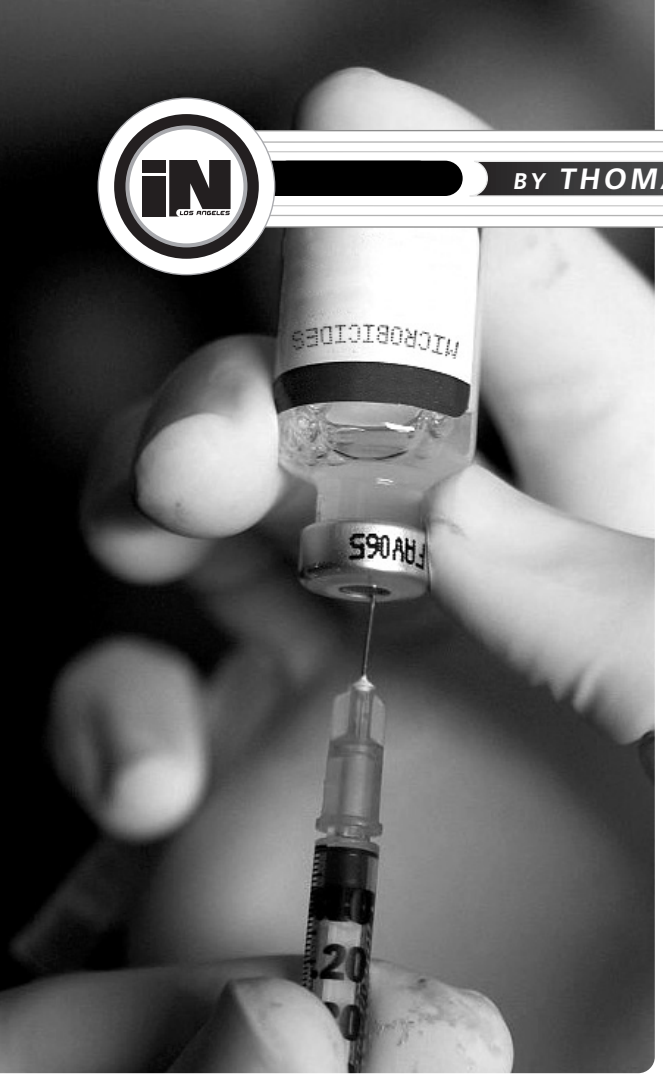
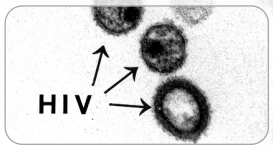


BY THOMAS TERRANOVA



A New Direction for Prevention

Due to the tenacious work of Drs. McGowan and Anton, microbicides move to the forefront as a new weapon to prevent the spread of HIV.

Microbicides—substances that can be used topically to prevent sexually transmitted diseases (STDs) such as HIV from infecting the body—are not a new idea. Spermicides have been used for years—so the idea of a microbicide is not a huge ideological leap. Perhaps because it was such a prosaic concept—stopping HIV right at the point of entry—the scientific community clamored past it as they searched for more complicated or foolproof measures. The scientific community is known for being slow to adopt new ideas—in fact, it's almost a point of pride. The dark side of this arrangement is that once they've committed to an idea, it can be even harder for them to let go of it. For the last 10 years, the study of HIV prevention has been stuck in exactly this kind of a rut.

Until recently, most research on HIV prevention focused on finding a vaccine. Microbicides—whether vaginal or rectal—were regarded as less desirable, low-tech concepts that were only partially effective. Condoms are proven to be more effective than microbicides, so why waste money on microbicide development instead of spending it on vaccine research? This logic almost made sense, until studies began to bring more clarity to the minutiae of the global HIV epidemic. It turns out that millions of people around the world—mostly women—are not in a position to negotiate for safe sex or condom usage, the only preventive measure currently available.

Despite this knowledge, research on vaginal microbicides stayed on the back burner. Research on rectal microbicides was practically non-existent because it was stigmatized as being of relevance only to MSM (men who have sex with men). As studies continued, more and more surprising facts and figures began to come to light, most notably, the fact that seven times more women contract HIV from anal sex than do gay men. It sounds incredible, but the explanation is simple: there are many more heterosexual women than there are gay men. Until recently, there wasn't much behavioral data on sexual activities, but as we learn more, the implications are staggering. Even in the United States, where we have the luxury of education and prevention resources—studies have shown that one in four of all American women have engaged in anal sex, and that it was usually unprotected. Mistakenly, heterosexual women have typically regarded getting infected with HIV from anal intercourse as more of "a gay problem," but new data shows that—globally speaking—women and their unborn children are most at risk from this vector of infection.

It's in this new climate of understanding that two brilliant scientists from UCLA—co-directors of the Center for HIV and Digestive Disorders (CHADD)—have succeeded in winning a landmark $12 million research grant from the National Institute of Health (NIH) to begin work on developing the first rectal microbicides.

Dr. Peter Anton and Dr. Ian McGowan began their work quietly over 10 years ago, a time when most immunologists and virologists had committed themselves to working with models of HIV infection only in blood. When Anton and McGowan began suggesting that it might be equally important to study immune response to HIV in mucosa, they encountered skepticism and a lack of funding. After over 10 years of hard work (and annual support from the UCLA AIDS Institute and Macy's Passport fund-raisers) their groundbreaking assays on immune response to HIV in rectal mucosal tissues are the scientific foundation that is enabling this huge new study on rectal microbicides—a study whose results may eventually prevent millions of new HIV infections every year. The pioneering work of these two medical "rebels" heralds a huge paradigm shift in HIV research, and this new study is poised to spark a revolution in HIV prevention. By sticking with a unique, common-sense approach that was blatantly overlooked by mainstream science (studying immune response in mucosa as well as in blood), and then devoting themselves to the painstaking work of creating a framework for all future studies in this area, they have earned—and will continue to earn over the next five years— their place in medical history as the real fathers of rectal microbicide study and development.

A Brief Timeline

1989

Dr. McGowan, an HIV specialist, moves from treatment to research after winning an Oxford scholarship to do a Ph.D. in mucosal immunology. At the same time, Dr. Peter Anton establishes his career in academic gastroenterology, focusing on Irritable Bowel Syndrome (IBD), before transitioning to research.

1994

Anton founds the Center for HIV and Digestive Diseases (CHADD) with a $40,000 seed grant from the UCLA AIDS Institute. McGowan joins Anton to do post doctoral work. CHADD struggles to persuade scientific community of importance of looking at immune response to HIV in mucosa.

1994-2004

The Anton-McGowan Lab at CHADD develops a toolbox of assays for measuring HIV in mucosal tissue, creating a foundation that is necessary for all future research.

1996-2000

McGowan works in the pharmaceutical industry, where he helps to develop HIV drugs like abacavir and amprenavir and is responsible for the clinical development of Viread.

2000

McGowan rejoins Anton, who is already working on winning a research grant for rectal microbicides, and they continue their work.

2002

CHADD receives $12 million grant from the National Institute of Health.

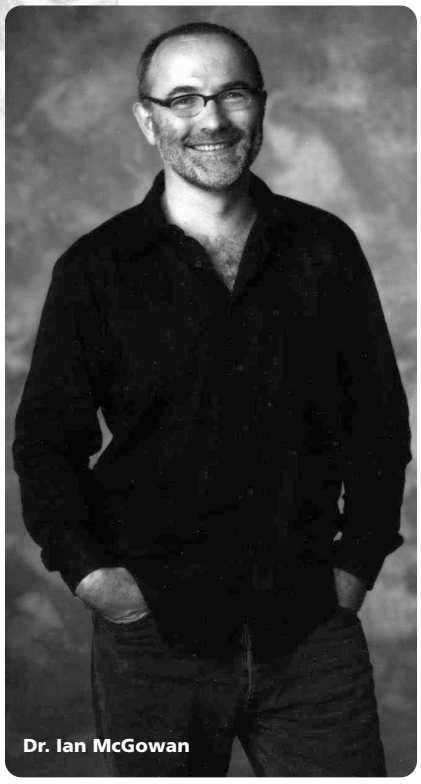
2004-and beyond

CHADD begins using their NIH grant to coordinate with groups in L.A., Seattle, Washington, and London that are focusing on the early development of a rectal microbicide incorporating one or more anti-retroviral drugs, placing CHADD and the UCLA AIDS Institute at the forefront of international research efforts. Anton and McGowan have each been asked to take on leadership positions with projects relating to their work for groups such as the World Health Organization (WHO.)

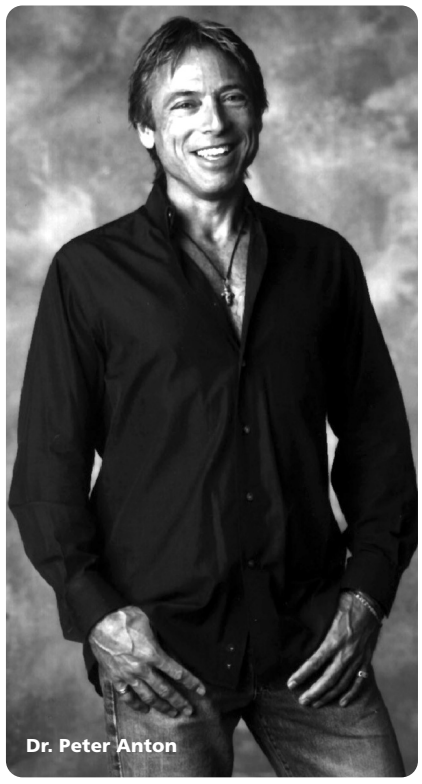
Overview: Rectal/Vaginal Microbicides

- Microbicides are substances that can be used either topically (in the form of lube, foam, cream, etc.) or as a suppository to prevent STDs such as HIV from infecting the body.
- Microbicides would not eliminate the need for condoms. Ideally, they would be used with condoms for an even greater level of security. For those who cannot or will not use condoms, however, microbicides will be a last, very important defense against HIV that could prevent millions of new infections each year.
- Rectal microbicides would benefit men, women, and unborn children around the world—even in countries where women can't negotiate condom use.
- Most microbicides in development work in one of the following ways:
    1. By killing or inactivating pathogens
    2. By creating physical barriers
    3. By strengthening the body's natural defenses
    4. By prohibiting viral entry
    5. By inhibiting viral replication

PHOTO CREDITS: JIM McHUGH



Dr. Ian McGowan



Dr. Peter Anton

• Despite two decades of HIV research (resulting in a portfolio of 18 effective anti-retroviral drugs), the number of new HIV infections each year remains shocking: 40,000 in the United States and five million worldwide. A vaccine may still be a decade away or more. Condoms and abstinence are not viable options for large portions of the world population, so other options—such as microbicides—are desperately needed.
• In countries with the highest HIV infection rates, women often do not have the luxury of asking for a condom. Husbands contract HIV from prostitutes and then come home—refusing to wear a condom—and infect their wives (and often their unborn children).
• Until recently, the erroneous perception was that anal intercourse was limited to men who have sex with men. New studies have shown that the number of women practicing anal sex in the United States is seven times greater than the number of gay men having anal sex. If this seems shocking, one need only consider the numbers—there are a lot more heterosexual women in the world than there are gay men. The social surprise: Anal sex and related HIV infections are not a gay problem. The political result: The stigma attached to anal sex slowly falls away so that the urgent, global need for rectal microbicides can take center stage.
• Approximately one-quarter of all American women have had anal sex—most of it unprotected.
• Women who have anal sex are three to five times more likely to contract HIV.
• A UCLA study found that 35-48 percent of gay men reported having unprotected anal sex in the last year.
• The idea of vaginal microbicides is not a new idea. However, until recently it was seen as a low-tech, low-priority solution.
• Because the vaginal cavity mucosa are so different from that of the rectum, products developed for vaginal use would probably not be tolerable (or safe) for rectal use. The rectum has only one layer of tissue between the virus and the immune system; whereas the vagina has a much more hearty seven layers. This means that the rectum is much more prone to both infection and irritation. Scientists aim to eventually create both vaginal microbicides and rectal microbicides. Rectal microbicides stand to benefit the largest cross-section of the population—straight women and their partners, as well as gay men.
• Over 60 microbicides are in the development pipeline and we should begin seeing the first effective products within 10 years—maybe sooner.
• You can help—keep your eyes open for opportunities to volunteer for upcoming studies coordinated by CHADD that will need thousands of volunteers for both medical and behavioral studies.

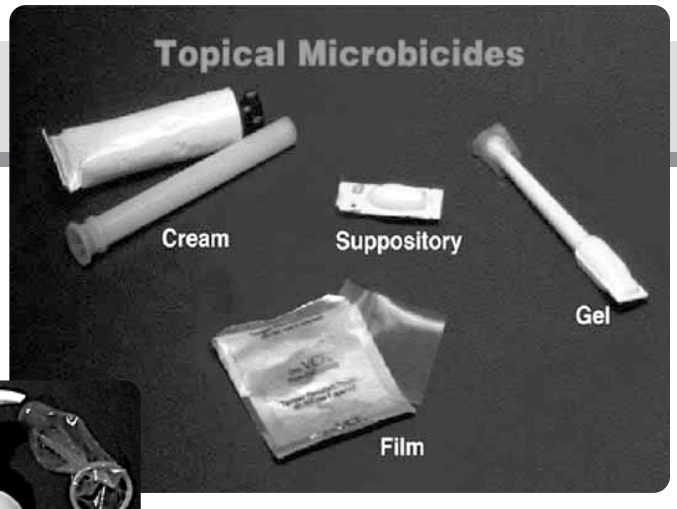
Q&A With Dr. Ian McGowan

What sparked your interest in HIV's effect on the gut?
Most people who aren't gastroenterologists or immunologists don't realize that the gut is the biggest collection of immune tissue in your body. It's about 60-70 percent of your immune cells that are in the gut—not in lymph nodes or in the blood—blood only has about one percent. That's why looking at HIV in the gut is such a paradigm shift. For the past 20 years, most immunologists and virologists have been looking at blood, just because it's easy, but that's not where the action is. The action is probably in the gut, because that's the main route of infection for a lot of people. It's also where the virus

Continued on page -

Continued from page -

A New Direction for Prevention



lingers—and the relationship of the virus to lymphocytes and microphages in the gut is probably different to the kind of relationship you see parenterally, or in the blood stream. The reason why not much work has been done [in this area] is that you really have to be a gastroenterologist to get tissue biopsies from the gut. An immunologist is used to putting in a syringe and drawing blood, but because [Dr. Anton and I are] both gastroenterologists, and also interested in HIV, we have the patience and the skill to actually get the tissue and move the research forward.

Why not just wait for vaccine work to come to fruition?

The reality is that we've actually done a lot of vaccine research—and we're still involved in it. We enroll patients in studies—some of who have had a [potential] HIV vaccine—and we measure any response in the gut. Because when you think about it, where is the virus going to attack a vaccinated person? Unless they're an IV drug user, it's probably not the bloodstream; it's across a mucosal surface. Very little work had been done to see if vaccines induced protective immune responses at the mucosal surface. The studies we have done have been small but meticulous and those data are being analyzed now. However, I think the bigger vaccine community is a little depressed at the moment because it looks as though it could be another 10 or 15 years before we get an HIV vaccine. With over five million new infections each year for 10 years, that's another 50 million people infected. So what else can we do? You can reinforce messages about safe sex, abstinence, and condoms; but in many environments, people either can't—or won't—use these methods. It's in this setting that microbicides have emerged. Also—there are vaginal microbicides which are almost reaching the finishing line in development and once they're available, we know that they're going to be used rectally because people have varied sexual repertoires. We really need to pay attention to these and ask, "are they safe given rectally?"

Why do you think it's time for people to become more aware of microbicide research?

We have this grant now and the science is being established. To do studies, however, we're going to need volunteers in the community who want to get involved in clinical research, so we need to begin educating people about rectal microbicides and how they might work. Probably the biggest challenge in the short term is going to be finding a large number of volunteers to take part in the studies. The kind of work we do is called translational science—it's science refracted through patients. It's not like studying a lab rat or a cell line; it's saying, "what's actually happening in the patient?" That area of science has been increasingly difficult because of human subjects' protections—which are very important.

Very few private researchers seem to return once they've made the move to corporate research, but you seem to have moved back and forth easily. What's your take on each sector?

Industry is very focused—you have a job and it's to get a drug licensed by the FDA. There's a corporate profit motive that drives the whole thing, so there are never roadblocks. There might be scientific roadblocks, but basically if there's a problem, money can solve it, and you just crash through it and carry on. For example, I set up two studies with about 1,200 patients covering 70 sites all over the world—and it was all set up in nine months. Doing that within the NIH would be incredibly difficult because of funding issues—that's the big challenge—but there's another side of the coin to that focus, you can't really wander off of it. In the private sector you can choose to look at new areas—providing that you can persuade someone that they make sense scientifically and are worth funding. It's difficult to choose one over the other. I'm happy here right now because I've got the freedom to explore.

Looking back, how has your career evolved over the past 20 years?

I'm now more aware of how important it is to prevent HIV. The first part of my career was spent looking after patients with HIV. Then I began looking at research questions and developing HIV drugs. Now I'm moving more into "This was all important, but let's stop it. No one else should become infected."