For those seeking exposure to pure science, there are many reasons not to attend the circus that is the biennial AIDS conference. Some distractions are at least entertaining: Buddhist monks looking lost; a self-declared Prince from Nigeria; a posse of African grannies sponsored by Stephen Lewis (the UN special envoy for AIDS in Africa); and a fashion exhibit of dresses made entirely of condoms. Others—such as the four-hour wait to register, self-serving speeches by ministers of health, activists popping up on stage like yo-yos, and Clinton-related mobs—are more irritating.

Yet researchers willing to embrace the event in all its craziness are exposed to a richness of experience—and an intertwining of science and society—that cannot be had at any other science-related conference. “For basic science, I couldn’t say it’s better than going to a focused meeting,” says Michael Tremblay (McGill University, Montreal, Canada). “But here it’s important because the entire planet is talking about HIV/AIDS.”

The evolution of a conference
In the last 25 years, 25 million people...
The ABCDEFGHI of prevention

Dutiful applause breaks out regularly at AIDS conferences in response to expected platitude...
The Bill effect. Billionaire philanthropist Bill Gates and ex-President Bill Clinton both drew attention to new prevention technologies (left), and increased the general level of chaos (right).
The emphasis on new prevention technologies has also resulted in stronger connections between researchers and field workers, as the researchers rely on the field workers to explain how communication strategies can be best used in prevention campaigns to increase compliance. “There is a new engagement, and I think it is very encouraging,” said David Cooper (University of New South Wales, Sydney, Australia). “It’s very different from...”

Interaction is also fostered by the shift from in vitro to patient studies, many of which are based in developing countries where NGOs may be important actors in the healthcare system. The early years of HIV research were concentrated on understanding the actions of individual HIV genes as revealed by in vitro assays. The newer research is focused on the immunological response to the virus. It was not always clear whether the conference was helping funnel community concerns from the field to those carrying out these studies in developing countries (see Science on safari), but at least the potential for interaction was there.

The connections to policy debates may be more obvious for clinical researchers, but there are other benefits for basic researchers. The conference gives everyone license to think not just about details of data but also more broadly about strategy. “It’s getting so focused doing basic science,” says Tremblay. “When you are always working in the same strain... maybe you are missing something.”

Keeping them honest
The presence of activists and scientists in one place results in a dialogue that “is very helpful both ways,” said Sharon Lewin (Monash University, Melbourne, Australia). “Basic scientists need to know what is important globally. What we probably don’t do well is to make [scientists and activists] intelligible to each other.”

Ideally, those who wander into the universe of basic science can bring a refreshing change in perspective. One researcher presented a study on virus entry into (and inactivation by) oral epithelial cells. It was a nice piece of science but somewhat shrouded in talk of monolayer cultures and markers of transcytosis pathways. Then came the questions—most from scientists and some from nonscientists. An audience member who appeared to fall into the latter camp asked, “What happens when you add virus-infected breast milk?” The researcher seemed amused by the naïveté of the question. But the facts in the field are simple: we know that HIV does not appreciably infect via the oral route except in babies receiving infected breast milk. In this context, the simple question was the only relevant question.

Other questioners were more direct. After a presentation by a student whose ample enthusiasm was not matched by his...
clarity, an audience member observed: “You mentioned several times that this was very exciting. Why?” For Killian O’Brien of AIDS Calgary (a service organization), his impatience with impenetrable science in a vaccine session was phrased more urgently. “I’m sure all this science stuff is very important,” he said, shaking with nervousness. “But I’d like something to bring back to my clients. Sometimes we need straight English.”

Some jargon will always be needed to communicate ideas that are buried deeply in a complex technological landscape of ideas. But that jargon need not preclude understanding by others. The AIDS conference featured perhaps the most science-literate nonscientists in the world—activists who tossed around names of cytokines and cell surface markers without a second thought. In O’Brien’s defense, I was completely stumped by most of the talks in the session that prompted his comment.

“We adopt jargon far too much,” agreed Kelly MacDonald, who chaired the symposium in question. With fewer big name scientists attending, the talks are often left to students, and many of them had clearly had insufficient guidance from their supervisors. “The [conference organizers] have set up for people to get tips on presentation... but the uptake has been very low,” said MacDonald. “We’re making this field completely inaccessible.”

Restoring that access is vital both for the HIV/AIDS community and for the research community in general. Marilyn Chase of the Wall Street Journal captured very well the unique nature and social impact of what is now undeniably an HIV/AIDS industry:

“AIDS has, in a way, changed everything. It’s changed the way we look at disease and its spread. It’s changed the way we look at research, how research is conducted, how we share the fruits of that research with the people who volunteer for studies, how the developed world shares with the developing world. It’s changed the way we look at treatment—it’s development, its pricing, its evolution, the way it’s administered. It’s changed the way we think about access to care. ... AIDS, in short, is a kind of crucible in which old protocols and assumptions are melted down and remade.”

This remaking is one justification for the size of the AIDS industry. Other industries are also important, but it is on the back of AIDS interventions that the possibilities of healthcare in developing countries are being redefined. Surely the scientific community should contribute to (or at least be aware of) this process?

The AIDS meeting is a place where researchers can witness, in one place, the winding path from basic discovery through clinical research to clinical impact in both familiar and less familiar environments. For those who are perceptive, it can give clues about how society prioritizes or fails to prioritize a particular research direction. At any one time there is at least one session that is purely basic science (see Tidbits from Toronto). The rest—the surrounding chaos of human contention—may not change the experiment that gets done tomorrow, but its long-term impact on personal motivation and research strategy should be profound.
So many of the academic musings at an AIDS conference have life and death implications, and the session on “responsible journalism” was no exception. The underlying question, said Daniel Kuritzkes (Brigham and Women’s Hospital, Boston, MA), was simple: “At what point can scientific controversies be considered settled?” The context was AIDS denialism—proposals such as those by Peter Duesberg (University of California, Berkeley) that HIV does not cause AIDS and by the Perth group (www.theperthgroup.com) that HIV may not even exist. As John Moore (Weill Medical College of Cornell University, New York, NY) stated: “This is dangerous stuff. AIDS denialism kills.”

All participants agreed on this statement and its underlying logic: public doubt about links between HIV and AIDS have caused countless people to have unsafe sex, stop taking life-saving antiretroviral drugs, avoid getting screened for HIV, and avoid taking drugs to prevent mother-to-child transmission of HIV. The consequences have been the worst in South Africa, where HIV prevalence is now 30% among mothers attending antenatal clinics, and only approximately one in five of those who need antiretroviral drugs can get them.

In South Africa, President Thabo Mbeki and Health Minister Manto Tshabalala-Msimang have been criticized for their very public doubts about HIV’s importance and the efficacy of antiretroviral drugs, and the vocal vitamin proponent Matthias Rath has loudly declared antiretrovirals to be toxic and multivitamins to be the correct solution to AIDS. The South African NGO Treatment Action Campaign (TAC) has led the fight against the government and Rath—in Toronto TAC stormed South Africa’s exhibit to protest the display of garlic, beetroot, and lemon (a mixture often promoted by the health minister) alongside antiretrovirals.

For the South African journalists on the panel, the question was how to cover this story without making things worse. “Does balanced reporting mean you give the lunatic fringe equal weight or rights—do they have right to reply?” asked Tamar Khan, from South Africa’s Business Day. “[With] the AIDS dissidents… we don’t cover blow-by-blow every activity they do. We try to be selective. But when these people are given an audience by your health minister, your readers need to know that.”

The evidence presented by the denialists is flimsy, according to Moore. They cite old, long-refuted papers, cherry pick data, use the evolution of scientific knowledge as evidence of errors, claim that acceptance of any research grant betrays a fatal bias in favor of the granting agency, and claim false affiliations to institutions that have long disowned them.

But the case is made worse by some journalists. Cited prominently was a recent Harper’s article, which is the latest attack on AIDS researchers by long-time activist reporter Celia Farber. The view from South Africa on this work was clear. Most at fault are “journalists who think that by doing a few hours of research on the Internet they can overthrow… millions of person-hours of research done by scientists,” said Nathan Geffen, policy coordinator at TAC. “That is a failure of ethics. That’s an arrogance.”

“Is it really the role of the media to challenge scientific consensus?” he continued. “Does the media have the expertise to challenge the scientific consensus? In my view, it doesn’t.”

This blanket statement drew a caution from Richard Horton, editor-in-chief of the Lancet. “Science is treated as truth—that anything that’s published in a journal has to be right,” he said. “That’s wrong. We publish stuff that’s wrong every day.” Without a critical media, he said, the scientific establishment can be let off the hook in a way that no other group ever is.

The last word came from the journalist Laurie Garrett. “A lot of science writers do overly rely on the journals and basically translating things straight from the journals without much critical analysis,” she admitted. But she sympathized with Geffen’s description of ”utter drivel that’s published daily” in South Africa. “For us in North America, it’s almost an intellectual debate,” she said. But at the conference “we’re trying to globalization this discussion and take it out of the comfortable place of Toronto into something larger”—into a place where it is a matter of life and death.
THE ULTIMATE HOPE

“AIDS vaccine is the only tool that can end the pandemic,” said Seth Berkley, CEO and president of the International AIDS Vaccine Initiative (IAVI). As Berkley explained, the costs for antiretroviral treatment in developing countries will reach $3–9 billion per year for 2007, so a gigantic effort to develop a vaccine is certainly warranted.

The gigantic part, at least, is coming to pass. The effort is so large that it doesn’t even need the word “vaccine” to be instantly recognized: it is called merely “The Enterprise.”

More formally it is the Global HIV Vaccine Enterprise, which acts as an umbrella for IAVI, CHAVI (Center for HIV/AIDS Vaccine Immunology; funded by the NIH), and the CAVD (Center for AIDS Vaccine Development; funded by the Bill and Melinda Gates Foundation). IAVI was founded in 1996 but its new friends are larger in dollar terms: CHAVI grants could total $300 million over 7 years, and CAVD recently announced its 16 grants totaling $287 million over five years.

Many observers are worried when the Enterprise is talked about in terms of simple engineering. But, said CHAVI director Barton Haynes, “we’re not a Manhattan Project— theirs was a technical issue. We have to define the enabling technology.” José Esparza, senior advisor on HIV Vaccines at the Bill & Melinda Gates Foundation, is also quick to reassure that more diverse lines of research will not be lost. “[The Enterprise] does not replace the creativity of individual investigators but tries to complement it,” he said.

Will science be heard?

Money does not guarantee success, however. “Up to now, the design of vaccine candidates has been mostly empirical design without enough scientific rationale,” said Francoise Barré-Sinoussi (Institut Pasteur, Paris, France). The new consortia include their fair share of common facilities aimed at streamlining the empirical testing of vaccines, but they also include many projects aimed at generating new ideas. CHAVI investigators, in particular, are putting a great deal of effort into understanding the initial immune response to HIV.

“How the time the immune response gets going,” said Haynes, “there is such a reservoir of integrated virus and depletion of central memory cells that the battle is lost.” He hopes that a vaccine that accelerates the early immune response might conquer the virus before it conquers the immune system.

Perhaps the biggest challenge is the lack of understanding about what kind of immune response is needed. “You don’t have people that are infected and then cured,” said IAVI’s Berkley. “We don’t have that natural model.”

There is even concern about activating the immune system too much (see Too much of a good thing). In one vaccine session a questioner noted that our best example of the control of HIV-like viruses is in certain monkey species, but even then the result has been a peaceful stalemate rather than victory. “How tremendous is the challenge to have [T cells] and antibody do something that evolution has not been capable of over thousands of years,” he said.

The number of vaccine trials is increasing sharply, and some themes have emerged. It is probably better to present multiple HIV proteins and to stimulate both B and T cell responses. But vast gaps in the underlying immunology remain. Some of the approaches to this that were covered at the conference are described below. Based on the conference proceedings, it appears that knowledge about the immune response to HIV is still fragmented. Comprehensive surveys of all HLA types, all HIV peptides, and a wide range of immune responses (B cell, T cell, innate, and all their molecular subdivisions) need to be systematically correlated with resistance to infection, and speed of disease progression. In facing a question of such monumental importance, piecemeal studies are tantalizing but not enough.

Models: HEPS, LTNPs, and macaques

If we made a successful vaccine, what would the winning immune reaction look like? Clues about these so-called “correlates of protection” come from various sources, including animal models, and people who are either highly exposed but persistently seronegative (HEPS; e.g., sex workers who have unprotected sex but remain uninfected) or long-term nonprogressors (LTNPs; people who are infected with HIV but do not succumb to AIDS).

Hope for an HIV vaccine got its biggest boost back in 2000 when macaques were protected from infection by infused antibodies. (The challenge virus was SHIV, which is based on simian immunodeficiency virus [SIV] but has the Env coat protein from HIV.)

Ruth Ruprecht (Harvard Medical School, Boston, MA) emphasized that such primate models for immunization protection must mimic the process of human infection as closely as possible. She suggested challenging with heterologous viruses in repeated low doses. But others emphasized that testing everything in monkeys, while useful, was not enough. If we base our strategy on the results of monkey trials, said Kelly MacDonald (University of Toronto, Canada), “we could be discarding developing an HIV vaccine is all the more difficult when we understand so little about the immune response to HIV.
Too much of a good thing

One of HIV’s tactics is to exhaust the immune system by activating it in unproductive ways. “There is so much immune activation,” said Photini Kiepiela (University of KwaZulu-Natal, Durban, South Africa). “It’s like the immune system is hitting the dart board but not the bulls eye.”

According to Angela Meier (Harvard Medical School, Boston, MA), one way that HIV does this is very direct. The ssRNA from HIV acts as a ligand for Toll-like receptors (TLRs), she said, leading to activation of CD8\(^+\) cells.

This particular pathway need not always be negative, however. T. Blake Ball (University of Manitoba, Winnipeg, Canada) reported a study using peripheral blood mononuclear cells (PBMCs) from highly exposed persistently seronegative (HEPS) women. These PBMCs respond to TLR stimulation by producing more immunosuppressive IL-10 rather than immune stimulatory IFN-\(\gamma\). The dampening effect of the IL-10 may help the women to avoid infection by reducing the target population of activated immune cells.

Negative regulation was also reported by Joseph Barbercheck (Tulane National Primate Research Center, Covington, LA). He found that the relatively less pathogenic SIV infection in African green monkeys correlates with a maintenance of inhibitory T regulatory cells, which were depleted during the more virulent SIV infection of macaques. Not reported was the situation in sooty mangabey monkeys, which show a greatly reduced response to SIV and a better outcome.

The overstimulation of the HIV-infected immune system can lead to replicative exhaustion. Telomerase has been shown to restore some of these lost functions to CD8\(^+\) cells, and Calvin Harley (Geron Corp., Menlo Park, CA) reported at the conference that TAT0002, a drug candidate and telomerase activator, can do the same. The drug enhanced cytokine production by CD8\(^+\) cells taken from three HIV-infected donors. With telomere restoration, “you may be taking these cells out of a DNA damage pathway and helping improve their function,” said Harley.

The issue of overstimulation has attracted attention for years, and there have been limited trials with immunosuppressants. The results have been equivocal. One HIV-positive delegate did, however, ascribe his lengthy good health to his taking low doses of the immunosuppressant prednisone. If this is true, said monkey researcher Ruth Ruprecht (Harvard Medical School, Boston, MA) with a smile, “then you are like a sooty mangabey.”

Slow down. Françoise Barré-Sinoussi, codiscoverer of HIV, explains the detrimental effects of excessive immune activation.

things prematurely. The SIV-macaque is such a crummy model.”

So the people are important. One of the biggest stories at the 1993 AIDS conference in Berlin was about a group of female sex workers in the Pumwani district of Nairobi, Kenya, who were seemingly resistant to HIV infection, despite repeated exposures. Rupert Kaul (University of Toronto) outlined the findings that have continued to emerge from this and similar cohorts of HEPS individuals. HIV resistance of HEPS individuals has been correlated with mutation of the CCR5 coreceptor, and the presence of specific cytotoxic T lymphocytes, neutralizing IgA antibodies, and genital innate factors such as the Trappin proteins. This diversity, he said, argues for larger and more rigorous studies to uncover all the means by which HEPS individuals escape HIV infection. It may then be possible to mimic these escape tactics (as was achieved by using CCR5 inhibitors) in the susceptible majority of the population.

Not quite as lucky as the HEPS individuals, but still very fortunate, are those who are LTNPs. The importance of HLA context for LTNPs was explained by Photini Kiepiela (University of KwaZulu-Natal, Durban, South Africa). Particular HLA types correlated strongly with either effective or ineffective HIV control. The favorable HLA types may grab hold of HIV peptides that make good targets for the immune system. Again, larger studies are needed to cover all the combinations of peptides and HLA genotypes.

Decoy responses

The human studies rely on correlations to identify possible vaccine targets. But targeting HIV epitopes that look good based on simple correlations may turn out to be harmful, suggested Natasha Christie (University of Toronto, Canada). She found that HIV may be maintaining epitopes unchanged not because the epitopes are needed for replication but because they lead the immune system down the wrong path.

Epitopes that are targeted by the immune system are usually put into one of two categories. There are those that change to avoid the immune system,
and those that cannot change because doing so would make the virus inviable. The latter group of epitopes would make good targets for a vaccine. But when Christie looked at some epitopes that do not normally mutate, and deliberately mutated them in vitro, she found that the resulting viruses were perfectly viable.

She suggested a very different explanation: these epitopes may be deliberately maintained by HIV because they engender detrimental immune responses. An example would be the phenotype seen by Yoav Peretz (McGill University, Montreal, Canada) in individuals with fast-progressing disease. These individuals’ immune responses were more likely to be to HIV peptides that prompt secretion of interferon (IFN-γ) alone. Slow progressors, by contrast, responded to peptides that cause the immune system to make the more productive combination of IFN-γ and interleukin (IL)-2.

Making a better immunogen
The one vaccine candidate that has been through phase III efficacy trials was the unsuccessful VaxGen vaccine. It was based on the gp120 surface protein of HIV. A better gp120 immunogen can be designed by pruning, said Ira Berkower (Food and Drug Administration, Bethesda, MD). He suggested that the key binding sites on gp120 are shielded by four protein loops. After he lopped off the loops, one such deletion increased antibody binding markedly. Entropy experiments suggested that the benefit came from a conformational change rather than the removal of a steric hindrance. “We removed something very essential [based on alanine scanning] and got back something that binds the CD4 receptor and binds antibody,” he said. The resulting molecule may make a much better immunogen than gp120.

Overlapping cycles
Appealing as the rational approach may be, “each of the successful vaccines that the world has made have been done in primarily an empirical way,” said Wayne Koff, vice-president for research and development at IAVI. That means a lot of trial and error. “The challenge is to compress this down as absolutely far as we possibly can,” says Berkley. Small trials in populations with high HIV incidence must be run quickly to get early clues to efficacy. To support this activity, “we need more clinical trial capacity in developing countries if we want to accelerate research,” said Pontiano Kaleebu (Uganda Virus Research Institute, Entebbe, Uganda). “We need to conduct these trials in parallel.”

Many early phase trials are underway, but the phase III trial data that everyone is waiting for will come in late 2007 or early 2008. This phase III trial is testing a Merck adenovirus vector carrying HIV gag, pol, and nef genes, and is designed to test the effect of cell-mediated immune responses. One observer of the field suggested that it would be “a miracle” if the vaccine candidates already in trials provided any meaningful protection, but other participants are putting on a brave face. “Either way, positive or negative, we’ll learn a lot,” said Haynes. He hopes the Merck vaccine will provide “a beachhead… of a vaccine that we can iteratively improve.”

Whether HIV will succumb to a neat trick or to brute force is really anyone’s guess. The one thing that we know for sure, said UN special envoy Stephen Lewis, is that the search for an HIV vaccine “is the most important quest on the planet.”