From the Gut

The next research frontier: HIV's intestinal hiding place. Peter Anton goes to the source.

November 1, 1999 Interview by Lark Lands, PhD

AIDS research has progressed by fits and fractures, with crucial advances often made by a lone scientist laboring with little funding in an otherwise-ignored field. One such pioneer is Peter Anton, MD, an associate professor of medicine at UCLA's Center for HIV and Digestive Diseases. As a gastrointestinal-tract expert treating patients with AIDS-related diarrhea and wasting, Anton was driven to figure out why the gut is so vulnerable to HIV. Now, after many scientific and financial struggles—and a little help from Macy's—Anton and his colleague Michael Poles, MD, may be on the brink of a major new treatment advance.

Lark Lands: Compared to other areas of HIV research, little attention has been paid to the intestinal tract. Why is it important?

Peter Anton: When they asked Willie Sutton why he robbed banks, he said, "That's where the money is." Well, the gut is where most HIV is. In fact, it's a very promising area to consider not only for new approaches to reducing the body's total viral burden but also for vaccine research.

The gut is the body's largest organ and contains more T-cells than anywhere else. It's estimated that 2 percent of T-cells are in the blood, and 98 percent are in the body's tissues—half or more of those in the gut lining. It makes sense that nature would provide immune protection there because the gut is roughly 26 feet long and has, in most areas, only a single cell layer separating the outer world from the inner body. The immune system must be vigilant along that frontier to distinguish between an invading pathogen that should be destroyed and an essential nutrient that the body needs. So the cells lining the intestine have to be both "activated" (ready) and imprinted with a "memory" of prior encounters (able to respond quickly to pathogens). Since HIV preferentially attacks activated memory T-cells, it's not surprising that the virus targets the intestinal lining and spreads rapidly there. The gut fast becomes the largest reservoir of infected cells. And our research has found detectable virus in the intestines of 66 to 88 percent of those whose blood viral loads have long been undetectable.

What research are you now doing on HIV in the gut?

We know that in a healthy HIV negative person, the gut is normally in a mild state of inflammation to ready itself for an outside attack. And we now have evidence that this state of inflammation is

further increased in HIV infection.

We also know that the activated memory T-cells in the gut have lots of the CCR5 chemokine receptors that allow HIV to bind to and enter cells—far more than are found on their counterparts in the blood. When you have inflammation, additional fighter T-cells are constantly being recruited to the site and become activated there in order to do their job. Unfortunately, this gives HIV its favorite target, increasing the potential for HIV replication. So we're looking at whether an anti-inflammatory drug can reduce the number of new cells that are recruited to the gut and then infected by HIV. This could slow disease progression.

Michael Poles and I are now conducting a Phase I (safety) study looking at the impact of mesalamine (Asacol), an anti-inflammatory drug, on both GI symptoms and viral load. The drug is already FDA-approved for other intestinal conditions, including ulcerative colitis. It only works on the lining of the gut, mainly in the colon, and because very little is absorbed, side effects are minimal. Compared to other therapies, it's relatively inexpensive—about $240 per month at the dose we're studying.

Is there a downside?

There is a small possibility that if you decrease intestinal inflammation, you could decrease the amount of RANTES—a chemokine that blocks HIV from infecting cells. So, theoretically, you might increase HIV's chance of getting into T-cells. We believe that this effect would be greatly outweighed by the reduction in new T-cells vulnerable to HIV that are recruited to the gut, but we need a responsible clinical trial to evaluate this.

Your approach involves a paradigm shift: Current antiretrovirals target the virus, while this medication alters the environment that HIV exploits. How will you measure success?

We plan to look both at symptoms and at the viral load in the intestine. We've developed important new tests using simple gut biopsies that will allow us to see if therapies are knocking down levels of virus in the body's largest reservoir, not just in the blood. We have also worked with VIRCO, a medical technology company, to develop phenotypic and genotypic tests of tissue virus. We hypothesize that because of the high rate of viral replication in the gut, resistance may develop there before it does in the blood. So these tests might tell us which drugs are failing people before blood tests do.

In our Phase I study, we are looking at 12 patients with detectable viral load while on HAART. In two people already biopsied, there were improvements in symptoms (diarrhea, gas and bloating) and decreases in inflammation. We are now assessing the viral load results. If safety is confirmed in this study, we are hoping to launch a Phase II trial in February 2000 at multiple sites.

You mentioned the gut's importance in vaccine research.

Yes, I believe that in the next decade we will harness the immune strength of the intestine in the development of an HIV vaccine. UCLA's Janis Giorgi, PhD, Tom Lehner, MD, of Guy's, King's, St. Thomas' Medical School in London, and I are beginning studies to see if priming the gut's immune cells to identify and attack parts of the virus can provide protection. This is extremely important when the gut is the site of infection (as with anal receptive sex or breast-feeding). However, we also know that virus homes to the gut, regardless of the route of entry, so having a protective response there may be very helpful in any case.

Have you had to fight for financial support for your research?

There's a Catch-22 for those doing research into new areas: Until you have preliminary data, you can't even put in a grant request. So you can't do the initial research because you have no money, and without results from such early research, you can't get funded. Early on at our HIV/GI clinic, we had promising ideas and tons of patient experience that made us think we were onto something important, but no data and no funding to begin the research. Finally, several years after we came up with these ideas, Macy's AIDS fundraisers heard of our plight and began giving us yearly grants of unrestricted funds for new research. Everyone who may ultimately benefit from these therapies will owe Macy's a big debt of gratitude.

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