Number 7 November, 1989

PI Perspective

Project Inform
San Francisco, California

Compound Q - The Real Story

Amidst a storm of controversy, organizational bickering, and legitimate scientific interest rivaling the concurrent San Francisco earthquake, Project Inform this month released preliminary data from its community-based treatment protocol using trichosanthin (Compound Q). The findings of the multi-center program give a mixed but intriguing picture of a drug which may offer a new kind of hope, along with serious side effects which may prevent its use at some stages of illness. Readers are invited to move to the section of the story of greatest personal interest: *In the Beginning* (background on trichosanthin and why and how of the protocol); *Outcomes* (findings regarding safety and efficacy, page 2); or *The Aftermath* (implications for personal use and where to go from here, page 6).

In the Beginning

Compound Q came to our attention in 1988. The AIDS networks learned that scientists at the University of California and in private industry (Genelabs) had filed a patent on new drug which appeared to selectively kill HIV-infected cells. The discovery came about through the work of Dr. Michael McGrath, who had been pursuing new observations about the pathology of HIV, namely that direct infection of T-cells alone could not account for the destructiveness of the disease. McGrath found that in addition to T4 cells, HIV was infecting macrophages, a common type of immune system cell found in the blood and many body organs. Unlike T4 cells, macrophages did not quickly die once infected, but lived for as long as a year and a half, always able to produce new virus. They appeared to be the missing reservoirs of HIV which kept the infection alive and well, despite the rapid death of infected T-cells. The infection of macrophages helped explain the disease, perhaps being a factor in all but its auto-immune aspects.

McGrath and company reasoned that HIV infection could be greatly moderated if the infected macrophages could be destroyed and replaced with healthy ones, which in turn could be protected from infection with conventional drugs like AZT. Without doing something about the infected cells, however, the fight against HIV was but a futile effort to slow down the spread of virus to new cells, while doing nothing about the existing infection.

Word of McGrath's findings slowly leaked out in 1987 and 1988, despite an official blackout while lab research continued, FDA forms were filed, and patent rights sought. Despite the blackout, some individuals learned of the Chinese version of drug and succeeded in importing it as early as November of 1988.

Chinese researchers brought trichosanthin to McGrath in late 1986. In his lab, one of a very few in the world capable of studying infected macrophages, it appeared to be a very powerful anti-viral against all forms of HIV expression, and at doses that appeared safe for human use. Using fresh human blood from AIDS patients, the drug appeared to selectively kill infected macrophages and infected T-cells, while doing little damage to healthy cells. In these *in vitro* tests, it was more potent and more selective than any other known anti-HIV drug, and it achieved its goals in an entirely different way.

In China, the drug had been used successfully for more than 20 years for certain cancers and to induce abortion. It had a good safety record when manufactured and used properly.

Word of McGrath's findings slowly leaked out in 1987 and 1988, despite an official blackout while lab research continued, FDA forms were filed, and patent rights sought. Despite the blackout, some individuals learned of the Chinese version of drug and succeeded in importing it as early as Novem-

In this issue:

ber of 1988. By January of 1989, several groups had found sources and some were beginning to experiment with it. In February, PI became aware of a pioneering effort in Florida to evaluate the safety and effectiveness of Chinese trichosanthin, as well as to treat significant numbers of patients. Compound Q suddenly had all the makings of becoming the next big "drug of the year."

While this sounded good to people interested in trying Q, it also raised serious concerns. True, Q might represent a new and more effective approach to therapy, one which would add to the benefits produced by any other approach. Some highly placed individuals had dared to use the "C" (cure) word in discussing it in the media. Yet Q was also a toxin by nature and it could also have dangerous side effects, effects perhaps unheard of in the Chinese experience. The thought of thousands of people self-medicating with Q was sobering.

At the same time, if Q did have the capabilities *in vivo* that it showed in vitro, a disaster of another type awaited. Two and a half years had already passed since its discovery, and its development had proceeded in secret and at the glacially slow pace of U.S. drug development. How many more years would pass slowly away while people died in ever-increasing numbers? How long would traditional methods take to determine the usefulness of the drug? Or how quickly could they develop credible data to discourage its use, now that the genie was out of the bottle?

Project Inform decided to take action, following the very model upon which the organization was formed in 1985 - the development of community-based treatment protocols and data gathering. It was critical to develop information on the safety or usefulness of Q to guide or discourage community use. We convened a team of physicians and researchers who had knowledge of this class of drugs, along with people from the patient community, attorneys, activists and other interested parties. Collectively, a protocol was drawn up to treat 60 people in four groups. The protocol was reviewed by 7 community physicians, at least half a dozen researchers, several lawyers and regulatory experts in 3 states, and an uncounted number of community representatives and potential patients. Agreement was reached about the objectives and design of a program which was scientifically comprehensive, morally expedient, and completely ethical. The protocol was in keeping with Project Inform's original mission - the creation of community-based research following a treatment model for clinicians, rather than the research model of academics. The complex activity sheet which guided the program is shown in Figure 1.

To ascertain the quality of the Chinese drug and to conduct necessary animal toxicology studies, medical director Dr. Alan Levin established a relationship with the noted cancer research center at the University of Nottingham in England. Later, the laboratory conducted follow-up studies to look for the development of antibodies against Q in the patient's blood. In this and in many other regards, the PI study exceeded the complexity and scientific sophistication of most other community based programs.

The objectives are simply described:

- first and foremost, to treat patients who were failing conventional therapy or who had exhausted their treatment options;
- to learn from the experiences of these first courageous patients by treating them under a fixed protocol and collecting lab and clinical data as would be done in a research program;
- as much as possible, to make a preliminary evaluation of the safety of using Chinese trichosanthin while gaining as much data about its efficacy as possible; this data in turn would be used to guide or dissuade community use of drug.

With these objectives and the design of the treatment protocol in place, and the experiences of the pioneering Florida group to guide us, the first patients were treated under the program in the last week of May. The groups consisted of a total of 19 people in San Francisco (under Drs. Larry Waites and Alan Levin), 17 in New York (under Dr. Barbara Starrett), and 15 in Los Angeles (under Drs. Don Long and Paul Rothman). In Florida, the separate program already underway for two months began using our case report forms to collect and report their data. Dr. Robert Mayer and the group in Ft. Lauderdale followed their own program design, which addressed many variables not part of the program followed at the other three centers.

Program Outcomes

A final assessment of the protocol outcomes will not be completed for several more months, as participants will be followed for a total of six months. Reports of toxicity and preliminary reports on efficacy, however, were made to the community in San Francisco on September 19 and to the FDA in Washington on October 6. Toxicity reports are considered reliable at this stage since patients have already completed their scheduled administrations of the drug. Efficacy reports, however, are very preliminary and cannot be considered definitive.

Toxicity

Most participants tolerated the drug quite well, with the vast majority reporting only minor toxicities reminiscent of flu-like symptoms. More serious toxicity was noted in a small subset of six participants. The implications of the toxicity findings must be stated up front. Although we are not recommending that anyone use the drug, *Q should definitely not be used by the following types of patients:*

- people with very low T4 counts (less than 100)
- people with any evidence of HIV infection in the brain or nervous system
- people with active opportunistic infections
- people who are severly debilitated or near death

The reasons for this warning are evident in the toxicity findings.

Minor toxicities were experienced to some degree by almost all, although very few found the problems bad enough to warrant dose reduction or drop-out. The most common problems included mild fevers lasting for up to 2 to 5 days,

muscle aches and pains, joint pain and swelling, various rashes, and some hives (only in people who received intramuscular injections). These symptoms cleared with time after treatment, with the strongest effects occurring after the third treatment. These problems were not serious enough to discourage use of the drug.

Six people also experienced a more serious form of side effect best described as *mental status change*. This ranged from brief periods of confusion or disorientation, to reversible coma and seizure at the extreme. Although media reports have varied, as have initial descriptions by medical personnel, the current official breakdown is as follows: one person experienced a reversible coma; two experienced temporary seizures; three others experienced periods of disorientation or confusion ranging from a few hours to a week.

The patient who experienced coma awoke in 48 hours after treatment with the steroid Decadron (commonly used in head injuries). Six days later, he aspirated (vomited and inhaled) in his sleep and was not resuscitated in time to recover. The cause of aspiration is unclear; it may be related to the prior coma, to any possible use of sleeping or pain medications or any other medications, or even to digestive upset. Some confusion exists about the events at the hospital on the morning of his death, but it appears that hospital staff believed the patient suffered brain death as a result of lack of oxygen due to the aspiration. Consequently, a recommendation was made to his family to withdraw life support. Contrary to early media reports, there is no suggestion that this action was taken inappropriately. The family acted on medical advice and later sought, along with the program physicians, to have an autopsy performed. It is unfortunate that the neither the hospital nor the coroner would permit an autopsy. Even though the drug would have cleared from his body several days previously (the drug's half life is less than 2 hours), physicians needed to know whether it played any role in the cause of death. Without the autopsy, we will never know.

One patient who experienced a seizure and disorientation was briefly hospitalized but released in 24 hours. In subsequent weeks, he rejoined program activities, testifying to others about his experience. He also repeatedly sought retreatment, but was refused because of the doctor's concern about his initial experience. Approximately 6 weeks after his treatment, the patient died of what his doctor felt were unrelated causes or causes which pre-existed his use of Compound Q. After the New York Times printed a spectacularly inaccurate account of the circumstances surrounding the patient's death, a firestorm of controversy engulfed the treatment program and unfairly maligned the highly respected New York physician conducting it.

A second patient who suffered a seizure in San Francisco recovered without incident. The remaining 3 patients who suffered less severe mental status change responded positively to treatment with Decadron.

One patient in the "official" study of GLQ223 at San Francisco General Hospital also suffered a coma, from which he has only partially recovered. In this instance, however, the patient was not immediately treated with Decadron. He remained semi-comatose for more than 10 days before treatment with Decadron was attempted, and awoke 48 hours later.

This mental status change was never an immediate result of treatment, but occurred 24 to 60 hours later. It always began with mild confusion or disorientation, but in some instances became more severe over time. Treating patients with Decadron at the first sign of disorientation, and continuing treatment for 72 hours, appears to keep the problem from worsening into coma or seizure. But no one can be certain of this without more experience.

There were three key things learned in these incidents. First, the occurrence of mental status change was not related to the dose used. The problem occurred in some patients receiving only 10 micrograms (per kilogram of body weight) in the PI program, and in the patient received 36 micrograms in the "official" program. Even the distinction between coma and mild confusion did not appear to be dose related. Instead, the factors which predicted mental status change were the patients' T4 count and their history of nervous system involvement with HIV. The mean (average) T4 count of patients who had a mental status change was 23, while in patients who didn't have the problem it was 169. Also, 3 of 4 patients who received MRI (Magnetic Resonance Imaging) brain scans prior to treatment showed evidence of HIV-related problems in the brain. Others were not tested.

Another type of toxicity noted was more difficult to categorize since it was infrequently and inconsistently seen. In one center, two patients with KS were believed to worsen, with spreading of lesions. This occurred in patients treated intramuscularly, an approach abandoned and not used elsewhere because of the severity of side effects. When given intramuscularly, the drug appears to remain in the system far longer than it needs to. In other centers, the response to KS was mixed, with no hard evidence of either worsening or improving. Two patients reported clearing of minor lesions, but this is not well documented.

A last type of toxicity is one which is indirect. While in the body, trichosanthin is somewhat immunosuppressive for a short period. In the earliest patient groups, steroids were given along with the trichosanthin to moderate expected side

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?

- About 3 times per years, 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.

effects, such as fever and muscle aches. The combination of the immunosuppressive effects of the drug, as well as those of the steroids, may have worsened an existing opportunistic infection in one patient. Because of this, the program later switched to the use of non-steroidal anti-inflammatory drugs, such as Motrin, to moderate fever and muscle ache.

Summary, Toxicity:

In sum, the toxicity picture of Compound Q is mostly similar to that reported in China, with the exception of the mental status change which appears to be unique to HIV infection. Because this toxicity is potentially deadly, it argues against any form of self-medication or self-experimentation with Q. Clearly, this drug should only be administered in a sophisticated clinical setting by experienced medical personnel. Afterwards, patients must remain under observation in some form for at least 60 hours, and problems must be reported to medical professionals immediately. Patients with KS should avoid use of the drug until a clearer picture emerges of its effect, as should anyone with active opportunistic infections.

Despite these concerns, however, the toxicity appears to be sufficiently manageable when the drug is given in a proper medical setting by experienced personnel and should not hinder its future development. Unfortunately, critics of the drug, or the theory of AIDS it represents, are already using the toxicity evidence gathered here to condemn the drug. We find this foolish, short-sighted, and scientifically dishonest. In our belief, anyone expecting to find a completely non-toxic, utterly natural treatment for AIDS (which tastes good, too!) is engaged in magical thinking. AIDS is one of the most toxic and destructive diseases known, and it works by destroying the body's ability to fend off the invader. We reluctantly accept the notion that treating it, managing it, or eventually curing it, will never be a piece of cake.

Efficacy

It is critical to put any findings of efficacy in perspective, as there are several reasons that they must not be seen as definitive or conclusive. The data represent a snapshot in time, not a final result, and is reported part-way through the program using the latest data common to the centers. It may improve or worsen over time. Also, the data lack a traditional control group for comparison (although in some instances it is possible to use the patients' medical histories as the control). Another limitation is that the data reported thus far only incorporates part of the study groups. It may not be possible to fairly directly incorporate the Florida data, since the program design there was different in very significant ways. The data from the Los Angeles arm has not been incorporated because case report forms - the key study document - are not yet completed. Thus, at the time of this writing, the efficacy data primarily represents the combined findings of San Francisco and New York, since these groups operated in essentially the same fashion and submitted completed data by deadline. The Florida group has already released a separate summary of their findings. Finally, we must remember that Phase 1 data is never conclusive. It is typically not statistically significant because of the lack of control groups.

Yet, despite the concerns, there is some reason for confidence in the findings. While the markers are considered "soft," they all point in thesame direction. Clinical observations appear to support and even extend the lab data. The findings occurred primarily in patients who were failing despite long-term AZT use, making this a *worst case* analysis. That a drug would have any effect at all in such a circumstance is encouraging. As much as possible, the treatment program followed the conventions of good research: close, elaborate follow-up, use of a single, central lab, and had a very high degree of patient compliance. In these regards, as well as the lab numbers, the program outcome might be favorably compared to the data submitted in the DDI Treatment IND application.

Efficacy was measured in both anti-viral properties as well as immune responses. For anti-viral activity, patients were tracked with the p24 antigen test (Coulter Counter). Because this test is not legal except in "official" research programs in New York, the data presented is based on the San Francisco arm. All San Francisco patients were considered AZT failures, most with active or high p24 values despite long-term AZT use. Data were collected weekly and then monthly. At the last data collection point (2 to 3 months after beginning treatment),

- 8 of 14 patients with positive p24 showed a sustained drop, averaging about 50% (remember, these numbers are generated several weeks *after* the last treatment).

- 6 patients who had high p24 values at baseline (more than 100), all 6 had a sustained drop averaging 67% (graph shown).

- 4 of the 4 patients who were p24 positive in Florida experienced a sustained decline of about 50%.

The decline in many had been greater shortly after treatment, but levels were edging back toward baseline at the late data point. It appears that the higher the starting p24, the bigger the benefits. Some of the remaining patients also experienced initial drops, but their counts had returned to baseline at the last data collection point.

At least one critic has pointed out that AZT reduces p24 to undetectable levels, at least for a while, in some patients. What's so good about these results, he asked? What's good is that these results occurred after 2 or three injections of a tiny amount of fluid - not months of daily therapy. Also, they occurred in patients in whom AZT was already failing to control p24.

There was also some preliminary evidence of efficacy in T4 counts, although the degree of benefit varied both by the starting health of the patient and by the dose of the drug used. The T4 data are drawn exclusively from the New York and San Francisco arms of the program.

Mean T4 counts were calculated at baseline and were again at the latest data point all patients had in common, a period two months after therapy began. The results were as follows:

T-Cell Response, Group Means

Subgroup	Baseline	Post Rx	Chge.
All SF	91	102	+12%
All NY	119	169	+42%
All starting >100 T4	225	286	+27%
All starting <100 T4	27	33	+22%
All using low dose	58	88	+52%
All using high dose	160	183	+14%
High dose, >100 T4	245	261	+7%
High dose, <100 T4	33	66	+101%
Low dose, >100 T4	182	342	+88%
Low dose, <100 T4	57	34	-19%

It is important to remember that these are changes in the mean T4 counts of the groups and subgroups. Some individuals did better than figures suggest, while other did not do as well. A clear majority, however, experienced gains rather than losses. Some critics have pointed out that not all of these changes represent clinically significant changes. Whether or not this is the case, they fail to note that this is the method - reporting

of changes in group means - by which the T4 impact of all other drugs, such as AZT and DDI, is measured. By this standard of comparison, Q is doing very well at this stage.

The Florida group's separate findings showed an overall increase in percentage of T4 helper cells, but not an increase in the total mean T4 counts. Since this group represents many different methods of administration and dosing schedules, it is more difficult to interpret and is inherently less able to demonstrate credible efficacy findings. Nonetheless, in addition to pioneering the treatment use of trichosanthin, this group explored several important approaches to treatment from which all other groups learned.

As might be expected from these data, improvements were also noted in T4/T8 ratios (up 16% in SF, 43% in NY) and T8 levels overall decreased (after an initial increase). ESR (sedimentation rates, an overall indication of inflammation or infective activity) declined substantially - down 39% in SF, 15% in NY. Beta2 microglobulin levels initially increased in most patients, as would be expected if cell death were occurring, but declined over time in the healthier patients. The New York group showed a 34% drop in beta2, while the San Francisco group showed a slight 10% increase. Nearly all patients experienced a short term increase in white blood count, with most patients have a slight, sustained increase of less than 10% overall.

Clinical responses

In addition to lab marker improvements, physicians have reported clinical improvements in many of the patients. Although such measures are more subjective, they are perhaps more significant to the HIV patient, who often finds his/her feelings at odds with the lab data. The most common clinical response, reported by a majority of patients, was a marked and lasting increase in energy levels. A few participants have returned to work or full-time school for the first time in years. Others have reported clearing of long-running minor OIs, such as hairy leukoplakia and thrush (although such symptoms often worsened briefly shortly after taking the drug). In future programs, greater care will be taken to measure functional levels, such as Karnofsky scores, before and after treatment.

Efficacy summary

Although the data are only suggestive and inconclusive, they appear to indicate the possibility of benefit for many types of patients after using trichosanthin just three times. All benefits noted thus far seem temporary, with declines beginning to show up 6 to 8 weeks after treatment. The presence of additional benefits from repeated, regular use, such as once a month, or once per quarter, awaits further study.

The fact that any efficacy data emerged in a short treatment protocol is in itself cause for hope. Perhaps what is most important about any possible benefits from trichosanthin is to reflect upon the mechanism of its action. Whatever it is doing, it is reasonable to suspect that it is doing it by killing infected cells. That it can work at all by killing cells opens up new horizons for AIDS research. Whatever its benefits, they should be additive to those of any other therapy. Many possible combination therapies are immediately suggested.

Two factors have previously given some researchers qualms about the potential for using trichosanthin - the possibility of allergic or anaphylactic reactions, and the development of antibodies against the drug itself. Either would seriously limit the usefulness of the drug. Both of these concerns have been answered, at least partially. No patient in our groups or in the "official" study have so far experienced allergic or anaphylactic reactions. Also, work conducted by PI with the University of Nottingham (U.K.) has so far found only a single patient who has produced a mild antibody response to trichosanthin. In this instance, the patient has already been successfully retreated without incident.

The Aftermath

On October 6, 1989, PI and the treating physicians met with the FDA in Washington for what all involved concluded to be a remarkable meeting. One senior FDA official privately called it "day one of the revolution." A senior executive of one of the world's largest pharmaceutical firms (who attended) called it the "most exciting - and most terrifying" meeting he had attended. "Exciting" because it represented approaches to research that many had long believed necessary; "terrifying" because of its implications for business-as-usual in the pharmaceutical industry. Rather than the chastisements critics had called for at the meeting, a respectful scientific discussion took place, one which assumed and demonstrated integrity on all sides. The outcomes of this meeting, which we feel are very positive and which break new ground, must await a final joint announcement. But for now, we can say that both treatment and research with trichosanthin will continue as long as the data and clinical findings deem it appropriate. And Project Inform will be an active player in that process.

While this scenario continues to unfold, many patients will feel caught in a terrible bind of wanting to use the drug as a last resort, or as a bold first step. Those who seek to use the Chinese drug - without waiting for additional information, unfortunately must be discouraged from doing so. The risks are high for the very type of patient who is likely to feel most desperate to try something. For those who fear for their lives in the very short term, trichosanthin may never be a good option, as it is so demanding of the patient's strength. For those less ill, other options should be exhausted first. It makes little sense for someone who hasn't tried AZT to demand trichosanthin.

Dilemmas exist for people at all ends of the spectrum of HIV. It is futile to argue against the feeling of the sickest patients that they have nothing left to lose. It is easy to see why healthy seropositives feel that the drug is unlikely to put them at any great risk. And those in the middle can convincingly assert their right to try to stop the decline of the immune system before they fall into a high risk category. Yet these arguments are generic to almost any new drug. For now, we can only say that the drug's benefits are not so well proven that serious risks should be casually accepted in using it. Yet this is only an opinion. Neither Project Inform - nor anyone else - has the right to tell individuals what they can and cannot do, what risks they can and cannot choose to accept. We feel we have already accomplished our primary goal, that of clarifying the safety and risks of using Chinese trichosanthin. The risks are very real, but probably limited to a certain class of patients. The benefits are as yet more ephemeral, but enticing. Whatever personal decision individuals choose to make, a few points are clear:

- Trichosanthin should never be self-administered or given by anyone less than fully qualified medical personnel. In the PI program, this meant an anesthesiologist to set the IV, a resuscitation specialist and kit, a bee-sting kit and experience in using it, at least one primary physician, and a watchful companion for at least 60 hours.

- The drug is very dangerous for people with T4 counts below 50 (or even below 100), especially in the presence of even the slightest evidence of HIV involvement in the brain or

nervous system.

- People on or near the deathbed have little chance of being helped by trichosanthin, but a good chance of being harmed by it (the same might be said about AZT, however).

- We don't yet know the best way to use the drug, to harness its cell killing powers. Although the PI program has gathered more data on this than anyone, it is incomplete.

- Despite these considerations, there is a substantial subset of people who have used the drug who report strong and lasting improvements. Their experiences are verified both by their lab numbers and the judgments of their physicians.

These are tough, individual decisions and, once fully informed, we must be willing to entrust others with their own destinies. Trichosanthin is far from a perfect option, but it shares imperfection with all of the other alternatives. Whether it is an appropriate alternative for anyone at this stage of its development, or ever will be, remains a matter of personal choice.

It is futile to argue against the feeling of the sickest patients that they have nothing left to lose. It is easy to see why healthy seropositives feel that Q is unlikely to put them at any great risk. And those in the middle can convincingly assert their right to try to stop the decline of the immune system before they fall into a high risk category. Yet these arguments are generic to almost any new drug... Neither Project Inform - nor anyone else - has the right to tell individuals what they can and cannot do, what risks they can and cannot choose to accept.

Informed Consent

An essential part of the Project Inform trichosanthin treatment protocol was a level of informed consent that even critics acknowledged to be unprecedented. Many patients, physicians, and (to our surprise) regulatory officials have admitted to us that the traditional informed consent and review process does little except increase bureaucratic delays and protect research institutions, while often leaving the patients to fend for themselves. Patients complain that the informed consent process is little more than a signature on a poorly understood and awkwardly-written document, signed blindly in a hasty and desperate effort to secure access to a treatment otherwise unavailable. It is not unusual for such informed consent documents to overlook key side effects of drugs (as occurred in the suramin disaster of 1986). Under the traditional system, once a study has been approved by a nameless, faceless Institutional Review Board, and once the patient has signed a poorly understood consent document, all rights are given up.

The informed consent process established by attorneys working with PI differed in key ways. The consent document, a lengthy but simply written piece, ran 13 pages and was given to patients at least 24 hours prior to signing. Next, the patient selected a personal friend or witness to join him/her at a video-taped consent discussion. This half hour discussion included the patient, the witness, the treating physician, and a "patient advocate" who was typically an attorney and who led the discussion. The advocate's duty was to make sure that the patient understood the risks, the lack of any proven benefits, and the availability of other treatments. The patient's experience with other treatments and the reason for failure were documented. The patient's witness was present so that all might determine that the patient was of sound mind in making the decision to seek treatment with trichosanthin. When all points were clear, and after the advocate challenged the patient on each key point, the patient made a closing statement to his/her loved ones or relatives, explaining why he/she was doing this. As any patient who has gone through this process can attest, their consent was, perhaps for the first time, truly informed.

Consent, however, did not end with the signing and video-taping. Instead, each time a significant adverse event happened to anyone, all the patients in the program were notified, typically within 24 hours, and invited to reconsider their participation. This is in stark contrast to the "official" "approved" model, in which such data are discussed and kept secret by data safety monitoring boards, IRBs, and researchers. A terrifying example of this was the 1986 suramin study. Long after several patients had died from complications of the drug, others were still being urged to continue taking it, but weren't being told of the newly understood risks. In the recent AZT seropositives study, "informed consent" erroneously meant telling patients that there was no need for PCP prophylaxis, that AZT itself would do the job (PCP prophylaxis was finally added in February of 1989, almost a year and half after the start of the study).

As new experimental treatments become more widely available under such programs as parallel track, it will critical that new and better approaches to informed consent be used. We believe that the steps taken in the trichosanthin treatment protocol, while not perfect, point in the proper direction. It is not enough to sign a complex piece of paper, nor is it enough to think that some nameless, faceless institutional review board will look after your rights. The patient him or herself must be better informed, and a determination should be made that true understanding exists. Education, not bureaucracy, is the best form of consumer protection.

Project Inform expresses its deepest gratitude for the support, both personal and financial given during the trichosanthin program by our members and constituents. The program was costly (but a fraction of the cost of standard research), but our supporters didn't flinch.

Innovative work such as this cannot be done without your assistance. Your contributions truly make a difference.

Q-Induced Mental Status Change

One of the most intriguing, and most discouraging learnings of the Project Inform trichosanthin treatment program was the discovery of mental status changes ranging from disorientation to coma. Most certainly, these events, however infrequent, are related to the effects of HIV on the brain and nervous system. Researchers studying the problem hope that this new knowledge will lead to a better understanding of AIDS dementia.

There are two possible causes of the mental status change. The first and most obvious is the possibility that Q is directly killing infected cells in the brain. HIV infection comes to the brain in a form of macrophage called micro glial cells. These cells are transient, moving through the brain, and are not part of its permanent structure. While in the brain, they provide nutrients and act to some degree as insulators. Thus, it is theorized that if many infected glial cells are killed at once, some disruption of brain activity would be expected, accounting for the mental status change. This explanation would require that Q cross the blood/brain barrier, which is uncertain because of the fairly large size of the molecule. The blood/brain barrier of HIV-infected people, however, is believed to be seriously weakened, making more possible that the drug could cross over. If this explanation is correct, the problem might be solved by treating slowly at very low doses, thus more gradually clearing out the infected cells while causing less disruption. This theory is consistent with the finding of some patients that their mental acuity improved substantially after treatment.

The second theory is that the problem is "factor mediated," in other words, it is caused by some substance or "factor" being released in the blood. There is growing evidence that AIDS dementia itself is caused by a factor, called a cytokine, which is being released by infected cells. When this cytokine reaches the brain, it apparently disrupts neurotransmitter (electrochemical) activity, thus causing dementia or mental status change. At the extreme, it causes coma, just as we have seen with Q. Research at San Francisco General Hospital is underway to identify this substance and then see if it is perhaps being released by dying cells after

AZT News: The Final Chapter?

In recent months, new studies on the efficacy of AZT have been presented both by government scientists and private researchers. The conclusions reached by the new studies have profound importance but sound remarkably familiar to people who have previously subscribed to the Basic Message of Project Inform. It is still too early, however, to say that we have the final word on AZT use.

The three key studies reported: (1) the benefits of AZT for people with early ARC symptoms and having between 200 and 500 T4 helper cells; (2) the benefits of AZT in healthy asymptomatics with fewer than 500 T4 helper cells, and (3) the impact of AZT on the development of AIDS dementia in a long-term Dutch study. Since these studies have been reported on in the media and in most AIDS news sources, and because the data has not yet been published, we will only briefly discuss the primary findings and focus instead on the practical implications and the questions which remain in their wake.

In a fourth and very important study, also not yet published, new data was reported which confirmed for the first time that lower doses of AZT may be just as effective as the higher ones in common use.

Primary Findings

Study 1: A placebo-controlled study of AZT in 713 people with ARC was conducted by the National Institute of Allergy and Infectious Diseases (NIAID). Volunteers were required to have one or two ARC symptoms and a T4 helper cell count between 200 and 500. The most important benefit noted after two years was a lower incidence of progression to AIDS among those who received the real drug. Some 36 people in the placebo group progressed to AIDS, as compared to 14 receiving AZT. Few other details have been released since the study outcome was announced in a press release, rather than in a completed journal article. While some have criticized NIAID for this, we support their efforts to release important news without waiting the extra 6 months or more needed for acceptance and printing of a completed journal article.

Additional information about the incidences and severity of opportunistic infections, the impact on T-helper cells and p24 antigen levels, as well as data on other key parameters, would be helpful and should be forthcoming. The bottom line, however, seems clear: AZT significantly reduces the progression to AIDS when used in early intervention by people with minor symptoms of ARC. This should surprise no one.

This study also reported a far lower incidence of side effects from AZT in this healthier patient group. As PI has pointed out for more than 2 years now, reports of the most serious AZT side effects have always been based on the experiences of late-stage AIDS patients, in whom nearly 50% have shown significant side effects. Most physicians have long noted that side effects were much less severe in healthier patients, a point well established in even the earliest AZT studies. In this study, significant side effects were noted in less than 5% of the patients receiving AZT.

Study 2: An arm of the giant, placebo-controlled AZT seropositives study, which is following nearly 3000 healthy people with HIV but no symptoms, was brought to a halt by the Data Safety and Monitoring Board which controls the study. As in the early study of AZT with AIDS patients, the Board ended the study early when it found a statistically significant advantage for people receiving real drug. Even fewer side effects were seen from AZT in this study, even though half of those on the drug were receiving a higher dose (1500 mg. per day) than had been used previously. Neither this group, nor one receiving 500 mg. of AZT per day, experienced any greater level of side effects than the placebo group. The sole exception to this was minor nausea, which occurred slightly more often among those receiving real AZT.

Like the previous study, results were announced in a press conference, leading to the same criticism. The insistence on awaiting acceptance of a journal article would have added at least 6 months to the process - an unacceptable delay in the context of an infectious, often-fatal epidemic.

Other controversies exist over this study, principally whether or not the trial might have been terminated too early (it sounds strange indeed to hear AIDS activists wondering whether things should go slower). Skeptics question whether the advantage for AZT recipients would hold up over a longer period. Still others contend that the advantage for AZT was demonstrated only during a period of the study in which preventive treatment against PCP was not yet permitted. They argue that the benefit - preventing progression to AIDS - might have been achieved less expensively and with less risk of side effects.

Study 3: This important research from Dutch scientists suggests that continuous AZT use begun early in HIV infection may completely prevent the occurrence of AIDS-related dementia. While not absolutely conclusive in this regard, the Dutch study at least demonstrates a dramatic and clear advantage against the development of dementia in patients who used AZT early on.

Study 4: This research, reported but not yet published by Dr. Margaret Fischl of Miami, seemed to show that a 600 mg. daily dose of AZT was just as effective in prolonging survival as the higher, 1200 mg. recommended for the last few years. While this comes again as no surprise to community physicians (and Project Inform), it is extremely important that hard data from rigidly controlled studies now confirms it. A previous French study drew similar conclusions last year. New labeling indications will be required now, which will have the effect of cutting the cost of AZT in half for those who weren't already following this path. A low dose AZT regimen, using only 500 mg. daily, has already been accepted as a criteria in new studies of DDI. Physicians who have long advocated lower dose AZT are now quick to point out that many patients thrive on as little as 300 mg. per day, although this has not yet been confirmed by hard evidence. Certainly, doses this low are already being used in studies which combine AZT use with other drugs, such as alpha interferon. The message is not that people

In memory...

We dedicate this issue of PI Perspective to Dennis Hathaway, Robert Parr, Ron Fisher, Richard Livingstone, Steve Whittaker, Scott Schaefer, and all the others this year for whom the system didn't move fast enough or try hard enough.

Their memory lives on in the work that remains.

who are doing well on full dose must immediately switch to lower doses, but that those who could not tolerate 1200 mg. should try lower doses before abandoning the drug altogether. Whether there is an advantage in switching to lower doses is less clear, but there is at least some suggestion that the lower doses are less immuno-suppressive and may thus sustain T-cell increases longer than the high dose.

Implications for Use

PI has long advocated the strategies implied by these findings. Common sense and logic always suggested that if AZT diminished viral levels in the sickest patients, and its side effects were less severe in healthier ones, then it was likely that early intervention would work. For those who were willing, in the face of a life threatening epidemic, to act on the dictates of common sense without waiting for hard proof, the benefits of early intervention became available in 1987. For those who needed the hard proof, it now stands before them. Great credit must be given to team of the researchers who did the hard work of proving the argument for early intervention - without their efforts and determination, the debate would rage endlessly while the death toll continued to rise. But credit must also be given to physicians and researchers who saw that early intervention was a rational, if unproven, course from the beginning. Some who argued on its behalf in 1987 and 1988 were unfairly accused of selling false hope or over-medicating their patients for profit. Must this be the price paid for challenging medical orthodoxy, even in times of plague? Time has exhonerated the foresight of these pioneers, but it doesn't always correct the damage done their reputations and spirit.

As of fall 1989, clinical trials have demonstrated benefits from AZT use for the following HIV-infected groups:

- People with AIDS
- People with symptoms of ARC or who have fewer than 200 T4 helper cells
- People with minor symptoms, regardless of T4 counts
- People without symptoms but who have fewer than 500 T4 helper cells

The only HIV-infected group for whom AZT is not yet formally recommended are healthy people without symptoms of any kind with greater than 500 T4 helper cells. This group is still under study in the remaining arm of the large seropositives study. This does not mean, however, that there is any evidence which suggests that such people should not begin antiviral treatment. Instead, it merely points out that the benefits of doing so have not yet been proven in the study. It was always expected that it would take longer to prove benefits in this group since the patients' good health makes its difficult to tell whether a treatment is working. The same logic which suggested broad AZT use before clinical studies proved its value, today suggests that even healthy asymptomatics with high T4 counts may benefit from treatment.

For many, the question now is whether to begin early intervention simply on the basis of being seropositive. At the very least, it is one rationally supportable course of action, perhaps moreso than the opposite view. To some, the reasoning is simple: if a potentially lethal virus is slowly destroying your immune system, doesn't it make sense to hinder its activity, even if the infection isn't yet making one feel ill? This view holds up as long as the side effects of early treatment use are less harmful than the gradual decline of the immune system common to HIV infection. One might ask: just how much immune system capacity do you wish to lose, perhaps permanently, before doing something about it? The current evidence demonstrates that AZT side effects are minimal with healthy people. Still, only completion of the on-going clinical trial will produce a conclusive answer. In the meantime, each individual must make a choice he or she can feel comfortable with.

Remaining Questions

Despite the news these findings bring for clinical use, legitimate questions remain. The questions, and an attempt to answer them, follows.

Does the fact of AZT resistance suggest that, despite these findings, it might still be better to delay AZT use until a late stage of AIDS or ARC is reached? Some physicians believe this is the case, arguing that since AZT only works for a limited time, it's still best to save it for when you need it most. Although well-intentioned and rational, this argument may overlook three key facts: (1) new and better antivirals are already coming to market, so alternative antivirals will almost certainly be available later if needed; (2) by using AZT now, many more people simply won't progress to the point at which AZT becomes critical; and (3) the assumption that AZT only works for a limited time is based on the experiences of later-stage AIDS patients. The duration of effectiveness in healthier people is still unknown, and a good case can already be made that it will be useful for longer than it is in AIDS patients.

Some researchers who have been right about just about everything else in the epidemic argue that the most reasonable strategy against HIV, given today's medicines, is to slow the progressive activity of the virus and preserve as much of the immune system as possible. Letting HIV run rampant in the body until some arbitrary level of possibly irreversible destruction is reached, such as 200 T4 cells, just doesn't make sense. This view is bolstered by the growing concern that immune function may not be easily restored once key markers falls into seriously deficient territory.

Couldn't progression to AIDS be slowed less expensively for the majority of people simply by the use of preventive medicine against PCP? On the surface, this seems to make sense since PCP has previously accounted for more than 60% of new cases of AIDS. Government scientists point out that this view again overlooks a key fact: PCP prophylaxis prevents AIDS only by delaying the onset of pneumocystis, while permitting continued degradation of the immune system as well as the onset of other opportunistic infections (which account for up to 40% of the cases of AIDS). AZT prevents AIDS by slowing the decline of the immune system, which should have a broader overall impact. The best solution includes both approaches.

Isn't is possible that long-term AZT use might cause side effects which haven't yet been discovered? This view argues that long-term use, even if beneficial for a few years, might result in long-term side effects, such as suppressed or destroyed bone-marrow activity. While this is not impossible, it fails to acknowledge the problems associated with *not* using AZT - continued destruction of the immune system. No one argues

AZT News: The Final Chapter?

that long-term AZT is a perfect solution - only that the evidence says the odds favor those who use it. Any possible unknowns of long-term AZT use must be balanced against the known decline of the immune system and decreased survival rates which occurs without it. On balance, it appears that using AZT presents fewer risks than not using it, though neither choice is perfect. It's important to remember also that people will not go on using AZT indefinitely, with cross-overs to new drugs such as DDI, DDC, D4T, AZDU, or others becoming increasingly likely.

Doesn't the evidence suggest that some people with HIV will never become ill? If so, why risk messing things up? This argument has been fueled lately by some offhand remarks by scientist Robert Gallo, which are often quoted out of context. Gallo said that a significant percentage of people with HIV will not develop AIDS. Other researchers have pointed out that Gallo is speaking out of his field here. Epidemiologists, which he is not, are the ones who study the matter of HIV progression in groups of people. They continue to report that more than 50% progress to AIDS within 10 years of infection, and predict that a much higher percentage will reach end state disease within 16 years - *if untreated*. The part of Gallo's remarks which are typically left unquoted is his admonition that the odds for any individual are in favor of progression to AIDS (*without treatment*). Gallo went on to say that he believed it appropriate to begin AZT treatment the minute a person knew he/she was infected.

While it is true that some people seem to show little decline of immunity even after 10 years of HIV infection, they are a small minority. It makes little sense to gamble that you will be one of the lucky ones.

Is it really worth the trouble of treating hundreds, if not thousands of seropositives with AZT just to prevent a small number from progressing to AIDS? Just ask one of those who was helped. This is perhaps the most callous argument of all. It suggests that this is all a game of numbers and money, not human lives. It is based on a short-term observation with asymptomatic patients, and completely overlooks the longer-term picture. Each person who can be kept from progressing to AIDS for an extra year or so is a person who's life may be spared forever as better treatments become available. Since data now shows that this can be done without unacceptable risk of side effects, it is our job, our moral duty, to preserve each and every last person for as long as we can.

Isn't the call for early intervention with the poisonous AZT all part of a government plot, a secret plan of genocide designed to kill gay people, IV drug users, and all people of color? Simply put, no. Our enemies aren't that effective. While no doubt there are some who secretly wish for such a plan, there is no credible evidence that one is underway. The AZT data comes from researchers and physicians whose findings have proven true over the years. In fact, some of the scientists involved are members of the risk groups the plot is supposedly killing. AZT is not a poison, and the government is not engaged in any widescale plan to kill us. This is paranoid thinking.Those who make such charges have failed over the years to demonstrate coherent evidence to prove their case. PI has followed and studied each new conspiracy theory over the years and so far finds all of them to be based on boundless assumptions, wild projections, misinformation, and an appalling lack of factual evidence. Such hysteria, while perhaps well-meaning, surfaces in every major crisis and natural disaster. True, society has failed to respond effectively to the crisis, but conscious genocide is simply not on the agenda.

AZT News: The Final Chapter?

Conclusion

The new evidence on AZT is good news, but new only to those who haven't been paying attention for the last 3 years. Now that the evidence has been presented, there is little room left to rail against AZT use. As new treatments such as DDI are added to the arsenal, there will be no room left at all. We must, however, remain vigilant in the fight to develop new and better treatments. AZT and most other current treatments are severely limited in their capabilities. Society cannot rest until we have developed the ability to truly reverse the course of HIV infection, if not eliminate it altogether.

This latest information should (but won't) sound the death knell for the views of those who have bitterly opposed AZT for the last 3 years. These views have been repeatedly discredited in every study conducted. While the debate raged, critics could be forgiven by the thousands who were mislead into forsaking some of their precious survival time. While AZT will never be the right drug for everyone and will always be a subject of personal choice, continued promotion by community leaders of the unbalanced view that "AZT is poison" must be seen for what it is - a desperate attempt to cling to long-discredited views. Such beliefs, now endangering the lives of our brothers and sisters, is more the product of political and personal positioning than sound medical reasoning. It must stop.

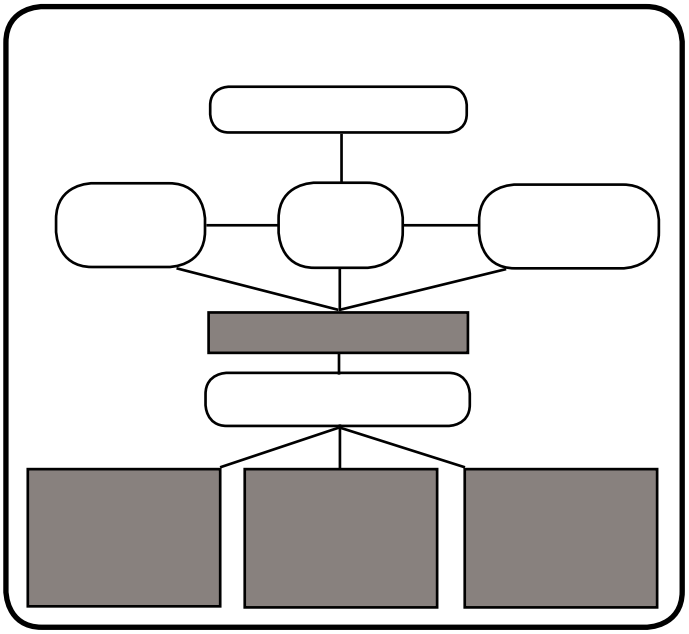
AZT is not a perfect drug, but it has extended the lives of tens of thousands of those stricken with HIV. It has been given every possible chance to fail in rigid, placebo-controlled studies and in the challenge of clinical practice. It has withstood the tests of time and its critics.

Using the PI Hotline

by Larry Tate

In the first four months of 1989, Project Inform's treatment hotline handled about 18,000 calls. To help you make the best use of the hotline, we'd like to say something about who we are, what we can do and can't do.

To begin with, the hotline is staffed entirely by volunteers. Many of us have AIDS, ARC, or HIV; others are closely involved with those who do. We have a whole range of personal experiences, opinions, and anecdotal information - just as you do.



But the most important thing we have is training in the use of the resources in the PI office. Among other things, these resources include:

- Our own fact sheets, newsletters, bulletins, memos, hotline updates.
- Other treatment newsletters, such as *AIDS Treatment News, BETA*, and *GMHC's Treatment Issues.*
- A forms bin stocked with the best and most current articles on treatments we're often asked about. These are available to us under the name of particular treatments, such as Foscarnet, and under listings for specific infections, such as MAI and CMV.
- Files on most known treatments and infections, filled with articles mostly from medical journals, but also from magazines, newspapers, or any other source which provides information.
- The AMFAR Directory, the CDC AIDS Weekly, the National AIDS Network directory, and miscellaneous publications from different agencies and foundations.

• Our own clinical trials binder.

• Binders with referral numbers for buyers' clubs, drug companies, PWA groups, other hotlines.

• A room filled with late notices taped to the walls, written on the blackboard and bulletin board, floating around the desks, sitting in bins, etc.

The goal of the PI hotline volunteers is to find, in all these resources, the information you want and to get it to you, over the phone or in the mail. Although we try to do our best, this isn't always possible, for the following reasons:

• Sometimes we have the information but can't find it quickly. Though we hope all these resources will at some point be available on a computer, usable by hotline operators, they aren't now and we do miss things from time to time. Sorry - nobody's perfect.

• Sometimes we don't have the information because it's too new. There's so much going on, it takes time for us to catch up with some things just coming into use. You can help by telling us about treatments we should know about, and sending us any information you think we should have. (And not just useful treatments: we're just as concerned with knowing about any likely ripoffs or harmful products as well, so we know what to say when others ask about them. The uncertainty of AIDS creates big opportunities for deliberate fraud as well as misguided quackery.)

- Sometimes we don't have the information because it doesn't exist, or we have no way of verifying it. There are many alleged treatments for which great claims are made, but which are documented poorly or not at all. We may tell you we have nothing worth sending, or may send something with a disclaimer saying we don't vouch for the contents.
- Sometimes the information is outside our field. We deal primarily with treatments, pharmaceu-

tical treatments in particular. We are less well covered on holistic treatments, partly because as a group they are less well documented. Although we don't deliberately discount them, we admit they are better covered elsewhere. We also track related issues, such as regulatory and research policies and insurance matters. Often, if we don't have something, we can suggest other resources. Still, sometimes we just can't help someone.

Because we're based in San Francisco, we have a wider range of information about local California resources than about other areas. If there is an AIDS agency near you, they'll often know more about your local resources than we will. They should.

- Sometimes the information requested is something only a doctor or researcher should be expected to interpret. We're not physicians, nor can we promise to have one on call, and very often even a physician couldn't or shouldn't say what to do without a personal examination. (Occasionally, in emergencies, we might try, as an aid to doctors, to investigate some particular medical issue. But this is rare, and we're not really set up to do it.) We know not all doctors are up to speed on AIDS issues, especially when it is only a small part of their practice. But we cannot be expected to provide a "second opinion." If a real problem exists, we can usually refer you or your doctor to medical authorities.

- Sometimes we're asked questions we have no right to answer, such as: *What treatment should I try? What should I do to get better? Should I change doctors? Is my doctor wrong?*

If you've read our treatment strategy, fact sheets, and newsletter - and keep up with most of what's written - you may know as much as we do. If we knew what was best for you, we'd tell you. The truth is, nobody can yet tell you what's best in each individual situation. AIDS and HIV vary widely from one person to the next. (Sometimes we may make a specific suggestion, such as using aerosol pentamidine if your T-cell count is under 200; but that's limited to what we call our "*Basic Strategy*.")

- Sometimes we're asked questions for which there is no real answer. The typical one is: what's new? Anybody who answers this is giving you their opinion, nothing more. It's okay to ask for updates on particular drugs; there are always developments between newsletters, and they don't always reach the media. But, most of the time, the answer to "What's new on drug X?" is: Nothing.

- Sometimes what our callers need most is not information but counselling. We know some people may be in tough situations without much in the way of support (we've been there too), and we try to listen sympathetically. But we're not trained to be counsellors, and it's not a good idea to expect it of us.

- Sometimes we can't answer because we don't have enough to go on. If you heard about some new drug on TV that morning, but you don't know what it's called or what it's supposed to do, neither do we. Also, by now you know how inaccurate media reports on AIDS can be, so don't be overly alarmed with us if we can't back up everything that's said on TV or in the newspapers.

- And, of course, sometimes we're asked questions whose answers are too large and depressing for anybody to answer: *Why are things moving so slowly? Why can't I get access to the treatment I need? Why won't anybody pay for it? Doesn't anybody care?* And so on. We're often asking the very same questions.

A technical note:
There are six lines and not more than four volunteers on a shift. If you get put on hold and forgotten, or get a busy signal or a machine, try again. If we sometimes rush you, forgive us. It's because there are several calls waiting, little lights blinking at us, and six people in the office wanting to talk to someone. If you just want to put a name on the mailing list, check or change an address, or ask for a particular fact sheet, it's safe to leave messages on the machines outside of hotline hours; the tapes are transcribed daily.

And finally, a personal note:
Working on the hotline is challenging and demanding. We do it on our own time without pay. And because PI is a small organization with minimal staff, we do it without the strokes, recognition, and support that might come from a larger, government-funded organization. Most of us find the work very satisfying. It provides a chance for us to make a contribution, and perhaps to get our minds off our own woes in the epidemic. We try to do our best. If we fail you in some way, we apologize. Because PI is a national organization with a high profile, few people realize how small and underfunded we really are. We are but three paid staff members and a crew of 70 volunteers in a few small rooms in old building full of community service organizations. Most of our volunteers are otherwise employed and/or not always in the best of health. The paid staff members are drastically overworked for their minimal salaries, and in major areas where we need paid staff, we have instead a few courageous and determined volunteers trying to respond to the most urgent needs, to keep us going. *If there is an AIDS gravy train, this isn't it*. We receive no government funds of any kind, support from only a few key (and deeply appreciated) foundations, no grants or help from larger AIDS organizations, and no celebrity or high society funding. But we believe absolutely in the mission of this organization, and only wish we had the facilities to do our jobs better. We hope that you understand our commitment as well as our limitations. We are deeply grateful for the support given directly by the community, and do our best to put what we receive directly back into services. We're in this together.

Clinical Trials: Evaluating, Choosing, Entering

By David Glassberg

With the coming of DDI, the issue of clinical trials is quickly becoming a key question on the minds of many people. More than two thousand people will be asked to participate in studies of the drug, while thousands more may be able to get the drug in special treatment programs. As never before, making decisions about clinical research programs has become a part of our lives. An increasing number of our hotline calls deal with such questions as "Should I join a clinical trial? Which one? What am I getting in to? How do I join one? What are my options?

Before it can be sold by prescription, any drug has to be licensed by the Food and Drug Administration (FDA) in order to prove its safety and effectiveness. After a drug is evaluated in the lab and then in animals, experimental testing on humans may be permitted. To do this, FDA grants a manufacturer IND (Investigational New Drug) status, which allows the sponsor to conduct human studies. This human or clinical testing is performed in three phases. Phase 1 evaluates

the drug's potential toxicity or side effects on a small number of patients, while also attempting to determine the proper dose to use. Phase 1 studies, however, aren't perfect in detecting toxicities. For example, AZT's bone marrow toxicity was not discovered until after it was used by more people with varying degrees of health and immune status in Phase 2 studies.

If a drug is well tolerated, Phase 2 testing is begun using a larger number of patients (from as few as 200-300 to as many as a few thousand). These studies are designed to determine the drug's effectiveness. Sometimes, preliminary indications of efficacy are found during Phase 1 testing, but they must still be confirmed by Phase 2 studies. AZT and DDI, for example, both showed efficacy in Phase 1, while CD4 did not. All three, however, went on to Phase 2 testing. Under new rules created in 1988, it is possible to license a drug at the end of Phase 2 testing, although this is not normally the case.

Phase III, called confirmatory testing, uses larger numbers of patients to confirm earlier efficacy studies and identify low-incidence adverse reactions. Together, these three phases can easily take 5 years, at which point the drug may then receive a FDA final approval which allows the drug to me marketed and available to physicians by prescription. When testing is completed, the manufacturer submits an NDA (New Drug Application), which - if approved - gives it the license to sell the drug.

Along the way between the three phases of research, every aspect of study design must be approved by FDA. Months go by while papers and proposals fly back and forth between FDA and the sponsor. When studies are completed, it often takes several more months to analyze the data, and more months for FDA to agree or disagree with the analysis. A typical data submission to FDA on a new drug may contain tens of thousands of pages of material. This is one of the reasons why its takes so incredibly long to get a new drug out.

Under new rules created in 1987, FDA can grant a "Treatment IND" for drugs that have proven safe and have shown some efficacy during Phase 2 trials. AZT was given a Treatment IND at the end of its Phase 2 testing. The Treatment IND was designed to provide faster access to promising treatments for life threatening diseases. In practice, it hasn't always done so due to conservative voices in the FDA who have traditionally placed safety above all other considerations, even in the face of a national health crisis. People who desperately need new treatments are still denied access.

In recent months, continued pressure by AIDS Activists, with Project Inform on the front lines, has resulted in a rethinking of these issues and has created a new concept called the "parallel track" (described elsewhere in this issue). Because of the successful negotiations held in Washington this year, a Treatment IND has now been granted for a drug, DDI, at the end of Phase 1 testing for the first time. In addition, thousands of people will have early access to this drug in a compassionate use program. The implementation of these programs fulfills a long-time PI goal of letting the people who are sick, not bureaucrats, determine what treatments they can use.

Clinical Trial Enrollment

You can volunteer in any of the three phases of clinical trials. First, you must know the trials in your local area. Clinical trials (most commonly Phase 1 and sometimes Phase 2) may require a short stay at a research clinic or hospital to monitor you for any toxic reactions. If you can't find a clinical trial you are interested in your local area, then you may have to relocate to another city. To locate trials for HIV infection you can contact the following organizations:

1. National Institute of Health Clinical Trials Info. line 1-800-TRIALS-1. This number is for NIH sponsored trials only.

2. American Foundation for AIDS Research (AMFAR) AIDS/HIV Experimental Treatment Directory. (212)719-0033 1515 Broadway Suite 3601, New York, New York 10036-8901. This quarterly publication is FREE to PWAS/PWARCs and contains updates on drug trials status, dosages, how the drug is administered and where trials are being conducted, including a map showing specific trials located throughout the country.

3. Call us at Project Inform. Trials conducted at small community research centers like the Community Research Alliance in San Francisco or the Community Research Initiative in New York may not be listed with the above resources. If you are looking for access to a specific drug , we may have information on who to contact to obtain access.

After locating a desired trial in your area, you can call the facility conducting the trial and inquire on their procedure for enrollment. Enrolling at a research center which conducts HIV testing is an excellent way to be at the top of their list when they begin recruiting for new or expanded trials.

What are the Benefits?

The most obvious benefit of participation in a clinical trial is to get access to a new drug that you might need or want to try. Other benefits, however, may be more important, especially as additional ways of getting new drugs become available. These other benefits include:

- Getting free medical care - especially attractive if you don't have insurance.

For your information

The last PI Perspective highlighted the benefits of an individual mail order pharmacy. It is is equally important to be aware of the advantages and benefits provided by local pharmacies. These include:

- ✓ *personalized, immediate service*
- ✓ *counselling regarding drug and food interactions, managing side effects, and the latest data on new treatments and dosage*
- ✓ *immediate, local response to your questions and concerns*
- ✓ *collaboration between your doctor and your pharmacist*
- ✓ *ability to work out payment plans*
- ✓ *referals to local support agencies and consumer bureaus*
- ✓ *information about alternate resources and programs*
- ✓ *knowing and caring about you as a whole person*
- ✓ *in some instances, acceptance of insurance as payment in full*

Whatever pharmacy you choose, it will be a critical partner in our health care. Choose wisely and seek to meet the broadest spectrum of your needs.

(Thanks to the Valley Medical Pharmacy, Sherman Oaks, CA for these valuable tips)

- Getting a drug for free. Thousands of people have gotten their AZT free by participation in clinical trials. Many trials promise to provide free drug for a long period after the trial is finished. This benefit will become more important in coming years if Congress becomes less willing to provide support programs for expensive new drugs (as many predict it will).

- Getting medical care at the top hospitals and research centers. This is especially attractive if you can't find a doctor particularly skilled in HIV infection. Usually, whatever happens to you while participating in clinical trial is handled by the research hospital.

- Getting free monitoring. Good management of HIV infection requires frequent and extensive lab tests, which can be very expensive. Such testing is always a part of clinical trials. In some cases, they will try to bill your insurance for the testing, but they are bound to cover it if your insurance refuses (or if you don't want your insurance billed).

- Getting medical care or free drug without having it show up on your insurance records. Many people are rightly concerned about possible discrimination when their employers or insurers find out about HIV.

- A final and very important benefit is the satisfaction of knowing that your contribution will advance our understanding of HIV and its treatment.

What are Your Risks? Your Rights?

Almost all drugs, not just HIV experimental drugs, have the potential for causing harm. After reviewing the known information on a drug, we suggest you also receive guidance from your personal physician or other trusted health professional. As a general rule, you can assume that the risks are highest in the earliest phases of research, since less in known about the drug. Most of the known risks of the drug or the study are listed in a Consent Agreement you will be asked to sign before entering a study. Realize, though, that such consent agreements don't cover everything and surprises are not uncommon. For example, the consent form for the study of suramin in 1986 failed to list the possibility of damage to the patient's adrenal glands. Many people in these studies suffered life-long injuries from this problem. In sum, don't fool yourself by believing that a consent document is all you need to make a decision.

It is often important to conduct a little research of your own before entering a study. Ask about the experiences of others who have participated at a local institutions. Was the study ethical? Did it meet the patient's needs? Was patient care as important at scientific discovery? What happened to people when the trial was over? Often, the best sources of information are people you know.

It's also critical to know what will happen if you experience a serious problem while on the study. Usually, the hospital will take of matters, but there are some exceptions, so it pays to ask. While most people are satisfied with the care they receive in studies, some are not. We hear a variety of complaints that differ from one study to the next. It helps to remember that the purpose of the studies is not primarily to treat you or make you well, although that is a hoped for side effect. The primary purpose of a study is to learn about a drug. The more you know going in, the less likely that you will be surprised or disappointed by anything that happens.

In the majority of clinical trials studies, all medical records and lab samples are coded with a number instead of the patient's name to ensure confidentiality. You are entitled to all information on the kind of drug being tested, its previous testing history results, the possible benefits and harmful effects it may have, how long is the study, if you will be hospitalized and for how long, the type of long-term follow up provided and what other medications can be used while in the study. You have the right to withdraw from any study at any time and for any reason without prejudice. You cannot be forced to continue in the study against your will.

What Happens When It's Over?

It is important to ask this question during the initial screening interview for entry into a clinical trial. Some pharmaceutical companies will allow patients to either enter the next phase of testing, or to receive the drug outside the study on a maintenance therapy basis IF the drug has shown to be harmless and there is evidence of some degree of effectiveness. Not all drug trials have this option. You have the right to ask for this information; use it!

Help Us Help Others

If you are on a study, Project Inform would like to hear from you. Many results are not released soon after a trials conclusion. This delay is often due to the need for researchers to publish in a medical journal before going public with new data. This can take many months. By keeping us informed of your experiences, we can keep our callers updated. Similarly, if you have problems with the way you are treated either in a study or applying for one, we may be able to help or refer you to someone else who can.

Also, small community trials and innovative treatment protocols are brought to our attention by people like yourself. Don't assume we have all the information on all trials in the U.S., because we don't! Call us or better yet, send us printed information on any studies you hear of. We appreciate your help, and so will others.

Organizational Update

Town Meetings: The fall and winter schedule for Project Inform town meetings in the Bay Area is listed below. The meetings will be held at 7:30 p.m. at the MCC Community Church, 150 Eureka (between 18th and 19th on Eureka), in San Francisco. Note that there will be no meeting on December 27th.

Project Inform Town Meeting Schedule

First-timers		Regulars
4	October	25
1	November	29
6	December	No meeting!
3	January 1990	31

San Francisco AIDS DANCE-A-THON: Project Inform is a beneficiary of this year's 5-hour DANCE-A-THON. This all-fun benefit will be held on December 3, 2 - 7PM at your choice of three popular Bay Area Clubs: the I-Beam (1748 Haight), the Kennel Club/Box (628 Divisidero), or the Club Townsend (177 Townsend). Participation simply requires a willingness to secure pledges (from friends, relatives, and co-workers) and a desire to dance 'til you drop. Call 415-863-4679 or the PI office for registration forms.

Holiday office and hotline schedule: The Project Inform office and hotline will be closed Thanksgiving Thurday and Friday, November 23 and 24, 1989. The office and hotline will be closed Christmas day, Monday December 25, 1989, and New Year's day, January 1, 1990. The office and hotline will operate on a reduced schedule and with a reduced staff for the week between Cristmas and New Year's, December 26 through 29. Hours for those days will be from 10 a.m. until 2 p.m. Pacific Time.

Bartender's Bash benefit for PI: Bench and Bar, located at 120 11th Street in Oakland, is hosting a benefit for Project Inform on Tuesday, November 7. Prizes will be raffled off, and the bar will feature specials throughout the evening. All bartenders and their friends are encouraged to attend. A $2.00 donation is requested. For more information, call 444-2266.

PI T-shirts for sale! Be the first on your block to wear a Project Inform T-shirt. Tastefully *au currant* with a southwest motif and a logo saying "It's never too early to take charge of your health," they are Santa Fe green and Taos red on white. $12 at the PI office or $14 by mail. Mail orders, send check or money order to the PI mailing address below, and mark the envelope T-shirt!

Wish List! *The following are just a few of the items needed at the PI office. Can you help?*

carpeting	conference table chairs	couch and endtable group
electric typewriters	lamps	room dividers
cubicles	locking file cabinets	VHS VCR
color television	step ladder	IBM AT compatible computers

If you can donate any of these items, give us a call at (415) 558-8669.

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.

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

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