BY STEPHEN M. EDGINGTON

Is An AIDS Vaccine Possible?

In 1984 then U.S. Secretary of Health and Human Services Margaret Heckler announced that the cause of AIDS had been discovered, and that a vaccine was just around the corner.

Having crossed the threshold of the 90s, Heckler's prophecy of an AIDS vaccine appears extremely optimistic. For most of the thousands of researchers who have worked ceaselessly to fulfill her vision, the consensus is that it may be the millennium before protective vaccines against HIV work.[1] "I've concluded it's very difficult to develop a vaccine for AIDS," says Harvard's Ronald Desrosiers (New England Primate Center, Southboro, MA). "We've not met with overwhelming success."

Traditional vaccine strategies that employ whole-killed HIV [2] don't seem to work as predicted. Some of the best animals results demonstrated only 50 percent protection—under idealized conditions. Beyond that, reported liability concerns seem to have stymied clinical testing—manufacturers don't want responsibility if a mistake could deliver AIDS.[3]

The same pattern of buoyant enthusiasm followed by disappointed pragmatism is reflected in the stock market. Immune Response (IR, San Diego, CA), a biotech vaccine company that poposes both therapeutic and protective HIV vaccines, enjoyed enviable over-the-counter trading after basketball-star Earvin "Magic" Johnson announced he was HIV positive. IR closed 1991 up 1,265 percent. But since January the stock has slipped 50 percent.

While there is a downtrend in biotech stocks generally, the recent $1.2 million sale of personally owned IR stock—by the company's president and director—prompted speculation that management thought their stock might drop even further.[4] An insider at IR has a more mundane explanation, "It was April and time to pay their personal income tax."

BLOCKING HIV

The National Institute of Allergy and Infectious Diseases' (NIAID, Rockville, MD) Peggy Johnston says all AIDS vaccines in clinical trial development have a singular goal: block HIV from infecting cells. "Since HIV is a retrovirus that integrates into host DNA," she says, "once integrated, it would be carried around forever and could be activated by a whole number of things." The HIV-blocking approach hinges on the concept that a vaccine can stimulate a high memory B cell titers. The constantly circulating B cells serve as immune system sentries, perpetually looking for pathogens they've encountered before. Once an HIV particle is recognized, the B-cell sends the signal to kill the particle and then triggers an antibody-producing response that creates more particle-specific antibodies—a process that usually takes seven days before becoming completely effective. A vaccine that blocks HIV would stimulate this humoral immune response to recognize the infecting strain before it could infect.

WHAT'S GONE WRONG?

Genentech's (So. San Francisco, CA) veteran AIDS-vaccine scientist, Philip Berman, say vaccine-makers uniformly made a wrong turn in applying this idea to the wrong strain of HIV. "Everyone in the past used III_b (human T cell lymphoma virus III_b, HTLV $III_{b)}$ because it was easy to grow," says Berman. But no one bothered to find out if III_b was representative of HIV in the infected population. It wasn't until 1990 that researchers discovered that the neutralizing epitopes on III_b are rare in HIV carriers.[5] Until that time, most of the protection studies employed this strain in their experiments. "Since III_b is one of the most difficult strains to neutralize," Berman suggests, "that may have been making the problem harder."

The time lost may multiply the complexity of the problem. According to Berman, "The diversity of the virus is proportional to its time in the population." While it has been reported that there are five families of HIV worldwide,[6] the virus is diverse in the U.S.—the MN straindominates 60-70 percent of those tested, but no individual strain accounts for more than five percent of remainder, Berman says.

Presently vaccine-makers blame this high viral mutation rate for the failure to produce a traditional vaccine. But so far, even animals injected with the same SIV strain contained in the vaccine exhibit protection levels of about 50 percent at best.[7] If the viral challenge is administered vaginally or anally—the proposed "real world" sites of entry—the ability to protect against the vaccinated strain drops precipitously.

REAL-WORLD STRATEGIES

Researchers troubled by these results suggest that true "real world" conditions also include urogenital lesions—avoiding the mucosal membrane barrier and making direct blood contact possible. These lesions, they suggest, might occur through sexually transmitted diseases (STDs) such as syphilis or herpes. But while everyone agrees that STDs—and the antibiotics to treat them—depress the immune system, no one has data demonstrating that the lesions existed at the time of contact, nor that sexually transmitted HIV-positives had these diseases.

These results convince most researchers that a single-shot protective vaccine isn't feasible. But Berman suggests that the discovery of a highly conserved region on HIV's coat may open doors to overcome existing obstacles. Since the third variable loop (V3) in the external envelope protein gp120 is the principal neutralizing determinant (PND) of HIV-1,[5] Berman thinks it may be possible to create PND-specific vaccine for distinctive strains.

Berman envisions researchers collecting and identifying HIV strains in the infected segment of the general popu-

lation destined to receive the vaccine. On the basis of this evidence, scientists could formulate a vaccine cocktail capable of binding the principal neutralizing determinants. But he admits that this strategy would necessitate up-dated booster shots at regular intervals. The boosters would serve to keep antibody titers high enough to protect as well as vaccinate against any new HIV coat mutations.

"That's a good question...."

The underlying premise of the HIV-blocking approach may prove more troublesome than technical attempts to improve the data collected so far. No matter how committed to the HIV-blocking vaccine, no one interviewed would hazard a guess about the time-space continuum that would allow the approach to work. What's generally accepted of HIV pathogenesis suggests that the virus infects in one to two days, produces antibodies in less than two months, and then appears to remain latent for 10 to 11 years—before manifesting AIDS. Since the initial viral load is thought to be small,[8,9] how is it possible for the immune system to mount a full-blown B-cell immune response to the virus in the initial two-day infection period? After the virus's introduction, high titers of naturally occurring antibodies are so prevalent as to serve as diagnostics of the disease.

"That's a good question," say Philip Berman, Peggy Johnston, Robert Gallo (NIH, Bethesda,MD), Luc Montagnier (Insitute Pasterur, Paris), and Peter Duesberg (University of California at Berkeley), in a unique display of agreement about AIDS.

"The very concept underlying vaccination, 'reinfection immunity', is not applicable for an infection from which there is no evidence that a person can recover," says Richard Young.[7] Young suggests that recombinant-vehicle live vaccines may emerge like a phoenix from attempts to produce a traditional vaccine for AIDS. His group engineered the human tuberculosis vaccine *Mycobacterium bovis* bacillus Calmette-Guerin (BCG) to express HIV-1 polypeptide subunits.[10] The advantage of this approach, he suggests, is the ability to convey both humoral (antibody) and cell-mediated (T-cell) immune responses. But Young cautions that effective use of this biotech approach may necessitate first understanding pathogenesis. Traditional vaccine development proceeds directly from pathogen discovery—the disease progress need not be well understood (see *Biotech Vaccines' Problematic Promise*, this issue).

Is it sufficient?

"We're really way beyond that question," says Robert Gallo. Defenders of the hypothesis that HIV is the necessary and sufficient cause of AIDS have always carefully separated etiology from pathogenesis in defending their position. "Knowledge of the cause of a disease (etiology) is important for control of that disease and gives a basis for

Data, Data, Data....

In fairness to all, everyone interviewed wants to see data. It's generally agreed that a reduction in rhetoric and emotion would clear the air for better scientific analysis. "We all talk too much," says Gallo, "we need to talk less and present more hard data." But the meaning of "data" differs radically, depending on who you talk to. The debate over proof boils down to epidemiology versus biochemistry, correlation versus direct evidence. Depending on scientific background, definitions of scientific rigor and analytical ability may differ radically (see the "What's Wrong with AIDS Research" sidebar).

The most radical challenge to HIV's necessity and sufficiency has been hurled at AIDS researchers by Peter Duesberg. A molecular biologist with impeccable scientific credentials, Duesberg took the charter of his National Institutes of Health (NIH, Bethesda, MD) Outstanding Investigator Grant into areas many AIDS researchers feel he should not meddle in. "The award states I'm to come up with original research, whether theoretical or applied," Duesberg says. "I chose AIDS." In two PNAS papers, put through the unusual requirement of being reviewed by at least nine anonymous peer reviewers, Duesberg outlines his views on why HIV could not cause AIDS.[15,16]

As a retrovirologist, Duesberg saw correlation but no direct evidence—and a lot of contradictions—for HIV's role as the sole agent of AIDS. His critique revolves around two points: failure to meet Koch's postulates, and HIV's failure to act like any other known pathogenic virus. Following Koch's postulates, Duesberg says that until the virus can be removed from a sick individual, purified, injected into a susceptible host and shown to cause the disease, his stated aim is to remain a thorn in the side of AIDS research. Since this type of proof requires an animal model that exactly duplicates AIDS—and none exist—researchers have depended on what they view as "overwhelming" correlative data to support the HIV hypothesis.

While the mere mention of his name enrages many AIDS researchers, Richard Young (Whitehead Institute, Cambridge, MA) says, "It's the Duesbergs of this world that keep challenging us to prove our hypotheses by questioning what seems obvious—the history of science shows they are a valuable part of the process."

Young disagrees with Duesberg and says that perhaps the best demonstration of Koch's postulates, to date, is the rarely mentioned simian immunodeficiency virus (SIV) model in monkeys. Ronald Desrosiers' group (New England Primate Research Center, Southborough, MA) fished out and cloned a virulent strain of SIV from rhesus monkeys suffering from an AIDS-like disease. They went on to show that injecting this strain in monkeys could induce the disease.[17]

But what they failed to show, according to Duesberg, was that the monkeys that got sick made an antibody response to SIV, as occurs in HIV infections in human AIDS. Duesberg claims that the monkeys that got sick made no antibody response and showed no viral latency before the AIDS-like symptoms appeared—typical of viremia, the viral overwhelming of a compromised immune system. "Desrosiers and co-workers have demonstrated unquestionably that SIV infects and kills monkeys," says Duesberg. "But SIV does not exhibit the conditions stated as the pathogenesis of HIV."

control of the disease. However, knowing the cause of a disease does not mean that there is complete understanding of its pathology."[11] Traditional vaccine technology supports this view by establishing etiology as sufficient for vaccine development. But the failure to develop a protective AIDS vaccine represents a challenge to the HIV is "necessary-and-sufficient" doctrine.

The infallibility of this doctrine was recently cast into doubt by the discoverer of HIV, Luc Montagnier.[12] "AIDS is a transmissible disease—without HIV there is no epidemic," says Montagnier. "But the big question in my mind is how is it amplified, are there many co-factors that contribute, or a single essential co-factor?" Montagnier plans a series of experiments to determine the role of mycoplasma in producing AIDS. He is intrigued by data suggesting synergism between HIV and the microbe may cause immune suppression. The idea that more than one factor comes into play suggests to him a possible explanation for the disease's long latency period. For now, he remains open to investigating a wide-range of possibilities. Montagnier's questions open a crack in the dam of opposition to exploring other possible explanations of AIDS pathogenesis.

Anti-idiotype networks?

One of the more intriguing alternatives suggests that AIDS may result from disregulation of the anti-idiotype network. This network is thought to regulate anti-self antibody and T-cell recognition by forming antibodies capable of eliminating these self-destructive elements of the immune system. Taking a cue from the number and variety of autoimmune diseases AIDS patients suffer, Robert Root-Bernstein (Michigan State University, E. Lansing) proposes idiotype—anti-idiotype complexes may result from antibodies to a number of infectious agents associated with AIDS—allowing disregulation of the network. He cites papers that propose HIV may resemble major histocompatibility complex (MHC) class II[13] to back up his own research: a number of infectious microbes found in AIDS patients, such as mycoplasma, produce antibodies that will cross-react with CD4+ T cells.[14] As a intial response, these cross-reactive antibodies might bind either MHC or CD4+ cells causing an autoimmune-like reaction and/or immunodeficiency. Since MHC and CD4+ cells bind to activate the immune system, this reaction could be further amplified by anti-idiotype antibodies binding to the highly variable region of the anti-MHC antibody or the ant-CD4+ antibody. The highly variable regions of these anti-idiotype antibodies would be chemically similar to the original binding region of either CD4+ or MHC. These mirror-image combinations might amplify the number of anti-self antibodies, resulting in T-cell immunodeficiency and specific autoimmune diseases. In this hypothesis, the timing of the infection of specific MHC- and CD4+-mimicking pathogens would explain the disease's latency as well as the variety of disease diagnostic for AIDS.

New animal models

If Root-Bernstein is correct, there is the disturbing possibility that traditional HIV vaccines could serve to stimulate the very antibodies that would disregulate the immune system.

But this hypothesis proposes another possibility that might go far to resolve

What's Wrong With AIDS Research?

A noted AIDS vaccine researcher, with outstanding credentials in both basic and applied research, listed the following problems with making progress in AIDS vaccine development. No disgruntled grant applicant, this person remains at the top of the profession, but is frustrated as a scientist with the level of debate. Recent predictions about the expanding AIDS epidemic prompt these remarks. The researcher hopes to stimulate colleagues to rethink their positions and act. Because of the political climate surrounding AIDS research, the researcher prefers to remain anonymous.

Vaccine literature lacks foundation

Perhaps more than any other field, the premises are more dogmatic than foundation-building. Vaccines have succeeded in the past on a trial and error basis. Until the immunology and pathogenesis of various diseases are more fully understood, vaccine research will not have a solid foundation on which to base any vaccine.

Personality over data

The hallmark of basic research is that the minority view, with its quirky challenges to the mainstream, is often the most exciting. In applied medical research, the complexity of extracting data from human subjects makes it more difficult to come up with clean data. Instead of debating the data, applied researchers frequently depend on forces of personality to sort it out. If anyone dares voice a minority view, it is often shouted down. As a result, new concepts in AIDS research originating from less well-known investigators gain acceptance more slowly than in other scientific areas.

Dogmatic experimental design

One way to prove a hypothesis is to design experiments that will disprove it. If the experiment fails with the proper controls in place you have good evidence to encourage pursuit of the hypothesis. This capability is precisely what made molecular biology move faster than any other biological science. In applied research on AIDS, the fundamental difference is that experiments are most often designed to prove a particular hypothesis—often without controls. If dogmatists push only one experimental design—what kind of people are they training?

Attracting rigorous scientists difficult

Older, more forceful researchers refuse to give way to younger scientists: prima donnas get all the press, publications, meeting invitations, more access to grant money, and the right to peer review their younger colleagues. This implies the power to destroy budding careers that don't follow the mainstream. Young scientists don't want to risk careers in fields that don't reward innovation.

Shaky foundations in the literature prevent clear-cut application of research skills. Even the most promising scientist might spend 10 years disproving hypotheses. A negative result doesn't earn much scientific credit unless it lays the groundwork for a new hypothesis.

Who are the pioneers, who are your colleagues? There is no James Watson-type in this field. How many AIDS researchers are there at Berkeley, MIT, Cal Tech?

It's dangerous to work with HIV.

etiologic and pathogenic issues. Researchers testing this hypothesis wouldn't need test animals that have naturally occurring AIDS-like symptoms nor HIV-like viruses to prove it. A chimpanzee simultaneously injected with HIV and mycoplasma should create the same idiotype-anti-idiotype disregulation Root-Bernstein suspects in AIDS. The resulting immunodeficiency and autoimmune diseases should be quantifiable. An animal model that directly mimics AIDS would go far to improve vaccine development. Scientists would finally have the needed tool to determine both the cause and progress of the disease.

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