

Rethinking AIDS

VOLUME 4, NUMBER 8

AUGUST 1996

Designer of Protease Inhibitors Speaks Out:

INHIBITORS OF HIV PROTEASE USELESS AGAINST AIDS BECAUSE HIV DOESN'T CAUSE AIDS

David Rasnick earns his living as a designer of protease inhibitors, the class of substances touted as the latest anti-AIDS miracle drug. Dr. Rasnick agrees that these drugs do indeed block HIV protease, and thus stop HIV replication. But he is sure that people diagnosed with AIDS are sick from a variety of non-contagious factors, not HIV. Here he explains.

As everyone knows, what is now called AIDS was first noticed around 1980, among gay men in Los Angeles, San Francisco, and New York. I had just moved to the San Francisco Bay area that fall to help establish a small bio-tech company. Within months of my arrival, stories were going around about a strange new disease that was affecting the immune systems of gay men. It was exhilarating that such an urgent and complex scientific conundrum appeared at a time when I had just reached a measure of confidence in my powers as a scientist—and there I was right in the middle of it, the most stimulating medical puzzle of the century. I haven't stopped learning and thinking about AIDS since then.

Whenever I gathered with other scientists for whatever reason, we invariably got around to discussing AIDS. What made AIDS such an interesting scientific subject was that it was bizarre and seemed to break all the rules. The technical aspects of this unprecedented disease marveled us. However, being an organic chemist—not an immunologist or physician—I felt there was little I could contribute scientifically toward unraveling the mysteries of AIDS. That inadequacy in no way dampened my enthusiasm or interest in studying the new disease, however.

Then Robert Gallo unveiled his HIV at the famous April, 1984 press conference. All the speculating, discussing, and hypothesizing about what causes AIDS ended in applause and backslapping. Gallo's virus provided clarity, and even purpose for me personally, in the form of a subject for my art as an organic chemist. The example of other retroviruses suggested that a likely

constituent of HIV was an aspartyl protease. As a designer of protease inhibitors, I immediately began studying the possibility of designing inhibitors of HIV protease, even before such an enzyme had been characterized.

About six months into the project I gave up trying to design inhibitors of HIV protease, figuring others had already cornered the market. A friend at Abbott Laboratories, Jake Plattner, had for years been designing anti-hypertensives by developing inhibitors of renin, a human aspartyl protease that regulates blood pressure. Jake already had thousands of these compounds in the bottle and I was sure some would inhibit HIV's protease as well. Today, Jake's group is one of the leading producers of HIV protease inhibitors in the world. One of his inhibitors was recently approved by the FDA for treatment of AIDS when used in conjunction with

AZT and other nucleoside analogs.

I'm glad I pulled out of the race for HIV protease

inhibitors. It wasn't long before I had serious doubts about the viral hypothesis of AIDS. I spent countless hours, as did many scientists throughout the world, devising ingenious explanations for how the so-called AIDS virus (HIV) destroyed the immune systems of its victims. By the end of 1985 the number of exotic hypotheses necessary to account for HIV being the sole cause of AIDS convinced me that something was fundamentally wrong with the basic assumptions that had become entrenched in the mega-institutions of science and medicine. The more I examined HIV, the less it made sense that this wimpy virus could cause such devastation. Sometime in 1987 I realized that HIV could not cause AIDS. Although I couldn't prove that HIV was innocent at

**HIV harmless; street drugs, AZT, malnutrition
among the real causes, corporate chemist concludes**

that time, I could show that the arguments for its guilt were unconvincing, though at the time I still thought AIDS might be infectious.

As late as 1988 I had no idea that there were many other people equally bothered by the inconsistencies of the HIV hypothesis of AIDS until I came across books and articles by such authors as Jad Adams, Jon Rappoport, Harris Coulter, and John Lauritsen. I learned about Peter Duesberg, the UC Berkeley biologist, from these sources. I immediately looked up Duesberg's 1987 *Cancer Research* paper refuting the HIV theory of AIDS. After reading it, I felt confident that the HIV theory would soon be discarded as the prevailing view, and replaced by a more logical explanation. Sadly, that still hasn't happened. I kept studying and thinking, however. The more I looked into it, the more clearly it appeared

that AIDS could not be infectious.

So what was it? Conversations with Joan McKenna, a Berkeley physiologist, and Joseph Sonnabend, a New York physician, led me to comfortable ground. They considered AIDS to result from a variety of factors, which perfectly fit the various risk profiles that characterize nearly all AIDS patients: gay men in the "fast lane," impoverished residents of developing nations, hemophiliacs, etc. Shifting to multiple, combined causes of immune suppression was a psychologically satisfying alternative to the failed hypothesis that pointed to a single cause, HIV. I remained comfortably among the ranks of the multi-factorialists for about five years. Although I did think that malnutrition could cause AIDS by itself, I resisted Duesberg's proposal that street drugs, AZT, and clotting factor therapy could as well. Such a claim

seemed as over-simplified as the HIV theory. However, Peter's relentless logic and superb arguments eventually eroded my skepticism: for three years now I have become evermore convinced that he is right.

It has taken me 15 years of curiosity, acceptance, doubt, study, understanding, new doubt, followed by new understanding, to come to terms with HIV/AIDS—and I'm a scientist, able to plow through the intimidating technical literature. No wonder the public has bought the contagious AIDS theory. The truth is guarded by experts and hidden by a thick forest of jargon, credentials, and all those papers. The fraud, incompetence and outright lies produced by the cult of HIV have already been documented. But holding the perpetrators accountable will not be easy. The institutions involved in the scandal have had a long time to hide their tracks. The only way the truth is going to get broad public exposure is for journalists to finally do their jobs, to dig up and examine the truth for themselves rather than parrot the unquestioned claims of pharmaceutical flacks and hack scientists. I have little confidence that this will happen anytime soon. Even though Professor Duesberg's

How Protease Inhibitors and AZT Work

Protease inhibitors are the newest class of drugs claimed to block HIV activity. Like nucleoside analogs—the family of drugs that includes AZT and ddI—protease inhibitors work by preventing HIV enzymes from doing their jobs. To understand how these drugs work, it is necessary to learn a little bit about proteins, enzymes, DNA, and how these molecules interact with each other.

Enzymes are proteins that join together or cut apart other molecules. There are said to be three HIV enzymes: reverse transcriptase, which uses an HIV RNA chain as a blueprint for joining together nucleotides into an HIV DNA chain; integrase, which cuts a host DNA chain at a particular site and inserts a chain of HIV DNA; and protease, which cuts HIV proteins apart.

The portions of the enzymes that do the joining or cutting are called "active sites." Molecules that fit into the active sites and get joined or cut are called "substrates." The joining and cutting occurs when the substrates fit into the active sites, and the enzyme contracts, either joining two substrates together, or cleaving one substrate into two. Nucleotides and the incomplete end of a DNA chain, then, are substrates that reverse transcriptase joins together, and the portion of a protein that gets cleaved in two is a substrate for protease.

HIV enzymes are all similar to various human enzymes. Polymerase, for example, joins nucleotides into human DNA, and there are all kinds of human proteases, including those that digest dietary proteins. In addition to the three HIV enzymes, there are six other proteins associated with HIV. One (p24) is the building block of the inner protective capsule, and five (gp120, gp41, gp160, p17, p32) decorate the outer membrane (Papadopoulos-Eleopoulos, *Bio/Technology* 11, June 1993, p696).

Just as DNA is made by stringing together nucleotides, proteins are made by stringing together amino acids. The function of DNA is to code for proteins: every three nucleotides in a DNA chain codes for one amino acid in a protein chain. A stretch of DNA that codes for one complete protein is called a "gene." HIV DNA consists of nine genes, one for each of the nine HIV proteins. When HIV DNA is translated into protein, the result is one long super protein ("polyprotein") consisting of the nine HIV proteins connected head-to-tail, with the protease on one end. In order to produce a new HIV, the protease must curl back on the rest of the super protein and clip it in eight spots (substrates), freeing the nine HIV proteins from each other.

Nucleoside analogs, like AZT, and protease inhibitors both work in similar ways: they block enzymes because they are dysfunctional, counterfeit substrates mistaken for the real thing. Nucleotides are made from nucleosides. A person taking AZT, for example, ends up with a lot of nucleotides made with AZT instead of real nucleosides. When reverse transcriptase or polymerase snaps one of these fake nucleotides onto a growing DNA chain, no more nucleotides can be added, because AZT acts like a cap. This is a problem: AZT is just as effective at blocking the construction of human DNA as it is at blocking HIV DNA.

Protease inhibitors work by clogging active sites. Dr. Rasnick says that HIV protease inhibitors only fit into active sites on retroviral proteases, not human proteases, as far as we know. But if these drugs don't inhibit healthy human proteases, then how does he account for their various side effects? Simple. He says that all lab-designed substances have unforeseen and unhealthy effects.

exhaustive exposé *Inventing the AIDS Virus* masterfully demolishes the HIV hypothesis, I'm afraid we have two or three more years before the "emperor's new clothes" become embarrassingly apparent to everyone.

In 1989 I decided to do my part by writing a book. There were already a number of excellent titles available that carefully illuminated the HIV/AIDS scandal using thorough referencing to the medical literature. But none had thwarted the HIV media blitz which used catchy slogans and celebrity endorsements rather than boring data. I wanted to try something new: to present the factual story of AIDS in the form of a novel. My thinking is that people may be more inclined to consider the technical hodgepodge of AIDS if it is presented as entertainment. Whether I'm the person to do it this way successfully I don't know—though I believe the idea is sound. But don't rush out to grab a copy of *Germ of Lies*—regrettably, it remains unpublished.

The Kuru Guru and I

I took a break from the laboratory in the fall of 1990 to finish my AIDS novel and spend a short Peace Corps tour in the Chimbu Province of Papua New Guinea teaching science and English. My Peace Corps training was conducted in Goroka in the Eastern Highlands Province, where the now-famous neurological disorder "kuru" was described by the American physician Carlton Gajdusek. Gajdusek, you may recall, speculated that kuru was caused by a hypothetical "slow virus," a novel concept that won him a Nobel Prize and provided a model and inspiration for the HIV/AIDS theory.

I have a Ph.D. in chemistry, so when I heard about Gajdusek's scientific institute in Goroka I had to go for a visit. I learned from a local that the "kuru guru" still ran the facility, which is the size of a small community college located three or four blocks from the Goroka airport. As a fellow American scientist who happened to find himself in the highlands of Papua New Guinea, I expected Gajdusek to receive me with the enthusiasm of a long lost relative. He didn't. I was greeted by a humorless old man who immediately escorted me through the labyrinth of hallways, passing familiar rotovaps, lyophilizers, general lab equipment and a library to what I anticipated would be his office where we could spend an enthusiastic hour or so talking about each other's science. Instead, the antediluvian gentleman deposited me into the keeping of a very young anthropologist/health-care-worker who nevertheless enthralled me with her stories of helicoptering twice a month to a remote village where a newly discovered tribe was dying out due to extreme infant mortality. I spent less than five minutes with Gajdusek.

He was the first scientist I had ever come across who showed no eagerness to talk shop. It was just unnatural. It is my experience that scientists have an uncontrollable urge to talk about what they do to just about anyone who will listen. Such reticence to talk with a fellow scientist puzzled me until Peter Duesberg and Bryan Ellison explained to me that Gajdusek's kuru work was as fraudulent as Gallo's, premised on his own false claims that kuru

victims practiced cannibalism and that kuru was infectious. His outlandish tales and "slow virus" theory were apparently accepted and even lauded not because they were supported by data or even logic, but because they permitted microbiologists to blame non-infectious diseases on harmless microbes.

Following the Peace Corps stint, I returned to the lab. In 1993 I began making protease inhibitors again for the same diseases I worked on in the 1980s. During my "sabbatical," HIV protease inhibitors had become a hot item. Several of the large drug companies had extensive programs underway. Roche had their inhibitors well into clinical trials. Merck had already spent \$500 million on their HIV protease inhibitor program, but the grapevine had it that Merck was seriously thinking of pulling out of the field for a number of reasons. The rumor was short-lived since Merck soon began construction of a plant in southern Georgia to produce commercial quantities of its HIV protease inhibitor. Nevertheless, from private conversations with colleagues, I learned that many of them wished they had never gotten involved in HIV work. Some openly acknowledged that HIV protease inhibitors weren't working and likely never would.

No Mutation to Resistant Forms

In 1994 I attended the Gordon Conference on Proteolytic Enzymes in New Hampshire where HIV protease inhibitor results were discussed. John Kay provided interesting information on the clinical trials of Roche's HIV protease inhibitor Ro 31-8959. He made the astounding claim that Roche had synthesized 800 tons (that's right: *tons*) of this compound. When given the opportunity to change his statement, he stuck to 800 tons. The clinical trial consisted of 400 AIDS patients receiving 2g of the Roche inhibitor per day. After 18 months there was no clinical difference between the group given the protease inhibitor and the controls. Kay announced that Roche was putting an information blackout on further reports on the HIV protease inhibitor clinical trials due to the disappointing results.

The vogue explanation for the failure of the inhibitors to benefit AIDS patients is that HIV replicates so fast that it eventually develops mutant forms of protease that resist the inhibitors. Even to this day, however, no one has ever found a resistant HIV protease in any patient, even in patients that are claimed to have them! The only inhibitor-resistant HIV proteases anybody has

ever examined are those produced in the lab using genetic engineering. Nevertheless, the mutation explanation, just like the HIV theory itself, was **c o m p l e t e l y a c c e p t e d — w i t h o u t**

"The more I looked into it, the more clearly it appeared that AIDS could not be infectious."

question—as soon as it was proposed.

The mutation theory is preposterous, but not just because its premise—that HIV replicates hyperactively—is false. The mutation theory is preposterous because it is illogical. Enzyme inhibitors work only because they are shaped like the substrates the enzymes act upon; when an inhibitor fits snugly into an enzyme's active site, then the substrate cannot. This is how inhibitors keep an enzyme from performing its task, which in this case is to pro-

duce HIV. Imagine one of these resistant, lab-created HIV proteases. It resists inhibitors because its active site is shaped in such a way that inhibitors cannot fit inside. That's great. But how in the world is the substrate going to fit? Remember, the inhibitor and the substrate have the same shape; they appear identical to the active site, the way a lock cannot tell the difference between a key and a copy of a key.

Yet a representative from Vertex presented a poster showing that some of these lab-created mutants did indeed retain most of their ability to act upon particular substrates. But could such a mutant still produce virus?

I reminded him that in order for an HIV protease to produce a new virus, it had to cleave eight different substrates, and pointed out that the ability to cut just one of those substrates did not represent the overall ability of the enzyme to produce HIV. Yet he was claiming that some of these resistant proteases were as much as 90% effective when compared to non-mutated protease. But these claims of high effectiveness were always for just one of the eight substrates. In every case, the effectiveness on the other substrates was absurdly low, numbers like 0.1%, or 0.01%, or even 0.001%. In order to calculate the total effectiveness of these mutant proteases, you must multiply together all eight percentages. And when you multiply even a very large percentage like 90% by a bunch of tiny percentages like 0.1%, what you end up with is essentially zero.

In other words, these drug-resistant proteases were effectively non-functional. They could not produce viruses.

At the discussion session the next day I argued that the Vertex data did not support the hypothesis that mutations of the HIV protease are responsible for the lack of clinical efficacy of the inhibitors: the drug-resistant proteases were just as inactive as if their active sites *were* plugged with inhibitors. Other explanations are called for.

I went on to propose that the HIV protease inhibitors were performing as designed—blocking HIV production—without be-

ing undermined by the emergence of drug-resistant mutant strains. The reason that these drugs did not alleviate AIDS is that HIV is not the cause of AIDS.

During private discussions, none of my colleagues found any flaws with my reasoning and even thought it was right. I left the meeting thinking that these fellows would continue the analysis where I left off. Well, that, of course, didn't happen. The HIV protease mutation hypothesis has become more entrenched with time.

None of the inhibitor-resistant mutant HIV proteases reported so far has come anywhere near the minimum level of overall activity necessary to produce relevant numbers of viable virus. It is extremely unlikely that mutations substantial enough to protect the protease against inhibition will at the same time leave virtually unimpaired its ability to produce viable viruses. The conclusion of my analysis is that inhibitor-resistant mutant HIV proteases are very unlikely to contribute to viral viability *in vivo*. Therefore, the failure of the HIV protease inhibitors to alter the progression of AIDS is not due to inhibitor-resistant mutations of this enzyme.

David Rasnick holds a Ph.D. in chemistry and has lived in San Francisco for over 15 years, designing protease inhibitors and studying AIDS and HIV.

Editorial Board

- Paul Philpott, M.S., Mech. Engineering, Publisher/Editor, Detroit
 Dr. Charles A. Thomas, Jr., PhD, Biochemistry, Prof. (ret.),
 Harvard Med. School, Johns Hopkins Univ., San Diego
 Dr. Hiram Caton, Ph.D., Prof. Medical Ethics, Author, Griffith Univ., Australia
 Dr. Harvey Bialy, Ph.D., Biology, Medical Journal Editor, New York City
 Cellia Farber, Magazine Journalist, New York City
 Dr. Philip Johnson, J.D., Author, Prof., UC-Berkeley School of Law
 Russell Schoch, Magazine Editor, Berkeley, CA
 Tom Bethell, Washington Correspondent of the *American Spectator*
 Dr. Charles Gesheker, Ph.D., Prof. African History, Cal. State Univ., Chico
 Dr. Gordon Stewart, Ph.D., MD, Prof. Public Health, Prof. (emer.), Univ. Glasgow
 Peter Plumley, F.S.A., Actuary Consultant, Chicago
 Dr. Peter H. Duesberg, Ph.D., Prof. Biology, NAS, UC-Berkeley
 Dr. David Rasnick, Ph.D., Chemist/Pharmacologist, San Francisco
 Dr. Mark Craddock, Ph.D., Mathematics, Univ. of Sydney
 Dr. Richard C. Strohman, Ph.D., Prof. (emer.), Biology, UC-Berkeley

Copy Editors: Christine Maggiore and Christine Johnson

The Editors welcome concise and appropriately referenced contributions reflecting all facets of this debate.

Rethinking AIDS

is a monthly publication of The Group for the Scientific Reappraisal of the HIV/AIDS Hypothesis.

There are many ways you can support our efforts. One way is to scrutinize the HIV/AIDS hypothesis in discussions with friends, classmates, and professors. Another is to make photocopies of this journal and distribute them to associates or leave them where free publications are displayed in book and health stores. You can also make a tax-deductible contribution to the Group that will help cover costs of publication, distribution and research. A \$25 donation (\$35 U.S. cash outside U.S.) will get you an annual subscription, although currently we survive only because many supporters donate more than \$25. Direct all correspondence to:

1354 East Ave., Suite R-120, Chico, CA 95926-7385
 fax 508-526-5944 Detroit

www.rethinkingaids.com (editor@rethinkingaids.com)

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.