

# Rethinking AIDS

Volume 5, Number 3

March 1997

## "NON-INFECTIOUS HIV IS PATHOGENIC"

### Ho, et al. duck questions, flee scrutiny, make absurd statements

Protease inhibitor researcher David Rasnick, PhD, finds no evidence to support claims that anti-HIV drugs help patients or that viral load tests provide meaningful information.

### Exclusive Report From the 1995 Gordon AIDS Conference

I JUST RETURNED from my first AIDS conference, the Gordon Conference on the Chemotherapy of AIDS, held March 9-14 in Ventura, California. I went to present a poster of a paper that refuted one of the fundamental concepts of the prevailing HIV-AIDS model. The paper had just been published in a scientific journal, and I was eager to defend it against the scrutiny of my peers.

Also I knew that David Ho and his co-workers would be making presentations advancing the HIV model. I was determined to subject their ideas to scientific scrutiny face-to-face.

Gordon conferences are some of the world's most prestigious scientific gatherings. Unlike nearly all other conferences, which seek to maximize the number of paying participants, Gordon conferences are generally limited to 100 attendees, all of whom must apply for acceptance. This makes them serious and productive events. All participants get a chance to attend every presentation, and to meet and

question every presenter, either during formal Q&A periods, or informally during the social breaks.

Over my 20-year career as a pharmaceutical drug designer, I've attended about nine Gordon conferences, where I have presented papers. Usually those conferences related to my specialty: proteases and the drugs that inhibit them.

### HO CHARMS CRITICS, DODGES QUESTIONS

Of the 100 attendees, 90% were American, and 43% were pharmaceutical company employees. I noticed something new to me at a Gordon conference: a non-scientist participant, specifically, a representative of Project Inform, a political group devoted to promoting the HIV hypothesis.

The six-day event began on a Sunday. The special opening lecture was given by David Ho, director of NYU Medical School's Aaron-Diamond AIDS Center, and TIME's 1996 Man of the Year.

His talk was titled, "Chemotherapy and Pathogenesis." Surprisingly, I was not the only critic in the audience.

Somebody in the front row challenged Ho's criteria for what constitutes an assay of infectious virus, a challenge that has profound implications for the basic tool of contemporary HIV science: the viral load test. He also disputed the mathematical basis of Ho's "virological mayhem" model, the paradigm upon which Ho wants to base "anti-HIV" therapy.

The specifics of these objections were never made clear because Ho sidestepped the questions with the skill of a seasoned bureaucrat, and in doing so chewed up all the discussion time.

Another surprise was an obvious lack of Ho supporters in the audience. In subsequent breaks I found several others who openly rejected the validity of the "viral load" test and Ho's model of HIV/T4-cell dynamics.

Ho could easily become the next Anthony Fauci, who — as Director of the NIH's Institute of Allergies and Infectious and Diseases — is the government's reigning king of HIV science. Ho is far more charming than Fauci and is coated with several layers of Teflon. Regrettably, Ho left the conference early Tuesday morning so I never got to talk with him. But I did get to take up the validity of the viral load test with one of his collaborators.

### COCKTAILS DON'T HELP PATIENTS

Martin Markowitz — coauthor on some of Ho's most famous papers, including the 1995 Nature article that introduced the virological mayhem model and popularized the viral load test — stayed

#### Breaking the rules

I know the rules of the Gordon conferences and have abided by them since attending my first one in 1980: no press, no cameras, no recording devices. Nothing revealed at a Gordon conference is to appear in print except by the original authors. You can take all the notes you like, and discuss the information with colleagues all you want. You just can't put it into the public domain via print.

I openly acknowledge that my report breaks these rules. I don't do this lightly. Gordon conferences are my favorite meetings. However, the HIV/AIDS scandal compels me to take this action. The information on what is wrong with the prevailing HIV dogma is almost totally hidden from the public. The travesty of the HIV protease inhibitor clinical trial results, for example, was clearly evident at this particular Gordon Conference, as well as one I attended in 1994 (see RA Aug., 1996). This information is just too important to be kept from the tax-payers and consumers who fund it all.

The rules might seem sinister, but they aren't. They enable scientists to present preliminary results without fear of being scooped by colleagues, or being held accountable for mistakes. Ordinarily these rules promote honest scientific discussion and exchange of ideas. But the AIDS industry has adopted them to hide facts that shouldn't be secrets.

I hope I have done the right thing. I might be banned from future Gordon conferences. **David Rasnick, PhD**

through the Wednesday presentations, and I was able to question him several times.

The first instance occurred during the question period of a lecture he gave on treating early HIV infection. He and Ho have been treating a cohort of 20 patients for close to a year with protease inhibitor/AZT cocktails. The study is on-going and no results have been published, so Markowitz was discussing preliminary data. He claimed most of the subjects already had AIDS symptoms at the start of the experimental therapy — including five who'd previously been hospitalized — although a few had no history of symptoms.

Once the therapy began, HIV "viral load" for each patient dropped below the level of detection and has stayed that way, Markowitz said. He considered this an indication that the therapy was a good one.

But did eliminating viral load make the patients healthier? Markowitz had nothing to say about this during his lecture. Surely if the patients had gotten better when their HIV viral load went down, Markowitz would have bragged about it. But the subject didn't come up until I raised it in the question period.

How are the patients doing? I asked. "Some are healthy enough to work," he said happily. The implication was that were it not for the cocktails, these patients would not be healthy enough to work, but I suspected this was not the case.

Markowitz's smile vanished when I asked, During the 11 months on therapy, when their viral loads were undetectable, did your patients do better, stay the same, or do worse? He did not answer. He didn't say a word. It was an embarrassing moment for the audience.

I interrupted the uncomfortable silence by restating the question. Your patients should be doing better, right? Again Markowitz was speechless. He either didn't know how his patients had done over the course of therapy (which is very unlikely) or they were not doing well — despite having HIV "viral loads" of zero. During this revealing silence the lecture was ended by the announcement of a coffee break.

I left with one of my curiosities satisfied: the press accounts of miracles attributed to cocktail therapy — the fabled "Lazarus effect" — weren't showing up in scientific studies.

## **NO VIABLE DRUG-RESISTANT VIRUS**

Monday and Tuesday afternoons were set aside for poster sessions. Since my paper on the kinetics of HIV protease undermined a crucial aspect of the current dogma, I wasn't sure how my poster would be received.

The paper, "Kinetics Analysis of Consecutive HIV Proteolytic Cleavages of the gag-pol Polyprotein," addressed the popular assumption that when antiviral therapy fails, it is because HIV has mutated into resistant forms (Rasnick, March 7, 1997, *Journal of Biological Chemistry*). In particular, the assumption that when protease inhibitor therapy fails, it is due to the emergence of HIV strains characterized by mutant proteases that are resistant to the inhibitors.

This belief is central to the HIV model. Protease inhibitors, especially when combined with AZT into a cocktail, often cause HIV "viral load" to disappear. When "viral load" counts start going back up or when AIDS symptoms manifest, it is assumed that new mutant strains of HIV have emerged, ones with proteases that resist the inhibitors.

But my calculations show that these theoretical mutant proteases could not be a part of a fully-functioning HIV. In order to produce

a fully-functioning HIV, the protease must cut an HIV super protein at eight different sites. Inhibitors work by plugging-up the protease's cutting site, blocking it from snipping the HIV super-protein into nine functioning parts.

A protease that would not accept an inhibitor into its active site — one that was resistant to the effects of these drugs — would also not be able to accept the HIV super protein into its active site. That the protease has to make eight successful cuts under these circumstances makes it demonstrably impossible that a resistant form could produce functional virus.

I noted that there is not one example in the literature of a human infected with viable, infectious HIV that possesses an inhibitor-resistant mutant protease. All the inhibitor-resistant mutants described so far were obtained from the proviral DNA of non-infectious virus. There was no reason, then, to think that "drug resistance" could explain instances where protease inhibitors failed to resolve AIDS or eliminate HIV "viral load."

The second major point of my kinetics analysis was that since the viral load test at best measures 99.8% non-infectious viral particles, it should be replaced by an assay that measures the level of infectious HIV particles in blood plasma. I was certain that this proposal would be greeted by a chorus of disapproval. Surprisingly, that did not happen.

No one disputed anything I said. A number of people, including John Erickson — an HIV protease expert from the National Cancer Institute — openly agreed with my analysis and conclusions.

## **CHASING MARKOWITZ**

Erickson left my poster and walked straight over to Markowitz, who was at the other end of the room. I knew Erickson wanted to discuss with Markowitz the points of my poster, and I went over to join them.

Sure enough, my poster was the topic. Markowitz greeted me with a smile. Perhaps he did not yet recognize me from his earlier lecture. I started asking about the infectivity assay used in the March 1996 article he wrote with Ho (*Science* 271, p. 1582), which I held in my hand. The paper concerned the administration of cocktail therapy to five patients. Prior to this treatment, the patients had HIV "viral loads" between 12,000 and 643,000 (per ml of plasma). After therapy began, the viral loads for each patient went to zero, and stayed at zero for the duration of the study.

I wanted to know about patient 105, the one who started with the largest viral load, 643,000. He was the only patient for which "tissue culture infectious doses" (TCID) were measured. Prior to therapy — when his "viral load" was 643,000 — he had 1,000 infectious doses of HIV (per ml of plasma). Two days after initiating therapy, his infectious doses dropped to zero, but his "viral load" had not dropped below 500,000.

I wanted to know the relationship between the "viral load" figure and the infectious dose figure. I started by asking, Did one "infectious dose" correspond to one infectious HIV?

Yes, Markowitz said, one infectious dose equaled one infectious virus.

How did you determine that an HIV (a "dose") was infectious? By looking for the p24 protein?

Yes, Markowitz replied. Detection of p24 was accepted as evidence of a fully functioning virus.

Well, I said, p24 is not good enough.

With this, I figured our scientific discourse would precede along predictable lines. He would ask me why p24 "wasn't good enough." I would explain, as documented in my paper, that p24 has been shown by many researchers, including John Erickson, not to be a reliable indicator of infectious virus. I was prepared with references to defend this statement. But Markowitz didn't bite.

As following his lecture when I had asked about the health of his patients, Markowitz simply said nothing.

I turned my attention to the disparity between "viral load" and infectious dose figures. If infectious doses equaled infectious HIV particles, then the difference between patient 105's infectious doses and his "viral load" must represent non-infectious HIV particles.

I showed Markowitz the graph he and Ho, *et al.* had published for patient 105. In one case a viral load of 643,000 corresponded with 1,000 infectious HIV particles, and in another case a viral load of over 500,000 corresponded with zero infectious HIV particles. Markowitz agreed with my interpretation of the data.

So I asked him, What was the significance of the hundreds of thousands of non-infectious viral particles per ml that you detected in the blood plasma of patient 105? He frowned, and seemed not to know what to do next. His puzzled look and silence lasted about 30 seconds. Then he simply turned and walked away.

It was the first time a scientist had ever run away from me. Typically scientists are bull dogs. They fight for their position. But the HIV guys don't. They run.

I noticed at this time that Erickson had vanished. He'd slipped away sometime during this strange exchange with Markowitz, and I never spoke with him again.

Were it not for Erickson's devotion to HIV, he and I could have been buddies and colleagues. He is otherwise a sharp scientist who knows enzymes and the technical particulars quite well. Regrettably, though, he yields to the virologists and physicians when it comes to HIV pathogenesis, and he takes his cues from the folks who run the HIV show.

As for Markowitz, I was determined to get an answer to my question. I cornered him two more times. On both occasions I had to literally stop him from walking away. In each instance I repeated my question about the significance of all that non-infectious HIV.

Both times he ran off without answering the question. In the midst of his second retreat he turned and called back with a meaningless response, devoid of even a hint of scientific or logistical merit: "Trust me!"

I cried back, "Trust has nothing to do with it!" It was an absurd exchange, and I would have laughed were it not so pathetic.

## DASHED HOPES

If I was going to get responses for my remaining questions, I would need a stationary target.

I found one at the week's most frightening session: Wednesday night's special lecture by John Mellors of the University of Pittsburgh Medical Center's Graduate School of Public Health. The topic: "Chemotherapy of HIV-1 Infection: The Past, Present, and Future."

Mellors painted an accurate picture of the dismal history of HIV chemotherapy prior to the current era of protease inhibitor/AZT cocktails. I found myself nodding in agreement as he listed many serious mistakes inherent in traditional therapy, which used a single nucleoside analog, like AZT. Perhaps Mellors was a sensible and independent thinker, the sort I'm used to dealing with at Gordon

conferences that don't focus on AIDS.

My hopes were dashed when he got to what he labeled the greatest mistake of the past ten years: treating AIDS patients with single rather than multiple "antiviral" drugs.

That's when it hit me: there was nothing courageous about Mellors' critique of the old therapy. In fact, it's the fashion now to recognize mono nucleoside protocols as flops — so long as cocktail therapy is promoted in their place, which is what Mellors was doing. But the failure of mono therapy was obvious long before protease inhibitors came along.

## ONE QUARTER BASKETBALL GAME

Mellors' talk assumed its frightening aspect with the appearance of a slide announcing: "Clinical Endpoints are Dead." In plain English, Mellors wants drug efficacy based solely on surrogate markers — like "viral load" and T4-counting — rather than clinical symptoms.

He justified this by saying that the recent termination of study ACTG-320 last February put the final nail in the coffin of future clinical endpoint trials.

ACTG-320 was a phase III clinical trial involving almost 1200 people, roughly half taking two AZT-style drugs, and the rest taking a cocktail consisting of those same two nucleoside analogs plus a protease inhibitor. The trial was stopped early for reasons that are unclear.

When the records were unblinded, the data showed that only 8 patients had died in the cocktail group, versus 18 in the group not taking the protease inhibitor. Based on these figures, Mellors and the rest of the medical establishment are saying that cocktail therapy reduces mortality 50% compared to treatment without protease inhibitors.

Mellors regards the results of ACTG-320 as conclusive on two counts: one, that cocktail therapy reduces mortality by half, and two, that this benefit is predicted by "viral load." Studies of future treatments should merely look for fluctuations in "viral load," he believes. Waiting for patients to die — or for other "clinical endpoints" to manifest — would be unethical and unnecessary since "viral load" measurements supposedly predict who will and who won't succumb to AIDS.

But the leader of the trial, Scott Hammer of Boston's Beth Israel Deaconess Medical Center, admitted that ACTG-320 had not proceeded long enough for differences in the two treatment groups to have reached statistical significance (Boston Globe, Feb 25). In over two decades earning my living as a scientist, I've never before witnessed scientists drawing conclusions of such import based on statistically insignificant data.

The concept of statistical significance is essential to the scientific method. Experimental results obtain meaning only after qualifying as statistically significant. Imagine declaring the winner of a basketball game after the first quarter, or the champion of the World Series after the first game.

Mellors didn't mention statistical significance, and I didn't get a chance to ask about it during discussion time. So I don't know how he might handle this objection, which I consider to be fatal.

Instead, Mellors accepts ACTG-320 as definitive, and sufficient to justify using surrogate markers as the sole criteria of whether or not therapies and drugs actually benefit patients. And he's not the only one. I'm afraid that the mood in AIDS drug research favors Mellors' view. I've heard others call for the end of clinical endpoints,

usually citing the statistically insignificant results of ACTG-320.

This is particularly frightening considering my earlier exchanges with Markowitz, who could claim no improvement in his patients who'd had their "viral loads" reduced to zero for extended periods of time, and who could attach no clinical meaning to the "viral load" test.

If the Markowitzs and the Mellors of the world have their way, the American public is in grave danger.

## KILLER CORPSES

In the discussion period of Mellors's lecture, I decided to return to the questions that I'd wanted Markowitz to answer, about the meaning of "viral load." After all, that was the heart of the matter: Mellors' call to discard clinical endpoints was only as valid as the "viral load" figures with which he wished to replace them.

For starters, I wanted to compare his answers to Markowitz's. So I repeated my question about the relation between "viral load" and infectious doses. Mellors responded by proclaiming, "Viral load has nothing to do with infectivity!"

Ah-ha! Now I had a second HIV big shot admitting that the "viral load" figures did not indicate infectious HIV.

Assuming that "viral load" testing accurately counted HIV, and that infectious dose testing accurately counted infectious HIV, I offered my 99.8% figure from the Ho/Markowitz paper as the fraction of circulating HIV that was non-infectious.

Non-infectious HIV, then, is the source of RNA and proteins — including protease — from which the genetics and other characteristics of HIV are derived.

He agreed. (How could he not?) Now I had him. Since non-infectious viruses have no conceivable clinical relevancy, then neither could any data derived from them.

What's the significance of all the non-infectious HIV? I asked. I had no idea how he could work himself out of this corner, but his response stunned even me: "The non-infectious particles [HIV] are pathogenic."

Now here was a first. I don't think that anybody's ever proposed that non-infectious virus could cause disease. The idea flatly overturns our

general understanding of the antibody response and the premise of vaccinations. Before I could point this out, I noticed that a murmur had erupted, and realized there was nothing else to say. The moderator mercifully ended the session, my cross examination having exhausted the time allotted for discussion, with no one else having had time to pose questions.

I did not feel alone in rejecting Mellors's absurd explanation. The murmur it inspired continued well after the session ended, and on the way out of the room an Indian scientist grabbed my arm and asked, "Did you hear that?"

Indeed I had. AIDS was caused by a deadly army of viral corpses.

## CURING THE HEALTHY

Though I looked far and wide, I could find not a single controlled experiment discussed anywhere at the conference. It appears that the only thing that exists in the entire world of AIDS is HIV. Anything bad that happens to HIV-positive people is due to HIV; any improvement is due to therapy.

There was even one presenter who took credit for curing people who accidentally pricked themselves with needles tainted by HIV-positive blood. The patients were "aggressively" treated immediately with antiviral drugs, and did not become positive. The scientist claimed this protocol was what prevented seroconversion, and he considered this to be curing them.

However, exposure to HIV via needle pricks only results in seroconversion one time in a thousand, a fact he did not mention. And neither did anybody else, though this fact is well known, and the attendees were all certified "AIDS experts."

Not only was he claiming credit for the effects of statistical probability, he was also claiming to have cured healthy people... and nobody called him on it. These HIV supporters are so desperate for good news that they'll say and accept anything that agrees with the HIV model.

## COLD SHOULDER

Early on it was clear that certain people at the meeting already knew of me. They avoided me.

Others, though, initially showed interest when I raised my objections. It was obvious that these problems were not new to them, they had just never discussed them before — or been around anyone who wanted to. However, once these potential allies continued the discussions with people like Markowitz — scientists with status and influence — then they as well avoided me from then on.

I found it a lonely business acting like a scientist at an AIDS conference.

## Mission Statement of the Rethinking AIDS Group

- 1 To develop, articulate, and promote rational scientific discourse on the subject of HIV and AIDS.
- 2 To advocate the absolute right of students, professors, physicians, scientists, government officials, and everyone else to think freely and speak openly on the subject of HIV and AIDS without fear of professional, social, political, economic, or criminal penalties.
- 3 To assemble scientists, physicians, and other informed people who support these views, and make those persons available for commentary and consultation to interested social groups, media outlets, government agencies, professional organizations, and individuals.

## Rethinking AIDS

is the monthly publication of the Group for the Scientific Reappraisal of AIDS, also known as the Rethinking AIDS Group.

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