drug. While this authoritarian perspective may be stricter than some of us would like, it neatly sidesteps the creation of legal language permitting release (in which the drug companies would certainly find loopholes). In the end, drugs could be prohibited simply because the Commissioner says so, based solely on his or her view of the evidence. Given the FDA's track record regarding safety, there is little reason to believe that the Commissioner would suddenly open the floodgates to unsafe or worthless drugs. Existing criteria for final release and full marketing approval of drugs would be unchanged by this proposal.

The Controversy

Since public commentary was invited on the FDA proposal, gay groups have taken positions both for and against the proposal. Some groups support it on the bottom line, despite concerns with one aspect or another. Others simply oppose it. It should be assumed that all groups are acting in good faith and with the best interest of their constituents in mind. If there is any failure here, it has been the lack of a national dialogue between the groups before positions were taken. Some groups have fought specifically for just this type of proposal for years, while for others, the proposal is only one item on a diverse agenda. We will attempt to describe our view and that of others below. The reader must know, however, that Project Inform, on the balance, supports the proposal.

Project Inform and other groups find this proposal, although less than perfect in some regards, to be a clear response to the demands gay people have made for improved access to experimental treatments. Similar interests have long been expressed by cancer patients and others with life threatening diseases. The policy represents a major change of philosophy for the FDA, a victory which was credited to the efforts of AIDS patients by none other than the conservative Wall Street Journal.

The position of the National Gay Rights Advocates (NGRA), based in San Francisco, was not inconsistent with our own, despite some initial misunderstandings. Press reports of the NGRA position implied that the

Major FDA Proposal (continued)

group opposed the proposal outright. Discussion with group members, however, clarified that they were in support of most aspects of the proposal, but had important reservations about allowing drug companies to charge for the experimental treatments. Others, such as AMFAR in New York, have expressed agreement but have sought additional clarification on matters of drug safety.

The National Gay and Lesbian Task Force (NGLTF), a Washington based lobby for gay causes, rejects the proposal as an attempt to permit profiteering by drug companies. Before publishing our official position here, we studied NGLTF's written statement and spoke with members of the NGLTF Board of Directors. Those we spoke with did not take strong stands but instead referred us to Jeff Levi, executive director, who they felt could explain their position. Martin Delaney of Project Inform discussed the NGLTF position with Jeff Levi, and our analysis includes information gathered in that conversation.

NGLTF voiced four major points:

1. *(a) It is wrong to allow drug companies to sell unproven treatments; (b) people shouldn't have to pay to take part in experimental drug trials; (c) only those who can afford them will have access this way, and the poor will be excluded.*
2. *(a) Under the new proposal, the burden of proving drug safety falls upon the FDA, instead of the drug companies. (b) This will result in increased deaths and illness from dangerously unproven drugs.*
- (3) *Ineffective drugs will be released; no one will be willing to volunteer for clinical trials if they can purchase treatments.*
- (4) *(a) The needs of AIDS patients can best be met by expanded clinical trials. (b) Jeff Levi pointed out that NGLTF has always supported more opportunities for admission to clinical trials. He felt that if current funding were used properly, as many as 10,000 positions would be available in such trials.*

Our response to each NGLTF point:

NGLTF point #1: *(a) It is wrong to allow drug companies to sell unproven treatments; (b) people shouldn't have to pay to take part in experimental drug trials; (c) only those who can afford them will have access this way, and the poor will be excluded.*

(A) A major motive of the FDA proposal is to make it financially feasible for more drug companies to participate in research. Currently, only the wealthiest drug companies can participate in AIDS research because of the high cost and financial risks. The FDA feels (and we agree) that more competition will enhance the speed of research. While we are reluctant to speak on behalf of the interests of drug companies, we do recognize that they are motivated by profits, not humanitarianism. If researching a solution for a particular illness is not at least a break-even proposition, there is little interest in doing the work. This phenomenon is well known by people with relatively rare illnesses, who dismay at the lack of research on their problem. The proposal seems to present a reasonable compromise and should give companies an added incentive to help solve the mysteries of AIDS.

The FDA proposal permits automatic charging only for drugs approved for treatment of "serious" illnesses, which must meet higher criteria of safety and efficacy than drugs for "life threatening" illnesses. Such drugs are far from unproven and must demonstrate a degree of efficacy before being allowed for sale. Sale is permitted of drugs for "life-threatening" illness only if the drug company demonstrates that it needs to be compensated in order to continue clinical trials. This provision, we feel, will contribute to rapid advances in medicine for illnesses which don't present big profit opportunities. Increased options can only benefit AIDS and ARC patients and break the monopoly of the big drug companies (many of the biggest drug companies OPPOSE the FDA proposal, since it will increase competition from smaller firms). The current monopoly on AIDS treatments enjoyed by Burroughs-Wellcome has resulted in the outrageous prices charged for AZT and must be broken the only means known to our system—competition.

(B) People are not always interested in participating in clinical trials, and addressing people as research subjects is not the intention of this proposal. Most people are interested in getting TREATMENT, not being guinea pigs. Companies simply can't afford to give free drug to the numbers of people currently afflicted by ARC or sero-positive (millions). People have already voted loudly and clearly on this point—they are willing to pay. Tens of thousands have already purchased unproven treatments, abroad and within the U.S. We must first make the drugs available; for those who can't afford them, we find the money (see point C below). If we insist that drug companies do it all for charity, few will

Major FDA Proposal (continued)

have any interest in the AIDS market and we will be at the mercy of Burrough-Wellcome style monopolies.

(C) The cost of paying for such treatments is a worthy, but separate issue. Is NGLTF suggesting that NO ONE should have access to treatments until they are provided free to EVERYONE? If so, they are entitled to pursue such an agenda, but we believe that not a single gay life should be sacrificed on its behalf or while awaiting its acceptance. This suggests the kind of *big brother* thinking we have fought against in Washington for years. NGLTF could better spend its energies demanding that insurance companies and federal funding be required to pay for such treatments, rather than acting to withhold them from those in need. This is what they are already doing regarding AZT pricing.

It is precisely because of the lack of this proposal's provisions that we are presently being overcharged for AZT. Had the proposal been in effect, the FDA could have released AZT under it and it would then be subject to the Commissioner's ruling on the fairness of its price. Under the current system, it is out of his control. In the long run, we cannot reasonably expect government funding for all our medicines under the present medical system, particularly in the present and foreseeable economic climate. Until subsidized national health care is a reality (and it's not in the near future), we must learn to negotiate over prices at the source as well. This policy creates a mechanism for doing so.

NGLTF point #2: (a) Under the new proposal, the burden of proving drug safety falls upon the FDA, instead of drug companies. (b) This will result in increased deaths and illness from unproven drugs.

(A) Under the proposal, the FDA need not DISPROVE safety to prevent a drug's distribution—there is no "burden of proof" issue here. The Commissioner need only be of the OPINION that a drug's safety record is unacceptable. The Commissioner retains dictatorial control over safety. Given the FDA's excessively over-protective history, there is little reason to believe that the agency will suddenly open the flood gates to dangerous remedies.

(B) Short term safety must be established by Phase One trials before release under the policy. Long term safety may not be fully proven under the proposal, but it is not proven under current treatment INDs either. The long term affects of AZT are completely unknown, yet thousands are taking it. When near certain death is the alternative, patients (and their physicians) must be in-

formed of potential risks and benefits, and must be allowed to make their own choices. The right to informed consent and access to treatment must not be abridged by any bureaucracy in Washington.

NGLTF point #3: Ineffective drugs will be released; no one will be willing to volunteer for clinical trials if they can purchase treatments.

It is possible that less than fully effective treatments might be released under the policy, although there is plenty of provision against it. The commissioner again retains unquestioned authority to remove treatments (by placing them "on hold") which fail to show evidence of efficacy. The risk entailed by possible ineffective treatments must be weighed against the very substantial benefit of early access to effective ones. How many thousand gay men would be alive today if AZT had been released a year earlier? How many thousand more will live if DDC and other promising new drugs are released in June of 1987, instead of 1988 or 1989? How many hundred thousand (or million) will not progress from ARC to AIDS if they get treatment now?

People will volunteer for clinical trials for the same reasons they always have: FREE treatment and free medical care, and access to the newest and most promising treatment options. Not one more gay man should be asked to run the risk of getting a placebo in a clinical trial. Too many have already been made into guinea pigs lured by hopes of getting access to treatment. Should we restrict access to treatment to make volunteering for clinical trials more attractive? Whose interests does this represent? Certainly not those of the sick. The clinical trial process, in fact, is currently being misused because of this desperation and lack of treatment options. Recent trials of Ribavirin for LAS patients were rendered almost meaningless by the inclusion of large numbers of patients who were much sicker than the trials called for. Sympathetic physicians misrepresented patients' health status desperately trying to get treatment for them. Clinical trials, particularly for ARC and LAS, will be rendered more effective by this proposal by removing the desperation factor.

NGLTF point #4: (a) The needs of AIDS patients can best be met by expanded clinical trials. (b) Jeff Levi pointed out that NGLTF has always supported more opportunities for admission to clinical trials. He felt that if current funding were used properly, as many as 10,000 positions would be available in such trials.

Major FDA Proposal (continued)

(A) IF an alternative proposal and program were at hand to provide treatment for all who wish it, and IF everyone were interested in participating, we could seriously consider it. But there is no such alternative, and in fact, the medical system is logistically incapable of providing one. The FDA proposal is the only option before us. Treatment—not opportunities to be research subjects—is what a great many people want and have an absolute right to.

(B) Treatment options are required for far more than 10,000 people. All ARC, LAS, and (some say) seropositive people have a need. The sooner it is met, the sooner the curve of new AIDS cases will flatten out. Waiting until full-blown AIDS before providing treatment options is a crime and runs counter to what's known about treating every other viral disease. Early treatment is the best long term hope, and we must press the FDA to make sure it is addressed by the current proposal.

In Conclusion:

While we understand and respect NGLTF's positions in this matter, we disagree with their conclusions. Some of the objections appear to be based more in suspicion than a clear reading of the FDA proposal. Project Inform is certainly not known to be a pushover for FDA views (ask Commissioner Young about us), yet we feel this proposal is proper step in the right direction. For a better defense of NGLTF's views, ask for their explanation. If you support the FDA proposal, write to Commissioner Young at the FDA to let him know, lest he believe that NGLTF represents your views. Write to us if you take issue with our view. And write to the National Gay and Lesbian Task Force or other groups to ask their support of your views.

Send comments to NGLTF

National Gay and Lesbian Task Force
1517 U. Street NW
Washington, D.C. 20009
(Phone: 202-332-6483)

Send comments to the FDA at:

Dockets Management Branch (HFA-305)
Food and Drug Administration, Rm. 4-62
5600 Fishers Lane
Rockville, MD 20857

FDA Rejects Ribavirin – What It Means

As many of you may have noted, Ribavirin has suffered a serious setback in the FDA licensing process. On April 10, the FDA sent a letter to the manufacturer, ICN, rejecting its request to have the drug released under a treatment IND for patients with lymphadenopathy syndrome. The request was based on last year's study of 163 patients in four centers, in which 10 people in the placebo (control) group progressed to AIDS, while none receiving 800 mg. of the drug did so. The data from the study has been presented at several scientific conferences around the country since January. On the surface, the FDA's action appears puzzling. At the same time, reports are rampant that the trials of the drug on ARC patients are inconclusive.

Business reports and brokerage house newsletters have told a variety of stories. What does all this mean? To get the answers, Project Inform spoke with numerous sources, including physicians who conducted the study, company spokespeople, and independent statistical experts. FDA spokespeople declined comment, saying the information was "privileged." (the FDA did confirm that it had received the data from the ARC trial during the week of April 6 and was currently analyzing it). We have attempted to discount information which is self serving to any of these sources in our analysis, since there is plenty of it on all sides of this issue.

In short, the FDA has ruled that the data submitted from the LAS trial was insufficient to justify a Treatment IND. Although the data looks strong on the surface, debates have arisen over the details. Specifically, it appears that a large number of people, perhaps as many 40, who took part in the trial were sicker than the study entry requirements permitted. Many patients had T-4 counts of less than 200, several less than 50, some less than 20. Many of these same people also had a variety of secondary infections and other symptoms which should have excluded them from the trials. The implication is that physicians or researchers understated their situations in a desperate effort to get them in a trial, which for many was the only access to treatment. This is a phenomenon we have long been aware of, and it was noted in the Bay Area Reporter in our response to a local doctor's early criticisms of the study. It is a sad testimonial to the lack of options provided by the current system.

While this was enough of a problem, it was further complicated by the randomization process used for placing patients in the 3 different treatment groups

FDA Rejects Ribavirin — What it means (continued)

(placebo, 600 mg. , and 800 mg.). While the mean (average) T-4 counts of the groups were quite equal at the start of the study, a disproportionate number of the people with T-4 counts below 200 fell into the placebo group. A similarly disproportionate number of those with counts higher than average were also in the group, thus resulting the seemingly appropriate average. There is no accusation from anyone that this effect was deliberate, since it would be virtually impossible to do it on purpose (no one connected with the study knew which group was getting what treatment).

Yet, the result is the same: with many of the most sick patients in the placebo group, it provides an explanation for the high incidence of AIDS in that group. Similarly, the lack of these patients in the drug group suggests that that is why no one progressed to AIDS — not because of the effect of the drug.

At this point, it would seem to be difficult to disagree with the FDA's conclusions. Yet, talking to biostatisticians told a very different story. The balance of sicker people in the placebo group, they said, was simply a factor that had to be accounted for in the analysis of data, which it was. In fact, we were told (not by anyone connected with ICN or the study), that such problems are fairly common in clinical trials and routinely adjusted for. ICN officials and the independent researchers who conducted the study insisted that this issue was known to the FDA and to scientific groups since January, and that no one seemed to see any problem with. Several people claimed that the problem is a classical and common confrontation between statisticians and clinicians. Statisticians say — "Fine, here's how you compensate for the imbalance, and here's what the results mean." Clinicians say "When you take away the sicker people, what's left isn't enough to prove anything."

In the confidential scientific analysis of the study, which Project Inform has obtained a copy of from outside sources, (after ICN refused to give us one for months), it is clear that this effect was known and adjusted for statistically as early as January. It was not, however, described in ICN's January press conference, and had it been, it probably wouldn't have been understood very well. The significance of the effect depends a great deal on how you choose to look at it. When the very sickest people, those with T-cells under 20 are removed from the study, a strong case is still made for the drug. When the line demarking the "very sick" is drawn (arbitrarily, as the FDA drew it) at T-4 counts of 200 or less, then the drug's efficacy, looks insignificant. If the line is

drawn instead at T-4 counts of 250, then the case for the drug looks stronger again. When all the people with T-4 counts over 289 (the mean or average) are taken out of the figures to compensate for those most well, the case for drug efficacy is again good.

The bottom line? This is very confusing. There appears to be legitimate difference of opinion among honorable people on all sides of the issue. We understand that there was great debate on it within the FDA as well, but that the clinical factions, led by Commissioner Cooper (a long time Ribavirin critic), not the statisticians, ultimately carried the day. We contacted two of the independent researchers who conducted the study and they remain adamant that the study proved the drug's effectiveness. They said the other two researchers agree. We spoke with ICN regulatory officials, who seemed the least upset by the whole mess. In their words, "Every letter from the FDA is a rejection and a request for more information until the letter comes which gives approval. More information and analysis is requested, more is being supplied. We simply aren't big enough or well enough staffed to provide the kind of in-depth analysis required overnight. Responding to FDA requests on the LAS study diverted our resources from analysis of the ARC study and delayed its submission."

One person who we might say was proven right in all this was Dr. Paul Volberding of San Francisco General Hospital. More than six months ago, he predicted (in response to our question) that the Ribavirin study of LAS and ARC patients would have a very difficult time proving anything to the FDA, since the studies wouldn't have the clearly defined "progression to death" measure that is used in studies of full blown AIDS patients (such as the AZT studies). Progression to AIDS (from ARC and LAS) would be a useful measure, but if study subjects are accurately selected, not enough can be predicted to make that progression in the time of a typical study. Thus, the study ends in scientific debate. There is plenty of precedent for this in FDA files.

The LAS and ARC studies continue now as "open" trials, which means that patients continue receiving the drug. There are, however, no controls, since patients on placebo have all been switched to the real drug. While this on-going study will provide additional data about progression to AIDS, it will not have the impact of a control study.

FDA Rejects Ribavirin – What it means (continued)

What about the ARC study?

Reports from all sources, though unofficial, suggest that nothing of importance happened to the people using the drug in that trial. An unattributed press report in the New York Times suggesting that people on the drug actually did worse is not true and is not supported in the least by study data. The rumor of harm began, apparently, from reports that some patients in the ARC trial died, including some in the drug group. As best we can tell, this is another manifestation of the phenomenon experienced in the LAS trial, in which very sick people were force-fit into the trial in an effort to get treatment for them. It appears that several full blown AIDS patients were deceptively admitted into the ARC trial.

What Does all this Mean to People Using Ribavirin?

This is the toughest question. We see three levels of answers.

(1) *LAS PATIENTS*: at worst, the FDA is saying that insufficient evidence has been shown to justify release of the drug for LAS patients. That doesn't mean that it is harmful, or even that it is worthless. If the drug, especially in combination with an immune booster, is working for you, there is little reason to change your therapy. We have seen far too many reports of good results to suggest that people should simply walk away based on this month's FDA position. Researchers will present new data on the LAS and ARC trials at the scientific conference in San Diego on May 2, 1987. And the opinion of the researchers (who conducted the study) that the case for efficacy is still strong should not be ignored. These researchers have virtually no motive for dishonesty, since there is no dishonor for them in conducting studies which disprove a drug. FDA positions in such matters is routinely negative until a drug is finally proven to its satisfaction, which often takes many years.

From our viewpoint, it is also not surprising that the FDA would choose an arbitrary perspective which led to a negative conclusion. Factions within the FDA have been opposed to Ribavirin from day one, and those researchers and officials who have discouraged people from using it for the last 3 years have a powerful motive for proving themselves right.

(2) *ARC PATIENTS*: though the data isn't public yet, there is little reason to believe that it will be positive. It appears that Ribavirin, used alone at 800 mg per day, is insufficient for ARC patients with serious symptoms. If

you are qualified for AZT (T-4 cells under 200), you might certainly apply for it as an alternative. If you don't experience side effects (many people don't) or can tolerate them, AZT would seem to be a reasonable choice. If AZT isn't possible or can't be tolerated, Ribavirin should probably be used only at higher dosages and/or in combination with other drugs (see point 3 below). AL 721 is finally becoming available in some form and has many strong believers behind it; DTC (Imuthiol) is making big press lately as a powerful immune booster and is available now; trials of DDC (dideoxycytidine), reportedly better than AZT and having fewer side effects, are beginning in many cities. Under new proposed FDA guidelines on experimental drugs (see the other article in this update), DDC could become available as early as this summer (unless opposing groups have their way and see the proposal rejected).

(3) *FOR ARC AND LAS PATIENTS*: proper dosage is a major factor that hasn't been given enough consideration. Had Ribavirin been tested at a dosage which permitted the level of serious side effects deemed acceptable in AZT tests, we suspect a very different picture would have arisen from the trials.

Before the Ribavirin trials began in 1986, Project Inform disputed the proper dosage with ICN officials. Prior to their trials, no one we knew believed that 800 mg. would be an effective dosage, not us, not users, not even the NIH. Yet company officials were frightened and excessively cautious in light of the side effect disaster caused by Suramin in later 1985 and chose to stick with the lower dose. They felt a good safety record was more important than good efficacy, since they could always retest at higher doses, but that they couldn't recover from a bad safety experience. We disagreed and still do, though we felt it responsible that we at least report the dosage being used in clinical trials without trying to persuade people one way or the other. We certainly didn't want to be blamed for serious side effects due to bad dosage advice if we were wrong.

Now, we're not so sure. Before the trials, most people used 1200 or 1800 mg of Ribavirin in combination with Isoprinosine or other immune boosters. Many used the drugs intermittently at 1800 mg, going off the drug for 5 days after every 5 or ten on it. This seemed to work very well and still does for many people. We know for a fact that many people tolerate doses higher than 800 mg. daily for long periods without side effects, though we also know some who experience side effects beginning at 1000 mg. Several physicians we know believe

FDA Rejects Ribavirin – What it means (continued)

the proper way to use this drug is to find each person's own tolerance level. They do this by gradually increasing the dosage until evidence of significant side effects (usually a 15% or more drop in hematocrit) shows up, and then reducing the dosage in 200 mg increments. At each increment, they wait for about two weeks and do blood tests to see if the side effect is lessening.

Some people—in fact all who have tried it—report that they have virtually eliminated anemia as a side effect by monitoring their testosterone levels, and taking testosterone injections to keep their levels normal. Many AIDS and ARC patients, they have found, have depressed testosterone levels. Testosterone stimulates red cell production, and thus seems to compensate for any anemia caused by Ribavirin. They also report it makes them hornier, but, hey, what's one more side effect, right? Whether this result can be achieved for AZT patients is unknown, since the anemia they experience is of a different type than that of Ribavirin users. People using this approach, however, need to be careful not to exceed normal testosterone levels, since doing so might be immuno-suppressive.

The Bottom, Bottom Line.

Ribavirin is certainly not dead in the licensing process, though it has lost this round. The FDA response is a disappointment and has caused people to reconsider their therapy. Most long term users we know haven't changed their opinion or their therapy, since their beliefs are based on personal experience rather than FDA or statistical arguments. People who have only recently begun using Ribavirin and who may not have seen results yet are more concerned. We suggest you consider your options and make an informed, personal decision after considering all the facts and viewpoints.

For those who want it, we can supply copies of the document we have obtained which details the complete Ribavirin study. Although we didn't get this from ICN, it must be based on their internal documents and was probably written by Dr. Roberts of New York, one of the investigators. Since it is a 40 page document, we have to ask a small donation (\$5) for reprints.

ADDENDA: Ribavirin Pricing

Mexico is locked in a classic wage/price spiral. The government is giving wage increases every 3 months, and allowing compensating price increases. Thus, the cost of Vilona (Ribavirin) is up again. Best prices (\$30.90 per box) are currently at Regis Pharmacy. This

price will spiral downward over the next 3 months as the peso continues to fall.

PROJECT INFORM: As Bad as the FDA?

We are under increasing and possibly appropriate criticism about the speed with which our own study results are reaching the public. Some say we've become as slow as the FDA. Ouch!

Rest assured, we are not hiding anything. Analysis of this very complex survey is far more difficult than we imagined. If we could do it over again, we would develop a much simpler survey instrument, although that would also make it less complete. We have completed frequency tallies for 125 valid surveys and are currently establishing parameters for analysis. We would like to have still more surveys, since this makes the data more valuable. If you haven't sent yours in, PLEASE!

There are hundreds, even thousands of possible correlations to look at it. We are meeting regularly with statisticians to get the work done. The flurry of greatly increased business at the PI office has further complicated matters. We apologize profusely, and in light of the FDA dispute, are making every effort to get our data together and reported to the public.

We can't say much else except that we're moving as fast as we can and will have at least some of the results in your hands before the summer solstice. For fairness, we will include an alternative analysis of the data as supplied by a respected local skeptic. Forgive us, for we have gotten in just a little over our budgets; we are coming up for air very, very shortly.

COMING VERY SHORTLY (to your mailbox:

New data sheets on Imuthiol (DTC), AL 721, and AZT.

We welcome any comments on our new mode of communication. Write to us at:

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