

Project Inform
San Francisco, California

New Virus Spreading in DC: Common Sense

Federal officials have demonstrated early signs that a new common-sense mentality may be infecting their thinking. In sharp contrast to its typical style, two recent FDA decisions give hope that rational, if not timely, behavior might be expected in at least some future decisions. One action — the Treatment IND approval of aerosolized pentamidine — was handled correctly on the first attempt and showed a refreshing new attitude toward preventive medicine and a willingness to play ball with the National Institutes of Health. In a far less laudatory example — the handling of ganciclovir — FDA eventually did the right thing, but only after its initial decision set off a firestorm of criticism. Although the agency’s performance in these matters does not guarantee future wisdom, they imply that someone in Washington is listening. Limited as they are, these positive steps should be recognized and applauded for the hope and they offer for the future and as evidence that AIDS activism is not in vain.

Despite these signs of growing enlightenment, we must not believe for one moment that the battle for access to treatment and FDA reform is over. HIV-infected people may still be dying needlessly who could be better served by a more rational and realistic regulatory policy (see *“Foscarnet: New Thorn in the FDA’s Eye”* and *“Seven Critical Issues at FDA”*)

The Aerosol Pentamidine Decision

In mid-February, FDA approved a Treatment IND for aerosolized pentamidine - “aeropen” - on the basis of data submitted by the San Francisco County Community Consortium (a “physician-initiated” community research group). Although not mentioned publicly by FDA, data from a similar study by New York’s Community Research Initiative (a “patient-initiated” research group) may also have contributed to the decision.

Limited as they are, these steps should be recognized and applauded for the hope and they offer for the future and as evidence that AIDS activism is not in vain.

The approval formally makes the drug available to everyone who has already had pneumocystis pneumonia (PCP), to everyone else with AIDS, and anyone whose T4 count has fallen below 200, as preventive medicine.

We see at least two signs of new thinking in this decision. First, approval for use by anyone with fewer than 200 T4 cells — without a prior bout of PCP — signals a commitment to preventive medicine, an approach not previously acknowledged by FDA in AIDS matters. In fact, there is little prior FDA support at all for *primary prevention* (preventing the first-time occurrence of a disease). Secondly, and perhaps more importantly, this historic move wasn’t based so much on hard

evidence from studies but on common sense. No major U.S. study of aeropen has focused on its use in primary prevention, let alone measured it against a control such as a placebo. Instead, the case was correctly inferred from similar data on *secondary* prevention (preventing the recurrence of a disease that has already struck once). While this may sound like an obvious thing to do, especially in the course of major health crisis, but to FDA, it represents a surprising stretch, one which could conceivably invite criticism from Congressional nit-pickers and tightwad insurers. Typical FDA thinking would have demanded new placebo-controlled studies of aeropen before approving primary prevention. The fact that they didn’t take this path shows a spark of urgency and common sense at the agency, a spark which we must now fan into flames. In a broader way, it sets an important precedent about how new conclusions can be inferred from existing data, a point we must be quick to build upon in future situations. The one way in which the decision could be improved upon is to simply leave up to the treating physician to determine when and with whom PCP prophylaxis

In this issue:

New Virus in DC: Common Sense	1
AZT-Resistant Virus	4
AZT: Current Realities/Safe Use	5
Tribute to Barry Gingell	7
Foscarnet	9
Dextran Sulfate Confusion	12
7 Critical Issues	14
Monitoring Immune Health	15
Organizational Update	17

New Virus Spreading in DC: Common Sense

is needed. Although the “under 200 T4 count” rule is generally effective, some people with higher counts still succumb to PCP, possible because their T-cells, while sufficient in number, are dysfunctional (a phenomenon which can be simply detected through skin antigen tests).

Despite these encouraging shifts, problems remain regarding aeropent, and initial public reaction to the decision were mixed. Some felt the approval was late in coming and that it merely formalized an already common practice. Others were disappointed that it was not a “full marketing” approval (called an “NDA”), since the Treatment IND status leaves unsettled questions of insurance coverage for the expensive drug. We find these criticisms completely understandable, though perhaps not as pertinent as they might seem.

Although aeropent has been widely believed to be effective for some time, important questions of dosage, administration schedules, and possible side-effects had not been answered prior to the recent studies. Although the drug was already available, its use was highly restricted in some locations. Outside of the major population centers and high-tech hospitals, aeropent was still considered experimental and was not easily obtained. It was routinely discouraged by conservative physicians, managed health care companies, public hospitals, clinics, and insurers alike. FDA’s approval elevates its status and credibility as a treatment. The study recently submitted by aeropent manufacturer LyphoMed was the first such data presented to the FDA in support of licensing approval. Prior to this, no sponsor had asked anything of FDA regarding aeropent except the right to conduct research with it.

It is true that Treatment IND status, as opposed to full marketing approval, does not force insurers to pay for the drug. Since this Treatment IND permits LyphoMed to sell the drug at an already inflated price, this is a serious concern. Technically, however, not even full marketing approval of a drug forces insurance companies to pay for it. That decision is based instead on the concept of “standard of care,” which is at best only loosely correlated with FDA approval. Discussions with the federal groups which control Medicare and Medicaid have attempted secure insurance support for aeropent. FDA and NIAID officials claim they have pulled every string they command in this regard. Pressure is being exerted on state health plans as well, and many major insurance companies are now reviewing their decisions.

One major insurer, John Hancock, had already done the simple arithmetic needed to show that it was cheaper to pay for aeropent than for hospital care for PCP. Hopefully, their lead will be followed, but as yet, the real outcome with insurers remains unknown - all we hear today is speculation. For whatever difference it will make, full marketing approval for aeropent is predicted to come within a few months, so the affect of Treatment IND status is only temporary.

We expect the National Institutes of Health to play a major role in defining the “standard of care.” Dr. Anthony Fauci recently told PI that the current analysis of the national MAC (Multiple AIDS Cohort) study confirms the belief that **people face the most serious risk of PCP when their T4 counts fall below 200, whether or not they have had PCP before, and whether or not**

they have other HIV-related symptoms (more symptoms, however, mean respectively greater risk of PCP). Fauci’s timely use of data from this as yet unpublished study weighed heavily in FDA’s decision to approve aeropent for people who fall in this group. Fauci is expected to soon make a broad public statement about the critical need for PCP prevention for HIV-infected people with low T4 counts. This should go a long way toward establishing the primary preventive use of aeropent as a “standard of care” and end forever any hesitancy to treat asymptomatic people until after they come down a first bout of PCP.

The bigger question insurers and researchers are now asking themselves is how the use of expensive aeropent compares with the use of inexpensive oral drugs, such as septrin and dapsone. For the moment, aeropent is better proven than the oral drugs, so a case could easily be made that insurers should pay up. Comparative studies will no doubt be conducted.

Although it is a pleasure to see the FDA, NIAID, and community research programs cooperate in bringing aeropent to wider use, we cannot overlook the problems faced along the way. But, in this instance, they can’t be laid at FDA’s feet. The

main federal mistake was the failure to promptly test the drug two or three years ago in light of the obvious promise it offered. Until some research had taken place, it was unrealistic to expect FDA to approve it. The approval was, at least by traditional FDA standards, rapid and concluded on the basis of a relative minimum of research findings.

The Ganciclovir Decisions #1 and #2

Ganciclovir, or DPHG, is a drug that has been used experimentally but extensively in the treatment of AIDS-related cytomegalovirus (CMV) infections of the eyes. If left untreated, this condition (called CMV retinitis) leads to blindness very quickly. Because ganciclovir seemed to work so well from the beginning, and because there no other treatment was available, its use quickly became routine, even without formal clinical study. Some 5,000 people were treated before any effort was made to get it approved. Virtually everyone who used it became convinced that it worked fairly well, certainly better than no treatment at all. During this time, the manufacturer, Syntex, somehow did not conduct the kind of controlled clinical studies that are so dear to FDA’s heart.

During 1988, the manufacturer made a number of efforts to get the drug licensed using the data derived from widespread compassionate use. FDA refused on the grounds that sufficient clinical research had not been conducted. In December, an FDA advisory panel again recommended against approval but instead granted Treatment IND status. Under a bizarre two-pronged Treatment IND, people who had eye infections which immediately threatened their eyesight would get the drug as before. But those in whom CMV infections did not yet reach the center of the retina (ridiculously described as “nonsight-threatening” CMV retinitis) were now to be forced into a clinical study if they wished to get the drug at all. Half of these people would be treated immediately, while the other half would receive no specific treatment until their condition worsened. The study sought to determine whether it is better to treat CMV right away, even if it isn’t immediately sight-threatening, or to keep the patient on AZT as long as possible before using ganciclovir.

Patients, physicians, and researchers across the nation erupted in anger against this decision and the forced clinical protocol. Physicians insisted that there was no such thing as “non-sight-threatening” CMV retinitis; patients decried losing access to a drug they were accustomed to getting; and activists denounced a system which was punishing patients for the supposed sins of a drug company.

New Virus Spreading in DC: Common Sense

Nowhere in all the shouting, even at FDA, were any concerns raised about whether the drug worked or not. It was presumed by all parties that ganciclovir helped. FDA was left in the unenviable position of making a decision that was procedurally correct, but morally, ethically, and medically all wrong. Even key FDA staffers were dismayed at having to support the decision, which they blamed both on the advisory committee — for making it — and on the drug company for making it necessary. No mention was made, though, of the agency's statutory authority to override the decision. Perhaps as never before, patients, physicians, researchers, and even the bureaucrats could see the inability of the regulatory system to cope with the demands of a life-threatening epidemic.

A series of actions followed which led to effective reversal of the decision. Throughout December and January, countless letters descended upon FDA and Congress. Researchers in the ACTG system communicated their utter dismay and anger. Activists, such as New York's ACT-UP raised hell at every opportunity. In January, Project Inform set up a meeting between Dr. Anthony Fauci of NIAID and three San Francisco CMV patients (including Terry Sutton, a key figure in drawing national attention to the problems of CMV retinitis, ganciclovir, and Foscarnet). Fauci acknowledged that he disagreed with FDA and consented to so testify before Congress. In early February, ACT-UP held a dramatic zap of FDA personnel at the second meeting of a national committee working on revisions to FDA procedures. Next, Fauci fulfilled his promise after being given his chance to testify in Congress by Congresswoman Nancy Pelosi (Democrat, San Francisco). In mid-February, PI and New York attorney Jay Lipner met first to plot strategy with NIAID officials and then with key FDA personnel involved in the ganciclovir decision. In the meeting, FDA formally agreed to recall the advisory committee on May 2 (to consider new evidence, a face saving gesture), and more importantly, to resume compassionate access to the drug in the interim, no longer forcing patients to participate in a study to get the drug. For the May meeting, NIH officials and others were asked to gather additional data which would make the licensing of the drug feasible. All were confident that the new data would give FDA what it needed.

As of now, FDA has corrected the disastrous ganciclovir error. For this, they should be acknowledged, as backpedaling at this point was not easy. We should be encouraged by this evidence that it is possible for the agency to see the light, at least when staring into the headlamps of an oncoming steamroller. FDA privately agreed that the outcome of its decision-making process had

appeared so irrational that it gave its critics the most dramatic argument yet that agency rules needed a major overhaul, a situation they wanted to change quickly.

To be fair, FDA was as much a victim of the ganciclovir mess as it was a perpetrator. They can be faulted not so much for creating the problem but for failing to force a fair solution which didn't penalize patients. The drug's manufacturer, despite three years of use with more than 5,000 patients somehow failed to collect sufficient clinical data to demonstrate its value. This seems especially inept in light of the fact that it was so clear to everyone else that the drug worked. How much effort would it have taken to arrange the data and obtain supporting documentation so as to approximate an orderly clinical trial? To paraphrase a key FDA staffer,

"The drug could have been licensed a long time ago if Syntex had simply given us 100 or so patient records which included careful documentation and before-and-after photos of patient lesions. Instead, they gave us hundreds upon hundreds of subjective evaluations by physicians, the kind of information that is impossible to rely on. This wasn't a question of the agency demanding placebo trials."

(Unfortunately, serious problems still remain for people with CMV retinitis, since ganciclovir is not a perfect solution. One of the dilemmas of the highly toxic drug is that it generally cannot be used with AZT, since, taken together, their cumulative and similar toxicities are intolerable for most patients. Thus, people are asked to choose between saving their eyesight with ganciclovir or fighting against the basic disease with AZT. These issues are addressed in a companion to this article, entitled "Foscarnet: New Thorn in the FDA's Eye.")

Implications for the Future

It is clearer than ever before that the efforts of activists throughout the nation are not in vain. For the first time in three years, we see concrete, measurable changes in thinking at the federal level, and even greater changes on the horizon. As strange as it may seem to hear Project Inform commending an FDA action, we think it is war-

ranted in this instance. For those who find this hard to swallow, we suggest you think of it as a form of behavior reinforcement. When the agency acts rationally, even if only in part or under pressure, it should be recognized. When it acts otherwise, it will be soundly challenged. We believe that, bit-by-bit, step-by-step, the Food and Drug Administration can be — must be — hammered into shape to better serve the needs of people with life-threatening illnesses.

PI Perspective...

- Distributes information on a limited number of well-qualified treatment options;
- Advises on access to treatment;
- Encourages personal empowerment through active treatment strategies;
- Increases awareness of the obstacles which heed progress in research.

How often does it come out?

- Once every quarter, or whenever we can afford it. PI is funded primarily by donations.

Do I pay for a subscription?

- It is free.

What does a donation pay for?

- A toll-free treatment hotline, the journal, outreach on early diagnosis and treatment strategies, and efforts to enable sane research and treatment access policies.

AZT-Resistant Strains of HIV Appear

Researchers from the University of California at San Francisco and the Wellcome Research Laboratories have provided the first confirmed evidence of strains of HIV with reduced sensitivity to AZT in a small group of patients. The data, based on blood samples from 11 patients with “severely damaged immune systems” were reported to physicians in a letter from Burroughs Wellcome, manufacturer of AZT. The researchers were quick to point out, however, that the appearance of strains with reduced sensitivity was not accompanied by a loss in clinical effectiveness of the drug. Top AIDS researcher Dr. Anthony Fauci cautioned patients and physicians not to misinterpret the data:

“People who are on AZT and are currently benefiting from it should not consider this a major setback. Just because one can isolate a resistant strain from patients doesn’t mean the drug is not effective in combatting most of the viral replication.” (SF Chronicle, 3/15/89)

Fauci’s statement points to key issue easily overlooked: the ability to find some resistant strains does not mean that all of the viral load has become resistant. Although resistant strains may develop, it is uncertain how prominent that strain will become or what percentage of the total viral load it represents.

Several other questions were raised by the discovery, which most scientists say was not unexpected and suggests no immediate change in how AZT is used.

1. It is unclear how much of this phenomenon is due to *mutation* and how much to *selection*: that is, whether new mutant viral strains develop more rapidly with time, or whether AZT-sensitive strains simply die off in long-term use. Many scientists believe that viral resistance can eventually be expected to any drug that doesn’t eliminate the virus altogether. Thus, what we are learning now about AZT can be expected of the other drugs currently in the pipeline. The discovery by no means suggests that we stop using the drug.
2. The impact on clinical use of AZT is uncertain. It is possible, but by no means proven, that the development of strains with reduced sensitivity may play a role in AZT’s diminishing clinical effectiveness over time in seriously ill patients. In the 11 people studied so far, this was not the case, since the clinical benefits of AZT continued. This gives credence to Fauci’s admonition. Resistance of a viral strain to a drug is no measure of the strains ability to cause disease. In the case of herpes, for instance, acyclovir-resistant strains have been shown to be less, rather than more infective in some studies, at least in people with healthy immune systems.

The ability of AZT-resistant strains of HIV to cause disease is unknown. It could be equally or less dangerous, more dangerous, or completely impotent.

3. The implications for long-term use by seropositives is uncertain. Some physicians we have spoken with feel that the development of AZT-resistant virus could bolster the view the drug should only be used in late stages when it is critically needed. Others disagree, contending that the benefits of early suppression of the virus will outweigh potential loss of sensitivity later, when other drugs will almost certainly be available. They argue that what’s going on with the virus is of secondary importance to what’s going on with the immune system. The more the immune system can be saved and its decline delayed, the better the clinical outcome for the patient.

Some physicians suspect the findings make early use of AZT even more important, since the rate of mutation is likely to be tied to the rate of viral activity. Thus, they argue, by keeping the virus as inactive as possible through early AZT use, the mutation may be slowed. If other viruses are any guide, viral resistance may be a random phenomenon — one in every so many thousands of instances of replication produces a resistant strain. Thus, the less replication and the less virus present, the fewer resistant strains. Acute outbreaks of resistant herpes are only common in immuno-suppressed patients. It may be that a strong immune system can resist what a long-term antiviral drug cannot.

4. The significance of AZT-resistance is also unclear regarding the use of alternating treatment regimens, such as the AZT/DDC approach now

being tested. Does the frequent substitution of DDC for AZT, counteract the problem, or merely slow down the development of resistant strains? Only additional research will tell, although some benefit seems likely.

The development of resistant strains of virus and bacteria is common in long-term administration of drugs. This does not suggest, however, that the virus or bacteria should therefore not be treated. Instead, it argues that we must always be looking for new treatments with different points of attack to use in conjunction with or in place of a drug known to induce resistance. This process of discovery has been going on for decades in the field of antibiotics, and we can expect to see it repeated in the field of antivirals.

It has long been our anecdotal experience that no one drug works indefinitely with HIV. Seriously ill people who claimed success with ribavirin in the early days of the epidemic often found that it only helped for around two years, after which its effectiveness diminished. To some extent, we already see a similar phenomenon with AZT, although the term of usefulness is less well defined.

We agree with Dr. Fauci that this data is no major cause for alarm. We expect, however, that AZT critics will do their best to make much of the data, further frightening current or potential AZT users. We remind them that no one ever suggested that AZT was a perfect solution, and that so far, no other anti-HIV drug has been proven to work at all, let alone long enough for viral mutation to become a factor. The fact that AZT’s effectiveness might diminish over time still leaves the drug an infinitely better choice than alternatives which have not been shown to work at all.

Transmission of AZT-resistant HIV raises a particularly fearsome issue, although we seriously doubt that many people in this category are actively spreading virus. But it is too early to swathe all AZT users in latex before research has learned whether the resistant strains can even be transmitted to a competent immune system. If so, we should hear reports of health care workers infected by needle sticks in whom AZT is noticeably ineffective; and the NIH’s own policy of administering AZT to staff who suffer such on-the-job accidents should have failed to protect at least some against infection. Certainly, neither has yet been reported, nor can either, at this point, be ruled out.

The greatest immediate implication of AZT-resistant HIV is in regard to the regulatory process and FDA decision-making. If AZT’s effectiveness will be short-lived for some, then

AZT-Resistant Strains of HIV Appear

the best known alternatives must be made readily available to supplement or replace it. For now, this means getting DDC and DDI on the market as quickly as possible, since they are the farthest along in their development. We urge FDA and the manufacturers to make them available *NOW*, at least for compassionate use with those already experiencing diminishing benefits from AZT. Further down the road, when people have a more ample menu of antivirals to choose from, we expect it will become common practice to change or alternate drugs periodically to keep the virus in check.

AZT: Current Realities and Safe Use

We present this article in hopes of making it easier for people to make reasoned, well-informed decisions about using, or not using, AZT.

Two years ago when it was first approved, there was widespread belief that AZT would be quickly replaced by other drugs with similar benefits and fewer side-effects. Unfortunately, those beliefs were a bit premature and AZT still remains as the front-line defense against HIV disease. Clinical use has confirmed both the best and worst aspects of AZT: that it offers real benefits for many people but at considerable risk of side-effects and that it doesn't provide its benefits indefinitely. Despite these acknowledged flaws, we believe the drug can be used safely and effectively with a large percentage of the infected population. We also believe that, after careful consideration, some people may still elect not to use it, and they should not be labelled as fools for making that choice.

Perhaps because AZT wasn't the completely safe, completely effective management tool we all hoped for, or perhaps because our friends continued to die despite its use, it has been the object of a great deal of criticism, much of it unproductive, and harmful when it renders people incapable of making an objective decision about the drug. It is the patient community itself which is damaged when misinformation and bias needlessly aggravate the inherent stress of coming to terms with a life-threatening disease.

One particularly harmful attack on AZT comes from a tiny number of publications which are driven by visions of conspiracy and the belief that something, anything other than HIV, must be the real cause of AIDS (swine fever virus? syphilis? chronic fatigue syndrome? dead dolphins? the CIA? Satan?). Accordingly, we are wasting our time with drugs that treat HIV. These same sources often give uncritical endorsement to a variety of completely unproven remedies, simply because they too are contrary and share an anti-establishment perspective. What they fail to point out, however, is that this is the portal through which medical quackery has always passed.

Such attacks lead either to total immobilization on treatment or to an endless pursuit of elusive and unproven "natural" remedies. A little questioning of authority is always wise, but when it asks people whose lives are threatened to abandon all belief in their doctors and medical science, it becomes dangerous and life-threatening itself.

By no means do we wish to say that AZT is the right solution for everyone, or that all those who chose not to use it are crazed. The choice of AZT must be carefully considered, even if only to use it correctly. A review of the available evidence leads Project Inform to several conclusions:

1. Although AZT has serious limitations, it is still the most reliable and best-understood means available for managing the underlying viral infection in HIV disease.
2. Follow-up studies of AZT have, on the whole, confirmed the benefits and side-effects noted in the original study which secured the drug's licensing.
3. New information and extensive clinical experience suggest that many problems with AZT are due to incorrect dosage and/or use at the wrong stages of the disease.
4. When used properly, AZT can be taken safely by a wide range of people.
5. The days of relying on AZT as the primary treatment are coming to an end; questions of how long it can be tolerated or how long it remains useful are becoming less relevant. It need only get us through the next year.

Each of these conclusions is discussed below.

(1. AZT limitations...)

Critics of AZT talk only of the deficiencies of the drug. No one disagrees that it has presented serious problems for some patients. When used by people with AIDS at full dose (1200 mg. per day), about half experience serious side-effects, often leading them to discontinue its use or reduce the dosage. Most critics, however, overlook or understate the benefits. Virtually every physician we have contacted who uses the drug regularly reports significant to dramatic benefits in about half their patients, with the greatest benefits in relatively healthier people or people who at least began using the drug earlier in the disease process.

The second most-noted limitation concerns how long AZT's benefits last. Some evidence suggests that the most pronounced benefits last from six to 18 months. This data primarily reflects the experiences of seriously ill people who only began using AZT after a diagnosis with AIDS. This tells us little about what happens when administration is begun earlier. Some of the original AZT study centers now have patients who are still using the drug successfully after more than two years, with a few patients on it for as long as three. While

Currently Available from PI: Standard Fact Sheets

Anti-virals	Most recent version
DTC/Imuthiol	6/88
Acylovir.....	8/88
AL721	8/88
AZT	6/88
Dextan Sulfate	8/88
Ribavirin	7/88

Immune Modulators

DNCB* 6/88	
DTC/Imuthiol	6/88
Naltrexone	6/88

Other

PCP Prophylaxis	10/88
The Syphilis Connection	4/88

Discussion Papers

1: Treatment Strategy	1/89
2: Managable, Chronic Illness ...	2/89
3: Doctor/Patient Relationship ..	6/88
4: Evaluating Alternatives.....	4/88
Response to Spin Magazine on typhoid vaccine	12/88

**not a PI publication*

Others available on special request

AZT: Current Realities and Safe Use

there is some evidence of the development of AZT-resistance strains of HIV, this was always expected and so far, it has not resulted in a direct loss in clinical benefits (see related article “AZT-Resistant Virus Develops”).

Yet at least for people with AIDS, the question remains: how much quality time does the drug buy? There is little doubt that the life expectancy of people with AIDS has increased with the availability of AZT. In pre-AZT days, the average survival time after diagnosis was around nine months, while today, it is over two years and climbing (San Francisco data). In fact, quite a number of people with AIDS are alive and well after five years, and more and more are moving into the “long-term survivor” category. *So much for the “invariably fatal” disease hyped in the media.* Of course, factors other than AZT have also contributed to survival, including better control of PCP with treatments such as aerosolized pentamidine, better and more creative use of antibiotic and antifungal drugs, and the improved clinical management skills of physicians and patients. Nonetheless, it is simply not honest to completely discount the contribution of AZT in extending life expectancy.

Whether it works for six months, 18 months, or 36 months, there is likely to be some limit to its usefulness. It is unclear whether this is due to the drug or simply to the continued advance of the disease. And even with greatly improved ability to manage, control, or prevent side-effects, it remains an imperfect drug. The question then is, how does it compare to its nearest competitors?

What competitors? We are still waiting for anything close to scientific consensus that any other available treatment provides measurable HIV antiviral activity or confers a statistically significant degree of clinical benefit. There is much hope that AZT alternatives under study but not yet available, such as DDC, DDI, and CD4 will meet this criteria, but they have yet to report data comparable to what we know about AZT. While there is much fervency and hope surrounding a variety of community favorites, herbal treatments, and other “natural” approaches, there is as yet no hard data proving their value.

Despite the shortcomings of AZT and its immorally high price, it continues to outscore its competitors by any scientific or common-sense measure of value. People may choose to invest strong belief in other treatments, but doing so is a matter of faith, more like religion than science.

(2. Follow-up studies...)

AZT critics question the quality of the original

study used to license AZT, contending that the benefits reported may have been due to something other than the drug. Project Inform initially led the nation in questioning the study, which for us raised the possibility — but not the certainty — that its findings may have been distorted. Our own position was that more information was needed to be sure of the conclusions, but that its possible flaws were not sufficient to completely discount the data. FDA reviewers privately acknowledged some shortcomings in the study, but were satisfied that its findings were nonetheless valid.

Several things have happened since then which have allayed our initial misgivings (no, we have not been paid-off by Burroughs Wellcome as some AZT critics blindly declare to be the case). First, the study has withstood the test of *peer review*, the process by which the work of researchers is reviewed for accuracy and objectivity by the larger community of scientists in the field. It was accepted for publication in a first-rank medical journal and has been discussed repeatedly in scientific conferences. With few exceptions, the original results have been accepted by researchers, among them many competitors of Burroughs Wellcome who would have been delighted to discredit the drug. They did not. Only a tiny number of skeptics continue to debate that study, endlessly attacking it as if it were the only information then or since about AZT. In light of the totality of clinical experience with AZT, such behavior looks more like obsession than reason.

Also persuasive in our thinking was the subsequent evaluation of some 5000 people treated with the drug under a Treatment IND. Although these findings do not carry the scientific weight of a carefully controlled study, they roughly parallel those of the original study, showing extended survival and reduced incidence and severity of opportunistic infections as compared to historical controls. For many, AZT use came before widespread availability of preventive treatment for PCP, so the benefits they experienced cannot be easily attributed to anything other than AZT.

In the subsequent two years, other studies of varying quality have been presented at medical conferences. These have also generally confirmed the original data, noting both short-term benefits and the risk of side-effects. Some reported still new positive findings, such as excellent effectiveness against AIDS-related dementia. If the original data were as hopelessly flawed as critics contend, certainly *some* subsequent studies would have shown contradictory results. None has. Even in the most pessimistic study (*Lancet*, Dec. 3, 1988), the same basic profile of benefits and toxicities

surfaced. This study showed declining benefits after the first months of treatment, in part reflecting the fact that the study subjects, on average, were weaker than those followed in the previous major study (as measured by lab values, such as T4 counts). Critics, unfortunately, misinterpret the data to suggest that AZT does more harm than good in the long term and hence should be discarded. That study’s authors drew no such conclusion, nor, in fact, has any other study.

Finally, our own thinking has been influenced by the indelible impression left by the countless numbers of AZT users we have seen first hand who benefitted from the drug. The differences in many peoples lives and well being is dramatic to say the least. We suspect that AZT critics unwittingly develop a skewed experience base, since people having trouble on the drug are drawn to them for support, while those doing well strive mightily to avoid their incessant negativity.

(3. Rethinking dosage and patient profiles...)

Virtually everyone now agrees that the weaker a person is when beginning AZT, the less can be expected of the drug. This is precisely what was reported in the original study. Increasingly, physicians and researchers alike are finding that many of the problems attributed to AZT actually stem from inexperience in using the drug.

Patients and physicians who have not yet done so need to rethink their notions of when, why, and how AZT should be used. Early practice recommended it only for those in the most desperate straits, on the belief that the risks would only be warranted in the face of dramatic need. It now appears that this is the group least likely to benefit from the drug. People with severely depressed white counts, anemia, platelet problems, or numerous infections are often too weak to tolerate AZT, at least at anywhere near the full 1200 mg. daily dosage. Experience has shown that adverse affects are more likely in these circumstances. Thus, if used here at all, AZT should be approached with caution and only at minimal doses. Once improvement is seen, a more aggressive treatment strategy may become possible over time.

Current thinking favors the drug more as a means of keeping people out of dire straits in the first place. More and more, AZT is used with ARC patients and asymptomatics in hopes of slowing progression to AIDS. Although hard proof is not yet available, experience and logic suggest that a drug which suppresses HIV would almost certainly impede the progressive damage it

AZT: Current Realities and Safe Use

does. Perhaps the most unfortunate result of the relentless criticism of AZT is that it frightens people away from using it until their situation is desperate, when the fewest benefits and worst side-effects can be expected. In this way, the critics' attacks become a self-fulfilling prophecy, to the profound detriment of the patient. We were recently moved by the remark of a Canadian AIDS activist who told PI:

"For a year and half, I was a leading anti-AZT advocate, describing AZT as government-sponsored poison. My

age. The once standard dosage of 1200 mg. per day now seems to be overkill. In long-term use (more than 6 months), full dose AZT itself becomes part of the problem. In addition to suppressing white and red cell production, it may be toxic to T-cells. In a recent discussion with Project Inform, Dr. Anthony Fauci of the National Institutes of Health acknowledged that he no longer has any patients on full-dose AZT, and that he now uses it in low doses, often in combination with other drugs. Planned studies at NIH use doses as low as 200 mg. per day, in combination with other treatments, such as alpha interferon.

One recently published study (*Lancet*, Dec. 3,

(4. Using AZT safely...)

The challenge before us is to prevent AZT's weaknesses, or misinformation (either from the critics or the "full-dose-only" advocates) from interfering with our ability to make informed choices. We suggest the following guidelines, some based on a projection of current research, others on the recommendations of physicians with wide experience in AZT use. They are presented as starting points, not hard, fast rules. We invite input from clinicians or users to add to or modify these guidelines over time.

health and concentration deteriorated over time and when I felt I had nothing left to lose, I was eventually persuaded to try it at low doses. To my great surprise, my mind cleared and I felt normal again for the first time in two years."

Rethinking AZT also means rethinking its dos-

1988) already concluded that half-dose seems as potent as full-dose by some measures, and perhaps *more* effective overall due to decreased toxicity. A large U.S. study, as yet unpublished, compared half to full-dose AZT in some 750 patients. Preliminary analysis concluded again that half-dose is just as, if not more, effective than full-dose. Clinics and medical practices in San Francisco and elsewhere report that doses as low as 300 mg. are clinically useful when applied in combination with other treatments.

Who are good candidates for AZT use?

- People with obvious evidence of viral activity, such as a positive p24 antigen (unless otherwise disqualified), or people with a beta2 microglobulin concentration substantially above normal
- People with ARC who hope to slow progression toward AIDS
- People with AIDS who have received their diagnosis within the last year and who are not seriously debilitated (invite your doctor's judgment)

AZT: Current Realities and Safe Use

- Asymptomatics with steadily falling T4 counts and/or other abnormal lab markers
- Asymptomatics who already believe in a strategy of early intervention and aren't willing to wait, regardless of their current lab numbers

Who seem most likely to have problems tolerating AZT?

- People with advanced ARC or AIDS who are seriously anemic, have seriously suppressed white counts, or who must concurrently use other toxic drugs, such as DHPG

What is the proper dosage?

- A growing body of evidence suggests there will never be one ideal dose for everyone; people vary in body weight, health, rate of metabolism, and reactions to the drug. The healthiest people have the highest tolerance, while the weakest have the lowest.
- In general, half-dose (600 mg. per day) seems a good level to strive for. For weaker patients, even smaller doses may be used initially to test their reaction, slowing building up to higher doses if the drug is tolerated.
- People who have already tolerated full dose (1200 mg.) for several months without serious side-effects and who have stable T4 counts may wish to continue on full-dose. It is unclear from the research, however, whether such full-dose use provides any advantage, even if it is tolerated.
- Some physicians urge people with high p24 antigen levels to use 1200 mg. per day until p24 levels go down and stay down for 30 days, after which 600 mg. may be appropriate.
- Some clinicians report that 300 mg. per day is effective when used in an overall combination therapy strategy (see *PI Discussion Paper #1* for more discussion of combinations). Some researchers believe that any dose, however low, might be better than none at all; others argue that there is some as yet undefined minimal dose below which there is nothing to be gained.
- People on low doses, either 600 mg. or 300 mg. should periodically monitor p24 levels, raising the dosage temporarily if the p24 count becomes positive or rises.
- Some physicians are now giving low dose AZT even to patients who are on DHPG (ganciclo-

vir), starting with a single 100mg. pill daily, and increasing by 100 mg. as long as the patient's white count remains acceptable

- Any dose can be lowered or even stopped temporarily if any sign of side-effects occurs
- There is no rationale for continuing full-dose AZT when doing so requires regular blood transfusions; dosage should always be lowered in this instance.
- Most physicians to report that side-effects almost always clear up after withdrawal from the drug. Some report that tolerance of the drug is best maintained when people are never allowed to get into serious trouble in the first place.

What is the proper administration schedule (how many times per day, how much time between pills)?

- No schedule results in constant AZT blood levels because the drug is broken down very quickly in the body.
 - Many physicians no longer consider the night-time pill essential; if waking up adds stress, many feel it can be skipped without dramatically lowering the value of the drug (an unproven, but logical assumption).
- In an effort to compensate for skipping the night-time dose, some physicians are advising people to take the take the bed-time dose with Tylenol or Probenicid, which are believed to extend the drug's half-life.

- *Sample 24 hour schedule* (including night-time pill), half- or full-dose:
 - one or two pills every four hours
- *Sample 16 waking-hour schedule, full or half-dose:*
 - full-dose:* three pills every four hours;
 - half-dose:* two before bed, two in the morning, one every four to six hours in between;
 - quarter dose:* approx. one every six hours

What can be done to manage AZT side-effects? (as reported by both patients and physicians)

- Begin with a low dose, gradually increasing the amount until the desired level is attained, thus giving the body a chance to adapt to the medication.

- Try to ride out any initial side-effects, such as nausea and headaches, if they occur, as they often clear up in a week or two.
- Experiment by taking the drug both with and without food; some groups recommend taking it on an empty stomach.
- If anemia is a problem, experiment with monthly vitamin B12 injections; if possible, get in a study or find access to EPO (erythropoietin), which may minimize or eliminate anemia. Although currently not available in the U.S., EPO can be brought in from other countries under the FDA Import Policy. Kidney disease patients regularly import it, although it is very expensive.
- Always challenge initial assumptions about "side-effects;" many people are primed to expect them and thus interpret everything that happens while on AZT as a drug effect; it might well be something else. In retrospect, many who initially had great fear of AZT side-effects now report that it is much easier to take, for example, than dextran sulfate, once thought to be a low-toxicity alternative.
- Some physicians are experimenting with the prescription drug lithium in hopes of increasing AZT-suppressed white counts; response is not universal and may be temporary.
- Some physicians recommend taking the pills every eight hours, in hopes of letting the bone marrow recover in between. This comes at the expense of having less consistent levels of antiviral activity, but the clinical significance of this is unknown.
- If serious side-effects occur, go off the drug entirely for about a month, then restart at a very low dose, increasing a small amount each week while being carefully monitored.
- An occasional transfusion might be tolerable in some cases, but repeated, regular transfusions are now discouraged by most physicians; if AZT use, even at low dose requires regular transfusions, the drug may be inappropriate for the patient. EPO might help.
- A few physicians have reported a rapid drop-off in lab numbers after abrupt withdrawal from AZT, suggesting that gradual withdrawal might be better. This is so far not supported by any hard data.
- When AZT at any dose seems intolerable, look for alternatives. At the moment, this usually

AZT: Current Realities and Safe Use

means entering a clinical trial, but some alternatives may be available under compassionate use or new Treatment INDs in the second half of 1989.

(5. AZT days are coming to an end...)

Effective alternatives are now actually in sight. The first likely to become formally available, possibly before the end of 1989, will be the alternating AZT/DDC regimen. In this approach, two drugs are used in alternation - AZT one week, DDC the next - in an effort to provide the benefits of both drugs without a buildup of the side-effects of either. Assuming all goes well, next may be DDI, another AZT-family drug expected to be more effective and to have fewer side-effects. It could become available within a year. Rapidly following DDI may be CD4, which is moving at near-record speed into phase II trials. At this pace, it could become available by late spring of 1990 if no problems develop. Beyond mid-1990, little more than year and half from now, several additional options could conceivably be ready, including better immune boosters, virus-binding inhibitors, and new antibiotics and antifungals.

Another factor which promises to increase treatment options is the rapidly shifting view of the scientific establishment, which is now beginning to demand early release of promising new drugs, well before the time FDA would otherwise be inclined to approve them. In short, the drought of AIDS drugs is nearing an end.

Conclusion

AZT is at the same time a flawed, risky drug and our current best option. We all wish there were a readily available, natural, non-toxic, effective alternative. At the moment, this remains a dream, one which is frequently exploited by promoters of snake oil. There is too much at stake to let this dream divert us from using the best of today's available medicines.

AZT is not the enemy, nor are rational AZT critics, who are acting in good faith according to their own consciences and experiences, just as we are. AIDS remains our common enemy. We, among many others, however, are increasingly fed up with seeing responsible voices in the community attacked by the *New York Native* for daring to see value in AZT. Far more importantly, we are concerned for the people who are left confused, misdirected, and frightened by ill-supported theories on AIDS, and all-too-often guided, by process of elimination, toward the least credible medical resources.

We owe it to ourselves and our communities to let each person make a rational, fully-informed decision about AZT use. The emotionally charged debate which surrounds AZT is and will remain counterproductive until a better alternative is proven and available. Those who already claim to offer a better alternative must prove their cases in clinical studies, not just on the altar of rhetoric. People who are troubled in making a decision about AZT need to know that there are safe and effective ways to use it, right now, at many stages in the spectrum of HIV infection. We hope that choice will be made easier and clearer by the growing awareness of lower doses, better patient profiling, and more flexible, responsive use of combination therapy.

There is no one to blame for any possible mis-use of AZT which has taken place until now. Patients and their advocates, including Project Inform, pushed the regulatory and research system hard to make AZT available as soon as possible. We should not be surprised that the drug came into common use while our understanding of it was still very crude. The point is to learn from our experience and make the best possible use of it now wherever it is an appropriate choice. The only thing we need ask of AZT is that it help keep the greatest possible number of people alive until better treatment becomes available. It need not be perfect, only good enough to fulfill this task. The record shows that, when used properly, at the right time, and with the right people, it is up to the job for those who chose to use it.

Foscarnet: Thorn in the FDA's Eye

Despite all the national hoopla over ganciclovir in recent days, many people with CMV retinitis believe that drug is a dead end and that activists energies should be directed elsewhere. Foscarnet may be the alternative that is needed, but access to it is currently blocked and patients may be needlessly suffering as a result.

Ganciclovir is not a cure for CMV, only a maintenance tool, and an imperfect one. Because of bone-marrow toxicity, ganciclovir prevents concurrent use of AZT and further suppresses what's left of a patient's immune system. People are asked to choose between their eyesight and their fight against HIV and immune disorder. Almost all elect to fight for their eyesight. In long-term use, most eventually succumb to CMV retinitis anyway, or reach a point where they have to quit ganciclovir because of side effects. It is possible that another drug, foscarnet, may work as well as ganciclovir without taking as high a toll.

Foscarnet is a Swedish drug which has action against both CMV and HIV, a neat combination. When using it to fight one, it also fights the other - quite opposite the result of using ganciclovir. In Europe, foscarnet has been the primary therapy for CMV for some time. It is not clear whether foscarnet works as well as ganciclovir (or better or worse), so further research is needed. Such studies are finally underway, after a nearly two-year delay.

People with CMV are now rightfully demanding that the foscarnet option be available to them. Without it, many continue to go blind after failing ganciclovir, while others desperately wane in the face of mounting immune disorders. FDA insists that clinical studies be done, not just compassionate distribution, in order to avoid the problems experienced in getting ganciclovir licensed. Those studies are now underway in several cities, but they cannot serve everyone. People who aren't in the right cities don't have this option, nor do those who haven't yet failed on ganciclovir, nor those who simply can't comply with the rigors of the protocol.

People who are using ganciclovir can only enter the foscarnet study if the first drug fails them. Just getting sicker due to untreated immune disorder

Foscarnet: Thorn in the FDA's Eye

doesn't qualify. Again, patients are faced with the absurd admonition to get worse before the government will allow them to get better. Furious behind-the-scenes activity regarding this problem has been underway for months, thanks to the pioneering work of San Francisco activists Terry Sutton and Tim Elliot.

What's needed is an open-label or compassionate protocol which permits the foscarnet option for those who aren't served by the current studies. FDA says it supports the idea in theory, but certainly has done little to encourage it, fearing that widespread compassionate use might render the studies less attractive. Foscarnet's manufacturer, the tiny Swedish company Astra, fears that compassionate distribution is a sure-fire way to invoke FDA's wrath, based on the handling of ganciclovir. In a recent instance, FDA itself called Astra and encouraged compassionate distribution for a specific patient, yet Astra still refused. Publicly, the company says it can't afford it. Privately, fear of FDA is identified as the real reason.

Whoever is fault here, it is the patient once again who is punished for it. This is unacceptable by any imaginable moral or ethical standards.

There are three related but independent problems which need to be fixed here.

1. Intended or not, FDA gave confusing signals on compassionate use in the ganciclovir/Syntex affair. This must be corrected. FDA must go on record, publicly and at the Commissioner's level, saying that it supports and encourages compassionate use of foscarnet in situations not served by the present studies. Dr. Fauci has recently come around to the belief that it is possible to have needed clinical studies simultaneous to compassionate use. Previously, most federal researchers and regulators believed that one interfered with the other. A Treatment IND can be requested by independent parties under new legislation passed in late 1988. Congresspeople Waxman and Pelosi have already made the request, and they need support for the effort, especially support from Congressman Ted Weiss of New York.

2. Sufficient public pressure must be exerted on Astra to cooperate with patient need if it wants to use AIDS patients to research its sure-to-be-profitable drug. This is a job for New York and Boston ACT-UP, as Astra's only U.S. office is in the Boston area. ACT-UP can be very effective in these matters, but so far, most of the concern over foscarnet has been voiced by West Coast AIDS patients who can't take the

case directly to Astra with force. Hopefully, this article will help make the problem better recognized nationally.

3. Funding must be established to help pay for treatment in cases like this. Even in the formal studies of foscarnet, patients are expected to pay for several days of hospitalization, which are required when starting on the drug.

Project Inform: The Basic Message

- Learn your options and line up your support.
- Get tested, *anonymously*.
- If positive, consider anti-viral treatment (and get a full immune health workup).
- Monitor T4 cells quarterly, charting the trend.
- If the trend of T4 cells is downward or falls consistently below 500, consider both anti-viral and immune boosting therapy.
- If the trend of T4 cells falls below 200, use prophylactic (preventive) treatment against pneumocystis (aerosol pentamidine, is possible).

Insurance is unlikely to pay since the drug is classified as experimental, and the NIH claims it doesn't have money to pay for hospital beds. This problem is becoming increasingly common for people with AIDS, especially when a small-time pharmaceutical company is involved. In this instance, Astra might be able to make a legitimate case that it has severe

financial limitations.

Two possible solutions come to mind: (a) a special Congressional fund, like that used to pay for AZT, or (b) creation of a privately supported national AIDS Treatment Emergency Fund. With grave budget deficits, a growing backlash against special AIDS treatment and research funding (by groups fighting for support for other diseases), we may need to begin thinking of new ways to support our people with the most desperate needs.

Whatever the solution, this problem demands immediate national attention. Access to foscarnet may be part of the answer. As long as that possibility is out there, it is inhumane to let another AIDS patient with CMV retinitis go blind or suffer a devastating and unnecessary collapse of the immune system. In the complex personal situation implied by an AIDS diagnosis plus CMV retinitis, patients' wishes and options must be given priority over the needs of drug companies and the regulatory system.

Clinic Update

Active Lipids: (Patent holder Ethigen has protested our use of the name "AL-721" or "AL-721 workalikes" on the grounds of their ownership of the name. We are pleased to accommodate their wishes. Other than that, there is little new to say about active lipids, since no additional study data has been reported for some time. New York's Community Research Initiative hasn't released any formal data from their study of the Jarrow lipid formula that is/was so popular. The National Institutes of Health likewise remains strangely silent about the outcome of their two Phase I studies.

We think it's time for the silence to end. If anyone has any good, solid results to report about the product or its derivatives, we're willing to listen. It is unfair, however, to leave the community hanging, in some cases still buying this fairly expensive product, without some further word from researchers. If the research establishment fears they will be criticized for debunking a one-time community favorite, they underestimate this community. If promoters of the product think people will keep buying it despite the silence, they too are mistaken. People want the truth, good or bad. Our ears remain open and we support Dr.

Clinic Update

Barry Gingell of GMHC for having the courage to raise questions about a sacred cow.

AZT: See "AZT: Current Reality and Safe Use" and "AZT-resistant Strains of Virus Appear."

CD4: Although available only in strictly controlled clinical trials, interest in CD4 is extremely high. We have contact with some of the researchers studying the product as well as some patients already using it. Only a small number of patients so far are on the dosage expected to be effective. Early reports from Phase 1 studies suggest that the drug is safe, with none of the predicted problems surfacing so far. We have heard from patients, however, who complain of central nervous system disturbances, such as sleeplessness and hypertension. So far, patients report little measurable benefit but seem to feel they are stable. This will not long be good enough, however, for a drug which seems to promise so much.

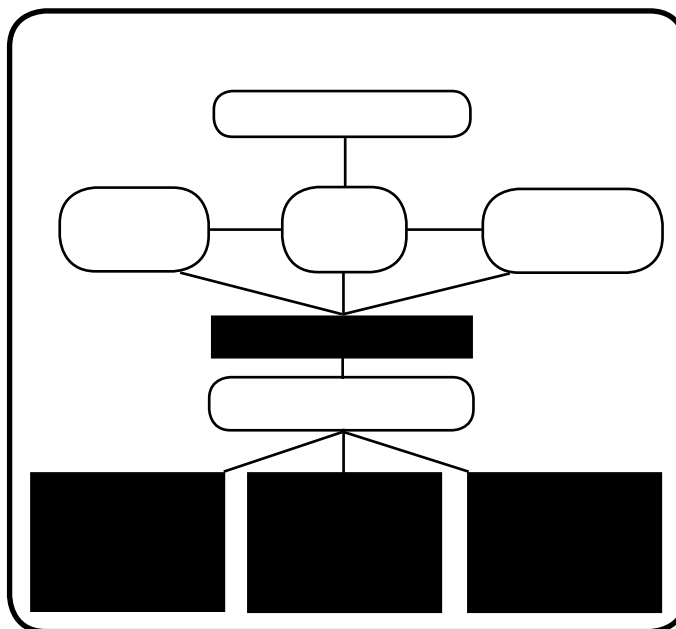
Phase 2 studies of CD4, soon to begin, will compare CD4 alone in one group, to CD4 plus AZT in another, and AZT alone in a third. This efficient study design will gain a great deal of knowledge in a single study and should serve as a model for future comparative studies.

DDC: Although little is said about it lately, DDC used in combination with AZT is likely to be the next major AIDS drug up for approval by FDA. Current studies, using the two drugs in alternation, will last until fall of 1989, at which time we can expect the manufacturer, Hoffman LaRoche, to apply either for marketing approval or a Treatment IND. Unlike AZT, DDC is a simple drug to make so there will be less justification for high prices. Reports from centers currently testing the DDC/AZT combination suggest that it is meeting its objectives of providing the benefits of both drugs with fewer side effects than either when used alone.

DDI: This drug, one in the series of "Broder's Babies" (AZT, DDC, DDA, and DDI — products of the research of Dr. Samuel Broder at the National Cancer Institute), is rapidly moving into Phase 2 tests. In theory, DDI is far more potent and specific than AZT, yet has so far demonstrated fewer and less severe side effects. Surprises are still possible, though and only a Phase 2 study will clarify things. Assuming DDI lives up to its promise, it could be moved into wider distribution by spring of 1990. Like DDC, it is not a complex product to make, so there is some chance that it

will be manufactured and distributed through the underground before then.

If this summer's studies of DDC and/or DDI continue to look promising, we would urge immediate compassionate access to these drugs for people whose tolerance of AZT is waning over time. Similarly, we would urge that every possible step be taken to allow these drugs early distribution in a manner which will encourage insurance repayment.



DTC/Imuthiol: French studies reported late in 1988 were again very promising, while the data from U.S. studies are now more than a year overdue. We are told, once again, the data analysis from the U.S. studies is imminent. Yawn.

Dextran Sulfate: See the article "Dextran Sulfate: Lost in a Sea of Confusion" in this issue. There are two key problems to face with dextran sulfate. First, we urge people who are in current studies of oral dextran sulfate not to drop out because of the incomplete and possibly misleading reports which have appeared widely in the mainstream and community press. It is only by completion of those studies that we will get a meaningful answer about oral dextran.

Secondly, whatever the outcome on oral dextran, research should move full speed ahead on IV dextran. A new European *in vitro* study is very high on the benefits of dextran sulfate. It would be a disaster if the political climate which has arisen in the U.S. around dextran sulfate should slow or stop future research. So far, there is no

alternative that has shown such solid lab evidence of affecting cluster formation, which may well be a more important problem than the direct infection of T4 cells.

Fluconazole: This drug, which works against a wide range of fungal diseases, including cryptococcal meningitis, is approved in several European countries (though not for AIDS). Its approval in the U.S. is described as "nearly imminent" by federal people who ought to know. In the meantime, New York's PWA Health Group has offered to secure its importation from Europe for anyone in critical need. Be forewarned, however, that the drug is very expensive. Look to see a full marketing approval or a Treatment IND from FDA before summer's end.

Prior to Fluconazole approval, people should know that the drug is currently available on a compassionate basis for patients who fail on Amphotericin B, the primary treatment for cryptococcal meningitis. Fluconazole is far simpler to use than Amphotericin B and is much better suited to long-term prophylactic use. At the moment though, the compassionate use program is strictly limited to those who fail or have trouble with Amphotericin B. It is not available to those folks who simply would prefer to use Fluconazole.

Hypericin: Due to a comprehensive review in John James' *AIDS Treatment News*, the herbal extract Hypericin is quickly gaining interest on the treatment scene. It is well qualified for this role, as it has proven very effective in lab studies conducted by independent researchers, showing an ability to block HIV action in multiple ways. The usual caution about the preliminary nature of such *in vitro* testing must be observed. To date, clinical use is extremely limited, with most reports being based on the anecdotal findings of a single physician. Plans are underway for more formal testing, but the first sanctioned clinical studies are a long way off. This would be an excellent opportunity for community research groups to undertake a structured study or monitoring project to determine whether there is value in this product. Whether or not research is begun quickly, it seems likely that Hypericin will become the next object of devoted use in the community. Several manufacturers are already supplying products of varying quality, with more to follow. As this market grows, we fear the price too will go up.

Imreg: The studies and evaluation of Imreg have

moved in regulatory twilight zone, as we feared. The manufacturer continues to claim that the drug showed significant benefits regarding slower progression to AIDS. FDA, however, blasted the company's studies in an unusual, command performance public hearing late last year. The hearing apparently came about as a result of public and congressional pressure, which were trying to get the drug a fair forum. Instead, the move appeared to backfire and served as a bully pulpit for FDA. In brief, FDA claims that serious problems in the randomization of patients and a possible unblinding of the treatment code make the results of the study meaningless. Since the company remains unwilling to share the key data publicly (they say to protect the opportunity get it published), there is no way that we or anyone else can make an independent evaluation of the situation. The company is currently in the process of answering FDA's objections and is trying to put the best face forward. From past experience, we fear this means little. No answers from Imreg are likely to satisfy FDA, especially since key NIH officials we have spoken with also believe that the data is fatally flawed. A second public hearing on the matter will be held in Washington in early April.

We would like to be in a position to form an independent opinion and would, if warranted, join forces with other activists who decry FDA's actions regarding Imreg. Some aspects of this case sound familiar since FDA's demanding views on randomization by T4 cell count have in the past seemed strange in light of the imprecise nature of T-cell testing. However, without actually seeing the data, it is difficult to know how good the case is for the drug.

Isoprinosine: This long-time player appeared to bite the dust late last year when the manufacturer announced that it was pulling out of its studies with ARC patients, having concluded that the drug did not help. Then, just when we thought shelf space was clearing up, the company released a press release saying that its long-running Swedish seropositives study had reported successful results. No data was supplied, only a vague statement that the drug had slowed progression to AIDS to a statistically significant degree. That line is getting to be familiar. Until other researchers have seen some specific data, a healthy dose of skepticism may be appropriate. Whatever the new data shows, it is already clear that the drug has no role for people with AIDS or ARC.

For your information:

American Preferred Plan (APP)

- APP is a membership organization which markets prescription drugs, delivering them directly to your door (or a selected address) anywhere in the country.
- APP accepts insurance reimbursement as payment in full, so members never have to pay out-of-pocket costs, even when your insurance plan pays only 80%.
- APP requires no filing of insurance forms, provides complete confidentiality and sensitivity to HIV-infected people, and takes orders by phone 24 hours a day for overnight delivery.

As far as PI knows, APP is the only service offering all these benefits. It may be especially useful for prescriptions that are refilled on a regular basis. PI neither recommends nor discourages use of this service; it is described here as a possible resource, like the Buyer's Clubs and other organizations mentioned in this newsletter.

APP: 1-800-227-1195 (national)
1-800-445-4519 (in NY)

*NOTE: APP makes a donation to non-profit AIDS organizations, such as PI, for each person referred to the service. So if you choose to use the service, **be sure to tell them PI sent you.** (Order forms are available from PI or directly from APP).*

Dextran Sulfate: Lost in a Sea of Confusion

During the month of February, the media wove together two unrelated events to reach an unsupported conclusion about the value of dextran sulfate. The Los Angeles Times began it all with an article claiming that researchers had proven the drug was not absorbed and therefore was ineffective. Linked to this were outtakes of a study by Dr. Donald Abrams of San Francisco General Hospital, along with a number of vague comments from Commissioner Young at FDA. Several local papers and some of the Gay press picked up on the story in a knee-jerk fashion, trumpeting the bottom line conclusion that dextran sulfate had been proven ineffective.

All of this bears little resemblance to what really happened. Three things actually occurred. (1) Last November, researchers at Johns-Hopkins University conducted an experiment to determine whether dextran sulfate was absorbed in the gut. (2) In February, the *Annals of Internal Medicine* finally published Dr. Abrams Phase 1 dextran study from last year, the study that was reported and discussed in Stockholm. (3) FDA Commissioner Young, despite explicit agreements not to discuss the matter in the press, pending a series of discussions, somehow managed to become the centerpiece of the Los Angeles Times story.

The Johns-Hopkins Experiment

AIDS researchers there, having been frustrated by an inability to directly measure dextran sulfate in the blood, proposed to measure a secondary effect they believed linked to dextran sulfate absorption. They chose to study its effect on blood coagulation, using a measure known as PTT. In the experiment, a total of 12 volunteers had their PTT times measured before administration of dextran sulfate, to create a baseline for comparison. Next, six of the volunteers were given a single dose of intravenous dextran sulfate, while another six were given a single 1800 mg. dose of dextran sulfate, as supplied by Ueno Fine Chemicals. After all 12 volunteers had received their doses, their PTT times were measured again several times over the next 24 hours.

The researchers noted that those who received intravenous doses showed a change in their PTT times, while those who received oral doses did not. As far as they were concerned, that was the end of the story, and they had proven that oral dextran sulfate was not being absorbed.

Several major questions remained unanswered by the Johns-Hopkins experiment:

Dextran Sulfate: Lost in a Sea of Confusion

1. No one has demonstrated conclusively that PTT times are a measure of oral dextran sulfate absorption. This remains, at best, a theory.
2. The fact that PTT times were not affected by a single oral dose tells us little or nothing about what happens in long-term, chronic administration of the drug.
3. The ability to absorb the dextran sulfate molecule may not be a constant among people. In other words, some may be capable of absorbing it and others may not. There have been indications that some people in studies seem to be “responders” - that is, they seem to get results from taking dextran sulfate orally. It is possible that some people’s digestive systems may be capable of passing the molecule, while others may not.
4. There have long been serious questions about quality differences in the enteric coating of different versions of oral dextran sulfate. Some information suggests that the Ueno Fine Chemicals version is among the worst in this regard, a factor which might well affect its absorption. FDA officials did not know whether this factor was measured in the Johns-Hopkins experiment, but conceded that it could well affect the outcome.

The Johns-Hopkins experiment quickly set off private debate among researchers. Some felt they should stop wasting time with dextran sulfate and disband the on-going studies, while others, led by Dr. Abrams, felt the results were inconclusive and that it would be a mistake to disband the studies in response to this data. Abrams contends that since hard data about absorption remains elusive, the studies should be completed as originally planned. Moreover, he points out that measuring absorption of the whole molecule is not the same thing as measuring whether oral dextran sulfate produces useful results in patients. The studies will answer the real question of effectiveness, and should be continued. This will give a more substantive answer than the Johns-Hopkins experiments. Even this, however, will not provide data on what on the key question of how dextran sulfate works in combination with low dose AZT.

Unfortunately, the headlines of LA Times story were widely read and led to additional inaccurate stories in the gay and local press. A careful reading even of that story showed that NIH researchers felt the data was very “preliminary” and that the drug might still be absorbed in long term use. Casual readers and other media writers, though, only saw the loud conclusions about “ineffective-

ness.” As a result, many patients have already dropped out of the dextran studies and at least one of the centers closed their study.

The New/Old Dr. Abrams Study

The LA Times article and subsequent spin-offs also used bits and pieces of the Abrams study published in the *Annals of Internal Medicine*. That study failed to find conclusive evidence of benefit from the use of oral dextran sulfate. None of the media people pointed out, however, that this was the same early Phase I study that Abrams reported on at Stockholm last year, a dose-ranging/toxicity study that was not designed to reach conclusions about effectiveness. Even so, Abrams concluded that further study was called for. Those additional studies he called for are already well underway, some nearly complete. Their status, however, is now jeopardized by the LA Times article and its spin-offs.

The FDA Connection

Somewhere in the midst of this mess, Dr. Young at FDA managed to put his two cents in. He spoke in the LA Times article as if he had conclusive knowledge on the subject. However, Martin Delaney of Project Inform and Jay Lipner of New York spoke directly with him about the matter at a meeting in Washington on the same day that the LA Times story was being written. In that conversation, it was clear that he had only superficial and confused knowledge. He didn’t know what the Johns-Hopkins experiment had measured or how, and he referred only vaguely to some FDA “chemical assay” that he thought was being used to measure dextran absorption in rats. He acknowledged that he was not well informed, and insisted on setting up a conference call with us and key FDA people on the following Tuesday to discuss the matter in detail. Meanwhile, he insisted, absolutely no one should talk to the press until “we all decided together how to handle the matter.” Much to our surprise, we read his comments in the LA Times story days before the scheduled conference call.

Further discussion with FDA officials confirms that the an agency lab has created a direct chemical measurement of dextran absorption, although it was never used in rats as the Commissioner contended. The assay was used to confirm the results of the Johns-Hopkins experiment. We urge the agency to share their assay with other scientists who can review it for accuracy. It seems strange after NIH has claimed for nearly a year that it was impossible to create a direct chemical measure of dextran in the blood, that an unheard of FDA lab suddenly creates such a test. Until the FDA assay has met the test of peer review, the proper scientific procedure is to best shut up

about it - the very same advice they consistently give to pharmaceutical companies.

What Does This Mean to the Dextran Sulfate User?

Mostly, it adds a great dose of confusion. Conclusive evidence has not been attained for or against the absorption of dextran sulfate in long-term use. Had the Johns-Hopkins data showed that coagulation (PTT) times were affected, we suspect that most observers would have discounted the conclusion, based as it was on the unproven assertion that changed PTT times were a measure of absorption. The fact that some physicians who have studied long-term dextran users and do find changed PTT times raises serious questions about the value of the Johns-Hopkins “single dose, single day” observation. If FDA really has an effective assay, it should be used to measure levels of dextran in the blood of patients who have used it for long periods in a study. No such test seems to be underway.

Thus, the bottom line is that we don’t really know any more about dextran sulfate today than we did last fall. The LA Times story is almost irrelevant. FDA’s behavior and that of scientists at Johns-Hopkins who released their data are both worthy of reprimand. Had any pharmaceutical company released such preliminary data to the press, prior to peer review or publication, FDA would complain loudly or even call for an investigation, as they have in the past. Yet, since government people did the naughty deed, somehow the behavior is deemed acceptable.

For dextran sulfate users, a far more serious problem is that of severe diarrhea. Large numbers of people tell us that the problem becomes severe in long term use and is only partially managed by use of anti-diarrhea drugs and lower or intermittent doses. For these people, continued use of dextran may not make sense. Still, we hear from others who do not experience diarrhea, and from a good number who report significant, sometimes even dramatic benefits. Perhaps those who do not experience diarrhea are “responders,” the ones who can absorb the whole dextran sulfate molecule. If so, it would be a great misfortune if they, or others who have had good results from dextran, were discouraged from using it because of half-baked stories in the media or unsupported conclusions drawn by researchers. Likewise, we urge people who are in dextran sulfate studies to continue their participation despite the news stories. It is from their experiences that we will finally get an honest answer about the drug.

Seven Critical Issues at FDA

In addition to the desperate need for FDA to support wider use of Foscarnet, several other important drugs are in need of a quick shot in the arm. Space doesn't permit listing every drug choking in red tape, but the following immediately come to mind. In a word, the problem in each comes down the sense of urgency, which seems sadly lacking.

FLUCONAZOLE: this antifungal drug, already available in several European countries, is needed immediately for treatment of cryptococcal meningitis and other fungal infections. The currently available treatment, amphotericin B, often has serious side effects and must be administered by IV, making long-term use painful and dangerous and greatly diminishing quality of life. Fluconazole could end all that. It is also likely to be effective in a broad range of other fungal infections. Fluconazole is late in coming to market in the U.S. because the manufacturer's previous efforts to license it (for vaginal yeast infections) failed. It is currently available on compassionate use for people who have failed on amphotericin B or who have experienced serious toxic side effects from it. The entry requirements for compassionate use are strictly enforced.

Required action: application for licensing of fluconazole is imminent, and FDA people take the drug seriously. Between now and licensing, we urge open label use or an immediately Treatment IND for anyone who needs it.

GM-CSF: This drug is critically needed by people with severely depressed white counts, for which there is no other therapy. GM-CSF has been studied for two years now, with considerable success, but is held up by tired concerns about "feeding the virus," a phenomenon that has been discussed for years, but has yet to be conclusively demonstrated. GM-CSF has also been used to supplement the use of white-count robbing drugs like ganciclovir, making it possible for patients to fight CMV retinitis without sacrificing what's left of their natural immunity.

Required action: Treatment IND for people with

critically low white counts and people forced to use drugs like ganciclovir.

ROXYTHROMYCIN: this French antibiotic, may be critically important in the treatment of toxoplasmosis. Study, let alone availability, of it is hampered in the U.S. by FDA insistence that the manufacturer go back to square one - animal toxicology work - before approving an IND to begin Phase 1 testing.

Required action: conditionally accept foreign toxicology and clinical data and begin Phase 2 testing immediately, alongside a program of compassionate use for people who fail other anti-toxo drugs. Simultaneously, if truly necessary, conduct any desired toxicology studies.

GL-223 (aka Compound Q): this Chinese drug, the subject of wild rumors, is suspected of having the ability to quickly hunt down and kill HIV-infected cells. Lab studies at San Francisco General confirmed the activity of this toxin which is said to affect only virally-infected cells. GL-223 is used in China to induce abortions, among other things. U.S. studies were about to proceed until FDA had its say, again pushing it back to square one for toxicology studies.

Required action: no drug already in human use should not be treated like a total unknown. New toxicology work should be scheduled and functioning to coincide with Phase 1 studies, rather than doing each in sequence. People are anxious to volunteer for human studies with GL-223 and it should be their right to do so. With or without FDA approval, underground sources will soon bring GL-223 into the U.S. Does FDA somehow think that's a better way to test drugs?

PEPTIDE T: this product, described as the "flip-side" of CD-4, has been enthusiastically touted by its backers for more than two years. Unanswered questions remain about the basic lab data, and very little human data has been reported. The backers say this is because of cold-shoulder treatment the drug has received from top federal scientists, who are backers of a different approach to antiviral therapy (the use of nucleoside analogues, such as AZT and DDI). The federal scientists say lab data on Peptide T is suspect because it hasn't been confirmed by their labs.

Required Action: use considerable FDA influence to force a serious study, whether federal scientists like it or not. This has already been done with

several other drugs (dextran sulfate, AL-721, ribavirin, etc.). Hold a public inquiry into the sponsor's charges that the drug is effectively black-balled, and the opponents charges that the drug's basic lab data is unsound.

DDC: enough is already known to make this available, in alternating combination with AZT, for all those who are failing on AZT alone (or developing AZT-resistant virus). Issue a Treatment IND. The manufacturer already has stockpiles of the drug for distribution - why should people be denied access?

DDI: for all the hope government officials hang on this one, there seems to be precious little research going on. Faster movement in Phase 2 studies is essential. Where is the urgency?

In memory...

We dedicate this issue of PI Perspective to Chuck Hansen, another PI warrior who gave selflessly until he could give no more.

His memory will live on in

Monitoring Immune Health

(The following article is part of the newest version of [Project Inform Discussion Paper #1 - Treatment Strategy](#). Because of its importance, it is reprinted here for all those who have not received the Discussion Paper separately. The entire Paper is available on request.)

There are, in general, two common approaches to monitoring immune health, each with its advantages and disadvantages.

1. SYMPTOM OBSERVATION:

This approach is based on the evidence presented by active infections and disease processes. In HIV, this means watching out for such things as thrush, pneumocystis, KS lesions, and so on.

Advantages:

It is easier to believe and take action when we are faced with an obvious illness. People who feel sick usually want to treat the illness as soon as possible.

Disadvantages:

HIV may progress quite far before symptoms appear, without patient awareness. By the time symptoms appear, options for treating the problem may be less effective because the body is left with only limited defenses.

2. LAB STUDIES AND BLOOD ANALYSIS

- a) anti-body testing
- b) T-cell testing
- c) p24 and beta-2 testing
- d) CBC - basic blood studies

Advantages:

Indications of illness show up well before illness becomes apparent. Taken together, the tests enable patient and doctor to act to prevent serious infections before they occur.

Disadvantage:

It is more difficult to act on test results, since the patient often feels fine. People who feel healthy may be less motivated to begin treatment. Test results are variable, changing for many reasons.

Because HIV infection can be a life-and-death matter, we believe it is critical to choose the second approach. Taking a *preventive* approach makes it possible to:

- Ê use treatments at the stage in which they are most effective
- Ê head off serious opportunistic infections and the further damage they do to the immune system
- Ê slow the spread and reproduction of the virus.

Some people hesitate to act in a preventive manner because the treatments currently available are

not perfect and the research on them is incomplete. Thus, they feel it might be best to wait for better treatments. However, no one knows when better treatments will become available - many hopes have been raised and dashed before. Although we don't know precisely the results of using current treatments in every case, we do know what happens without treatment:

Once infected by HIV, people do not get better naturally or by waiting. There is no natural remission.

The purpose of preventive treatment is to buy time, to slow the progress of the disease while researchers seek better treatments. Once infected, people have only one chance to manage HIV disease correctly. A preventive approach is the only one which offers clear hope.

Reducing Variability in T-Cell Testing

T-cell testing produces widely varying results. Some physicians fear that T-cell testing may be so variable as to be unreliable. There are two kinds of variations which affect the T4 count: real variations which reflect a person's immune health, and insignificant variations caused by factors unrelated to immune health. Thus, we need to know what causes these artificial, misleading variations and how to minimize them to get a more reliable picture of immune health. The value of T4 monitoring can be improved when you:

- *Look for trends, not individual numbers*
No single T4 test gives a complete picture of immune health. Ideally, T4 tests should be taken at least on a quarterly basis (every 3 months) for those with counts around or below 500, or every 6 months by those with higher counts. It is the overall trend of the numbers which tells which way things are going.
- *Test at a consistent time of day*
Early in the day and before eating, fewer of the T4 cells are circulating in the blood, and thus the count may be lower. Later in the day, more are in circulation and the numbers are likely to be higher. By testing at the same time of day, the numbers from one test to the next can be more validly compared.
- *Use the same lab for testing each time*
Different labs use different techniques and machines, producing different results. Work with your doctor to be sure the test is done at the same lab each time.
- *Test under normal conditions, avoiding periods of infection*
Even minor infections can affect the T4 count and give misleading results. A second blood test, called the ESR or sedimentation rate, can also be run, which may indicate whether the body is fighting infections, even if you are unaware of them. If an active infection is present, either delay the test or repeat it later to get a more accurate picture. If an ESR test suggests an infection was present at the time of testing, don't take the T4 count numbers too seriously.
- *Avoid acute stress, recreational drugs, and lack of sleep*
Acute stress (not everyday stress) can lower T-4 counts in some people. This effect is often greatest in periods of loneliness, depression, or lack of support. Drug use and lack of sleep can lower T4 counts.

The best way to achieve meaningful and comparable results in T-cell monitoring is to create a standard or routine climate for testing, so that variations which affect the count are held to a minimum.

Other Types of Testing

In recent years, other tests have become available which help measure immune health or reflect the progress of HIV infection. Using these additional tests gives a more accurate picture than that provided by T-cell testing alone. Three important

Monitoring Immune Health

tests are called p24 antigen, p24 antibody, and the beta-2 microglobulin test.

P24 ANTIGEN TEST:

What is it?

This test measures the level of a particular protein produced in the "core" of HIV. This protein or antigen, is known to scientists as "p24." Normally, the body produces antibodies to rid itself of antigens. When p24 antigen can be measured in the blood, the virus is believed to be actively reproducing itself so rapidly that the body cannot produce enough antibodies to overcome it. When this occurs, healthy cells may be infected at an increased rate. This imbalance between antigen and antibody is thought to occur for a brief period shortly after infection, and again much later when the immune system is breaking down at a more rapid rate.

What does it show?

Studies have found that people with high p24 antigen level (sometimes called a "positive" test result) are more likely to progress to a full AIDS diagnosis in the next few years, even if their T4 count doesn't suggest immediate danger. Thus, a positive or high p24 antigen test result is a serious warning sign.

P24 results are often reported as simply positive or negative, although the test actually measures the amount of p24, reported as a number. Numbers below 40 or 50 are called negative, numbers above, positive. A typical positive result might be a reading of 100 to 400, but can range into the thousands. The degree of positivity (how high the number goes) has so far not been shown to correspond to the risk of disease progression, that is, all results reported as positive suggest the same increased risk. However, no firm predictive value has yet been established for p24 readings for people already diagnosed with AIDS.

How is it used?

P24 is almost universally used in clinical studies to measure the effects of anti-viral medications. Many physicians recommend the test to determine when to treat aggressively and to measure the effects of treatment. This test is still classified as "investigational" by the FDA, and is not always available in every lab or every city. (p24 antigen and antibody tests can only be given to people who have tested positive in the usual HIV antibody tests.)

P24 ANTIBODY TEST

What is it?

High levels of antibodies to the p24 antigen seem to slow the progression of HIV. This test measures the level of these protective antibodies to p24 in the blood.

What does it show?

Antibodies and antigen normally bind together like lock and key. High levels of p24 antibody suggest that the body's defenses are still working properly and that new virus particles are rapidly being cleared from the body. Typically, p24 antibody levels remain high while the patient experiences few or no symptoms, then diminish over time. When p24 antibody levels have fallen, the p24 antigen can become detectable in the blood. So far, there is little understanding of what causes the drop in p24 antibody levels.

Thus, p24 antibody levels might be an earlier predictor of HIV progression in some people. One study showed that p24 antibody levels became negative up to 18 months before the first p24 antigen test became positive. When p24 antigen and p24 antibody are both positive, the body may be experiencing an "auto-immune" disorder, in which the immune system is attacking healthy cells and tissues.

How is it used?

Like the p24 antigen test, the p24 antibody test is still investigational and is even less widely available. The test is useful only as a predictor of HIV progression and has no established value in monitoring the effects of treatment.

BETA-2 MICROGLOBULIN TEST:

What is it?

The beta-2 microglobulin test measures the presence of a tiny protein particle found on almost all cells, including the T4 and other cells which HIV can infect or destroy. As cells die, the beta-2 is released in the blood. Thus, there is always some degree of beta-2 in the blood as a result of normal cell degeneration and replacement. In chronic illnesses, such as HIV, the level of beta-2 increases beyond normal levels, reflecting a more rapid rate of cell destruction.

What does it show?

Studies show that people with a high beta-2 level are much more likely to progress to AIDS in the near future. Some researchers believe this

test to be the most accurate of all predictors of progression to AIDS.

Beta-2 levels are usually reported as a single digit number, carried out to one decimal place, such as 2.3, 3.5, or 5.2. A number of about 2.6 or below is considered normal. A level of 5.0 or higher indicates the highest known risk of coming down with AIDS within 3 years. Even persons with readings between 3.0 and 5.0 are at increased risk.

How is it used?

Since beta-2 testing in HIV is new, its uses are still being researched. It seems likely that it will be used to monitor the effects of treatment and to identify patients who are at highest risk of an impending AIDS diagnosis. Other indirect markers, such as neopterin levels, are also being investigated as potential measures of HIV progression.

SUMMARY: TESTING

While no one of these tests gives a total picture of immune health, taken together they are very important. Some researchers believe that as we learn to manage HIV as a chronic illness, these tests will provide guidance about what treatments to use, when to use them, and how well they are working. Because some of these tests are new, they may not be as accurate as we'd like. Also, because of potential inaccuracies or misunderstandings of their proper use, some physicians are skeptical of their value or the cost of using them. Over time, these and other tests are likely to become the standard tools for monitoring and managing HIV infection.

Project Inform Videotape:

The Message is Hope

Now available!

This 75 minute videotape contains the dynamic message of realism and hope that is the heart of Project Inform Town Meetings. Thanks to a generous private donation, you can hear the message at home, at your own pace.

Available on VHS (beta by special request). A donation of \$25 is asked with your order.

Organizational Update

Correction: In the last issue of PI Perspective, we incorrectly named Pacific Telesis Corporation as the source of a grant to fund our new Spanish language treatment information materials. The donor was actually Pacific Telesis Foundation, which has since generously given a second grant to produce additional Spanish-language materials and a brochure.

Another correction (at least for our Bay Area correspondents): In a recent mailing, we announced our 1989 Town Meeting Schedule, without listing the location. So here it is: The meetings will be held at the MCC Community Church, 150 Eureka (between 18th and 19th on Eureka), in San Francisco at 7:30 PM.

Project Inform 1989 Town Meeting Schedule

First-timers		Regulars
5	April	26
3	May	31
7	June	28
5	July	26
2	August	30
6	September	27
4	October	25
1	November	29
6	December	27

Announcing: HIV Treatment Treatment Awareness Week, June 22-25. This major event, created by Project Inform, will

be held at the San Francisco Civic Auditorium. Its purpose is to increase awareness of the options available for treatment of HIV infection, and to encourage early diagnosis and intervention. It will be co-sponsored by the Bayview Hunter's Point Foundation, the Latino AIDS Project, Mobilization Against AIDS, the San Francisco AIDS Foundation, the San Francisco Department of Public Health, and the AIDS Service Providers of the Bay Area. It will feature three days of major events, including a medical symposium (keynote speaker, Dr. Anthony Fauci), a political and benefits forum, a Health Fair focusing on practical issues, and a major fund-raising benefit. Since the events will take place at the peak of Gay Pride week, conference registration is expected from throughout the nation. All are invited, so if you're planning to be here for Pride Week (*and there is no better place to be that week*), plan on attending. Pre-registration forms will be mailed to all PI correspondents in the immediate area.

PI, for the first time, has been selected to be a beneficiary of the AIDS Bike-a-Thon, sponsored by Different Spokes. This highly regarded San Francisco phenomenon is a key fund-raising and social event that shouldn't be missed. Festivities include food and entertainment. People sponsoring riders on behalf of Project Inform (or other groups) will find this a great way to support your local non-profit foundation.

Your Help Makes a Big Difference !

Please make a contribution, bequest, or give a gift in someone's name. All donations are tax deductible. Use this coupon: your name is on the other side, so there's no need to sign it.

\$25 \$50 \$75 \$100 \$250 \$500 \$1000

Or use the service for yourself or a friend.

In San Francisco, volunteer time or provide services or equipment. We need:

Hotline operators
Public-speaking professionals
Fund raising skills

Clerical assistance
Database input

Research assistance, writing
IBM and Macintosh computers

PROJECT INFORM
347 Dolores, Suite 301
San Francisco, CA 94110

National — 1-800-822-7422
California — 1-800-334-7422
Local — 415-558-9051