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#1 Prairie Fire

"Don't tell me nothin' about no AIDS because that won't impact me. And if I was to get it, all I'd have to do is take a pill in the morning and I'll be OK."

A 15-year old girl

"One in every 50 black American men is now infected with HIV."

Helene Gayle, Ph.D.
Centers for Disease Control and Prevention
Source: "The Quiet Scourge," Bob Herbert, The New York Times, January 11, 2001: A31.

#2 Pendulum Swing

Treatment Paradigms Come and Go, But the Virus and Its Problematic Potions Appear Intractable

'Imperative to go off'

Every now and again, it's helpful to take a reality check. The day to day world of HIV infection is rarely reflected in the halls of Congress, the plates and wells of biomedical research institutions or even the pages of Science and Nature. As the naval observatory's millennium officially draws to a close, we thought it might be interesting to visit with the front-line care givers at one of the country's largest comprehensive HIV care facilities. The docs and nurses at New York's St. Vincent's hospital were more than glad to sit down for a chat. And while some of their observations could have been predicted, it is still surprising to see how they (and we) have managed to do so well with so little. Heartfelt thanks (and a little nostalgia) to Drs. Fred Siegal, Bruce Olmscheid, Juan Bailey and the rest of the gang at SVH for their gracious cooperation with this little project.

TAGline: Okay. First things first. Last time we spoke you were confessing that your approach to clinical management of HIV infection has changed over the past year, year and a half. You mentioned something about the in-patient population... how it's not the ambulatory patients who are generating the income; rather, it's the folks who get admitted. That sounds just the opposite of the thinking a few years ago. I don't know how the in-patient census has changed since 1998, but weren't the business minded medical folks out there planning on getting rich through the provision of ambulatory services? That's not turned out to be the case.

Siegal: The truth is I don't even know. Some people had a weird idea of what you could earn from doing research in AIDS clinical trials. The whole model was built around making money from clinical trials, and that was a big turn off for me. But I thought it was mistaken, anyway, at the time. It's not easy to do AIDS clinical trials.

TAGline: And it's becoming trickier.

Siegal: Yes. First of all there are so many drugs out there that there is hardly any imperative [to enroll in a clinical trial] except for the people who are at the end of the line... to start something new and experimental. So there's less interest in the community for clinical trials when you can go on, for example, nelfinavir and Combivir and be well for years—which is often the case.

But the clinical trials business aside, our in-patient census is, for the most part, either people who are at

the end of the line (mostly admitted through private docs) who have been serial monotherapied and have sort of burnt out of options—even with some of the new options that are out there—or people who aren't taken care of to begin with.

TAGline: People who present for the first time?

Siegal: Occasionally people who present for the first time. Every so often we'll see someone who is newly diagnosed. I picked up 2 people last time I was on service: one who came in with an immune reconstitution syndrome, actually, and the other with a community acquired pneumonia with strep pneumonia and bacteremia who turned out to be HIV-infected.

Siegal: But that's the population we see—whereas the IDC (Infectious Disease Clinic) population doesn't heavily get admitted. I believe our census, just judging from the couple of weekends that I've been on call, if we have 5-6 people in the hospital at any one time—out of a 3,300 patient base—that's a lot. So it's a very small proportion of our population that actually needs admission at any one time. That could change, of course, but I think if anything it's going to go down.

TAGline: That's the other thing I was thinking. It seems that whether out of creative management or luck or earlier undue pessimism, the drugs are working longer than alot of us expected.

Siegal: Yes, they're working longer and they're also having this interesting effect of keeping people out of the hospital even when they're viremic. Which, I think, the consensus is that it's an issue of viral fitness and that maybe the virus doesn't have as many pathogenic qualities when it's being mutated heavily in response to drug-induced selection. But whatever the reasons are, if you think about the last 10 or 15 years, MAC prophylaxis was already available in 1990, and we had Pneumocystis prophylaxis long before that. They were pretty well established. I don't think that's the major difference.

And considering that at least 50% of our population is not without viral loads... many, many of our patients have viremia. The people who are doing the best, don't. But that again comes around to the question of, If they don't have viremia, why not? Did they need treatment at all? Because it's pretty clear that there are some people that we're treating because of the earlier paradigm of treat early, treat hard—who may not need therapy. And that whole issue is being approached at least by the sCPCRA with the SMART study.

The SMART study is going to look at the different long-term strategies of whether we follow the immune system and withhold antiretroviral therapy until the CD4 count approximates 250 or whether we start early with antiretrovirals and keep pushing, come hell or high water, to try to keep the viremia suppressed. And presumably you keep on going even when the virus is again out there and you have run out of drugs because of multidrug resistance. And the question is, well, Is a drug sparing strategy going to be better in the long run than a drug heavy using strategy? And nobody knows.

What concerns me about this is, I think you and I talked about this before, is the old time studies of prostate cancer—years ago at the V.A.—which showed that you could control people's prostrate cancer with hormone therapy but their death rates were exactly the same as if you didn't use hormone therapy—because of cardiovascular disease. So it was a wash. We now know that people with hypercholesterolemia already have narrowed carotids, that there's intimal thickening. And so the hypercholesterolemia, especially the hypertriglyceridemia, from the antiretroviral drugs is obviously taking its toll—forgetting about all the lypodystrophies, insulin resistance, osteonecrosis and the other side-effects that have emerged as we use this set of drugs longer and longer.

And so the price we're paying for long-term viral suppression in at least 50% of the people is fairly high—maybe higher than we know. Because the evolution of coronary artery disease obviously takes a while. And it's sort of amazing that we haven't seen more than we have, in such a diverse population.

TAGline: Do we have people showing up at the ER with drug-related cardiac events?

Siegal: Not that many. There's an experience with HIV-associated coronary disease. There are some

published case reports. There's no real good evidence as far as I'm aware that there's a statistically significant rise in coronary events in people who are being treated with antiretroviral regimens—yet. I mean, if there is I don't know the study. Nonetheless, it's obvious from these preliminary studies that there is intimal thickening and since there is a correlation between intimal thickening and coronary events in the general population that you could make the extrapolation that we're going to get into trouble with this soon. So there is a kind of imperative to take people who don't need these drugs off them.

To me the issue boils down to who really needs to be treated and who can afford to wait -- or to take a break. I'm not saying that taking people off antiretroviral therapy isn't scary. It is! Sometimes you stop their drugs and their viremia blasts off and their CD4 cell count drops in half and you say, "Oh god, we can't do this."

There's one young lady I'm just toughing it out with because there is no consensus about viral load cut-offs. She has 660,000 copies of virus, but she still has 800 CD4s. And this is one of the hardest people I've ever had to control. But we got her through her pregnancy. She's very young. To treat her forever, inevitably would mean incurring drug resistance because she was somewhat viremic on three different classes of drugs, and I finally decided, "Okay, I'm going to give her a rest." It's taken about a year for her virus load to go up that high; her T cells are still reasonable, and so I'm just sitting on it. There isn't any national consensus—even for the SMART study—about how high the virus load is allowed to go.

TAGline: The SMART study will pretty much focus on T cells, no?

Siegal: Yes. That endpoint at least is... wait until the immune system is dangerously compromised—because we have reasonable confidence now that we can put people back on their drugs. I've been doing what's come to be called "structured treatment interruptions" for at least 3-4 years where I thought the toxicities justified that. Sometimes I didn't I think I could get away with it, and I was always nervous that we couldn't reapply the same drug regimen and get back to where we were. Most of the studies that have come out so far (where there's been a formal look at that) have suggested that you can do that in all but 5-10% of the people who stop. Now, that 5-10% is a little worrisome, but fortunately we have enough alternative drugs now that we can reasonably expect to get them back to aviremic with... something.

So, there is no right answer to any of this. And I think in some respects you have to sort of individualize, and I've been trying to sell the SMART study to my patients. We're going to, I think, get into this in a very big way. It's a very good question, it's a very reasonable question, and nobody knows the answer.

Of course, alot of our patients would like to get off the drugs and they say, "Can I do it without being in the study?" And I say, "Well, we don't really know the answer and we need to find this out, so it'd be much better if you were in the study." Again it sort of depends on circumstances.

We're having a talk today from Kendall Smith who's going to talk about his strategy of immunization and IL-2 as a prelude to an STI. Which is kind of an interesting way to go. That's something people had been thinking about for a while, but nobody had an immunogen that seemed to make sense.

TAGline: What's his immunogen again?

Siegal: He's going to use ALVAC, the canarypox recombinant vaccine. In conjunction with IL-2. It's going to be a four arm study.

Bailey: Aaron Diamond was using that a couple of years ago.

Siegal: That particular vaccine?

Bailey: Yeh, the canarypox virus. I can't tell you off the top of my head what particular immunological markers they were measuring, but I don't recall there being any significant increase in those markers.

Siegal: What Kendall's going to tell us today is the immunological marker he's going to use is going to be fairly crude: What's the "set point" of the virus after the first, second and third STI? Is it going to go up and then come down to progressively lower levels with each cycle of treatment interruption?

Bailey: And there will be a placebo group, right?

Siegal: Right. There will be, of course, a placebo group. And I think it's a pretty well designed study. It's a fairly big study. Has to be.

TAGline: And he's doing that at?

Siegal: He's at Cornell.

Siegal: I mean, not that I have alot of confidence in anything that tries to immunize people to something they already have in spades. I mean, if you already have a zillion copies of virus, what could possibly be the difference in taking a non-homologous virus... how can you expect that to be more immunogenic than what the immune system is already being presented with? But I'm prepared to try... because we don't have a good strategy. And to take somebody whose virus has been suppressed for seven or eight years and stop them cold turkey without any kind of immune stimulation presumably opens the door to a larger burst of viremia. But I just did that with somebody—this week.

TAGline: Those are the results you're waiting to see?

Siegal: I did it because we had been talking about it for a year and we finally agreed that it was time to do this. Because is a young woman whose viremia was easily suppressed by two nucleosides, originally, and she hasn't had any virus in seven years. She's getting a little lipodystrophic and we just decided, well, maybe it's time to find out whether this trip was necessary.

Because of this swinging of the pendulum, I mean, this is something I never would have done two years ago. I would have said, "Well, we're getting ahead of the game." She had a normal ratio, a thousand or twelve hundred CD4s—but not a normal immune system. None of these people have normal immune systems.

TAGline: I have a friend who has been on nevirapine and two nukes for 3-4 years now, and after his face starting shrinking I suggested he talk to his doctor about going off the drugs for a time. His T-cells have always been in the six to eight hundreds, he's always been aviremic on the combination. Turns out he had had a history of viral load counts of about 1,200-2,000 when he was put on therapy and his doctor now says, "Why did we ever put you on treatment in the first place?" You know? Four years later!

Siegal: Well, I think the thinking has changed because of the evolution of our understanding that there's more to the toxicities than we originally thought. And the long term toxicities are still confusing. Because there are so many different morphologic changes that happen—heterogeneously correlated to lipid abnormalities and other things that we barely understand.

Bailey: A lot of us were drawn into this, certainly I was, with the thinking that you could eradicate the virus if you bring down someone to undetectable and maintain them there... originally, I think, David Ho said that this could be done within six months, then nine months, then a year, then a couple of years... [NB: the original Ho/Perelson estimate for eradication was somewhere in the range of 3 years.]

Siegal: Well, what David didn't understand was that the immune system has memory; that's what the anamnestic response is all about. And it's couched in the very cells that are infected. [NB: Ho underestimated the lifespan of memory T cells, and had not accounted for the latently infected pool in his and Alan Perelson's model.]

Bailey: But at that time, there was so much publicity... and even now, in retrospect, alot of people we started on therapy back then... was with the intent of... And, in fact, even in talking to the patients... one of the ideas of at least selling them on starting therapy was the whole notion that it's conceivable that if

we make you aviremic for X period of time, there is a chance that you can be cured.

Siegal: Yeh!

Bailey: And now in retrospect, there were alot of people there that I'm seeing right now that I wish I hadn't started therapy for.

Siegal: Why? Because they've failed now or because they didn't need it in the first place?

Bailey: Yeh, because of toxicities. Now, I clearly would not have started people. We were talking earlier about how the best marker in terms of immune reconstitution is really your CD4 count.

Siegal: Don't forget the PIPCS (interferon-producing cells which Dr. Siegal is currently investigating, pronounced "pipsies").

Bailey: And we relied heavily on the viral load. Not to disregard the viral load, but our knee jerk reaction was the viral load. If someone came in with 900 T cells and normal ratio, normal parameters, but their viral load was 50,000, automatically you put on therapy. I don't think that's the thinking anymore.

I just got a call from someone I haven't seen who got tested because he had an outbreak of herpes zoster. And the doctor who saw him initially—he had a CD4 count of 300 with a viral load of 64,000, otherwise asymptomatic except for that herpes zoster. Now the question comes in in someone who recently tested positive who probably has been chronically infected but has been asymptomatic and now presents for the first time with 64,000 viral load and a CD4 count of 300. Now, he's right at the cusp where I think you would have a lot of differences of opinion as to whether or not you start therapy in this gentleman. And even I question it. Because, now, "Is he symptomatic?" Well, one could say, "Yes, he is symptomatic" because he had an outbreak of herpes zoster. Does that really classify in terms of starting someone on therapy who is a college professor, who's teaching and otherwise feels fine?

Siegal: It wasn't multidermatomal, was it?

Bailey: We don't know yet.

Siegal: Because when you talk about zoster you have to think of the pitfalls of STIs also. I had a very interesting experience. One of my patients who is fairly elderly, he's a man in his early 70s now, presented with a Bell's palsy. That is how his HIV infection was diagnosed. I showed Juan this case. Very nice man, very diligent about taking his pills but hated taking them. Just kept agitating, you know, "Why do I have to take so many pills?" And he was doing great! He had, I don't know, how many CD4s, but he had plenty of room for maneuver. And so, about two months ago I stopped his antiretrovirals and, looking back, he had never had a very high viral load when we began to measure him. And lo and behold within a month he had his Bell's palsy back. And I put him back on HAART and on acyclovir, and it's gone away. But it was such a striking recapitulation of what had previously happened. And this is going to happen as we stop. And it's presumably the same kind of thing as having an acute retroviral syndrome, when you stop HAART.

TAGline: Does the viral load ever peak and come back down on its own?

Siegal: Yes... if you look on a weekly basis, or a twice a week basis. There's a little peak and then it comes down a little and reaches a plateau.

TAGline: Because I've heard anecdotes of cases where...

Siegal: But the question is, "Does that mean anything?"

TAGline: But if what freaks you out is the virus' going to 150,000 or 200,000, but then a month later it's back down.

Siegal: I've never looked at it that early.

Olmscheid: You have to wait until you're in that plateau phase to determine what someone's chronic viral load is.

Siegal: And it's not necessarily stable. The young woman I referred to before was somebody I stopped. At about a month she had about 7,000 copies. At about two months, she had about 15,000 copies. At about ten months, she had 660,000 copies. So it just kept going up, but it did it slowly. It didn't do it all that abruptly. She might have had an early peak, but she was completely symptomless and she's fine. Her T-cells are still excellent. I'm sitting on her but I'm biting my nails. But that's the kind of thing that happens. So there's an enormously heterogenous response to stopping therapy.

TAGline: But as the virus starts to go up, though, over that period of time, it seems like the T-cells don't really do anything. Is that true or not?

Siegal: Well, not much. At least they didn't with this woman. But I also have seen people whose number has fallen by fifty percent. And you do it again, and it's still in that range. And you say, "Well okay how much more can we tolerate?" And until I knew there were other people doing this and there was a big experience in it, my tendency was well if they fell fifty percent and it was confirmed then I put them back. But I think when you do an STI in somebody who starts out real high, at least you can do so with some confidence that...

TAGline: High...

Siegal: High CD4s. That you can do it without the bottom really falling out. Because even at fifty percent, if you start out with 800 CD4s you still have some what I call "room for maneuver." Whereas if you're starting with 250, forget it. I don't think you should be on an STI—because we know that OIs begin to develop.

Olmscheid: Are you talking specifically about STIs?

TAGline: Clinical management in general. Starting, stopping, switching.

Siegal: Yeh, how quickly do you react? When we started doing this, I felt it was sort of malpractice if I saw somebody who became a little viremic... To not change them right away and change the whole regimen was potentially catastrophic. I've learned that it isn't, probably. But, you know, our whole approach to that has evolved over time.

TAGline: I remember 2-3 years ago, you would switch like that. We were so afraid of resistance.

Olmscheid: I think that's where the data was at that time also. We were very afraid of resistance, and we switched much sooner, much earlier than we do now. But even among all of us who treat, I think we had different practice styles. Some of us tolerated viremia longer without switching than others did. And I think if you look at it, just among our group here, we may have had slightly different ways of approaching it and none of particularly had any more people in the hospital than the other one. That's not a controlled, documented study. We were talking about this a little bit earlier, you know, just thinking about the literature, the data, that's out there. And we're still flying by the seat of our pants. Juan looked at me the other day and said, "You'd feel comfortable stopping, wouldn't you?" I think to a certain extent we want to make sure our colleagues are doing the same thing we're doing.

TAGline: As a whole...

Olmscheid: As a whole, the pendulum has really swung back over the last 12 months towards less treatment, less drug exposure.

TAGline: Treating less. Waiting longer. Considering taking people off. Waiting to switch.

Olmscheid: Waiting longer to start. The switch thing, I still think we have to be very, very careful about the development of resistance in someone who has detectable viremia on a particular regimen that may, especially with the PIs, may be pushing them down the line towards more mutations.

Siegal: Even with an NNRTI. It doesn't take very long once somebody is viremic in the face of it before you have full drug resistance.

Olmscheid: The issue I struggle with right now, for instance, is someone, let me just pick an example, on two nukes and nelfinavir with a viral load of 5,000. Are they going to be developing the secondary PI mutations? And would I be better off stopping that regimen—especially if their CD4 count is 500 or 600? I may be better off stopping than continuing them on that regimen, and I just don't know where the answer is at this point.

TAGline: And will SMART answer that question?

Siegal: It would, yes. And I think the answer to that will come from studies like SMART, but in the meantime... because it's not even ready for prime time yet...

TAGline: It could be five years, right?

Siegal: Yeh. I would think that the answer is, yes. Rather than induce more drug resistance, you might say, "Okay, the cat is sort of out of the bag, but the bottom hasn't fallen out yet. Let's stop and watch." And I've been amazed at how well I can get by with some people who aren't on HAART at all. ¤

#3 Simian Success

Vaccine Study Seen as Significant Advance, But Questions Remain About Human Applicability

'The whole field energized'

Few monkey studies have attracted more attention than one recently published in Science (20 October 2000). Conducted by Harvard researchers and funded by the U.S. National Institute of Allergy and Infectious Diseases (NIAID), the study showed that monkeys immunized with a DNA vaccine and the cytokine Interleukin-2 (IL-2) fused to an immunoglobulin molecule (Ig) appear to be protected against simian AIDS. It is, in the view of many observers, a major step forward in AIDS vaccine research. The work also raises a number of broader questions applicable to other vaccine studies, including whether and how the approach will move into human trials. David Gold, of the International AIDS Vaccine Initiative (IAVI) prepared this report.

In the study, a team of scientists led by Norman Letvin and Dan Barouch immunized 4 monkeys with a DNA vaccine expressing SIV gag and HIV env at weeks 0,4,8,40. Another 8 monkeys received the same four DNA immunizations plus IL-2/Ig (either in the form of a protein or expressed in a plasmid) at weeks 0 and 4. A third group with 8 monkeys served as controls. Six weeks after the last immunization, all the monkeys were challenged intravenously with a pathogenic SHIV 89.6P. (SHIV viruses contain SIV core genes with the HIV envelope).

After challenge, all the monkeys become infected, but those vaccinated with DNA plus IL-2/Ig fared dramatically better: at 140 days, they had low or undetectable virus levels, significantly higher CD8+ T cells (an average of 5 times higher than controls), stable CD4 counts and no clinical disease or death. In contrast, the control animals had high viral loads and significant clinical disease; 4 of the 8 control monkeys died within this time.

IL-2 clearly boosted the effectiveness of the DNA vaccine, since monkeys receiving the DNA vaccine alone did not do nearly as well as those receiving the DNA plus IL-2/Ig. Two types of IL-2/Ig combinations were used. Of these, the plasmid expressing IL-2/Ig appeared to be more effective than the protein. Perhaps most significantly, the study, according to the researchers, "strongly suggests that the improved outcome of the monkeys receiving the cytokine-augmented DNA vaccine resulted from augmented vaccine-elicited CTLs."

The study adds to a growing body of data, from research in both monkeys and humans, that a potent cellular immune response can protect against AIDS. Some of these findings come from natural history studies of so-called "highly exposed but seronegative (ESN) individuals" and from HIV-infected, long-term non-progressors. Other studies (including one from Letvin's lab) have shown that when SIV-infected monkeys were depleted of their CD8 cells, virus levels showed a steep increase.

And in a field where researchers often complain about the way some groups conduct monkey studies (by using "weak" challenge viruses and a lack of standardization among different immunization regimens, etc.), this study appears to be rigorous, well-designed and well-executed. Moreover, the researchers involved, particularly Letvin and the Merck team (led by Emilio Emini), are credible and respected figures in the field.

By using a highly pathogenic challenge virus administered intravenously, the researchers were able to provide clear evidence of the vaccine's protective effect. Intrarectal challenges (which use a mucosal route more closely reflecting most transmission in humans) are considered far easier to protect against. In fact, most researchers now use intrarectal or intravaginal challenges in monkey studies.

This is clearly not the first vaccine that can protect monkeys against simian AIDS. In 1992, Harvard's Ron Desrosiers showed that a live attenuated SIV vaccine provides powerful protection against a pathogenic strain of SIV. But the live attenuated vaccines raised significant safety issues, particularly after some vaccinated monkeys began developing AIDS.

So far, no vaccine has conclusively demonstrated the ability to prevent infection in monkeys challenged with pathogenic SIV. However, in the last few years, a number of viral vector vaccines (used individually and in combination with a DNA vaccine) have begun to show some evidence of protecting monkeys against disease. The Letvin study adds strong new evidence that such protection is possible.

Yet these promising findings raise many questions, some of which are relevant to other vaccines in development. These include:

- Will the vaccine work in humans, and if so, for how long?
  The only way to know whether a vaccine works in humans is to test it in humans. Whether this particular approach can move into human studies, and if so, how rapidly, remains to be seen.

- How long will the protected monkeys stay protected?
  Letvin's data show that all 8 monkeys immunized with DNA and IL-2/Ig got infected with the challenge virus but remained healthy, with undetectable levels for 140 day of follow-up. But we don't know how long the animals will remain disease-free. Will the pathogenic challenge virus eventually break through and cause disease in the vaccinated monkeys? It is, of course, critically important to continue observing these monkeys to see how long they stay healthy.

  How durable are the protective immune responses generated by the vaccine? The monkeys in this study were challenged 6 weeks after receiving the last immunization. But how would the monkeys fare if they were challenged 6 months or 6 years after immunization, when higher cellular immune response levels are likely to have receded and protection would depend on memory? The only way to know is by doing more studies.

  One of the most important questions researchers face is how to maintain a potent HIV-specific CD8 T-cell response over the long-term. Some believe that doing so will require a vector (such as an attenuated herpes virus or an adeno-associated virus) that generates persistent antigen expression. It is now clear that some ESN sex workers became infected after stopping their work, suggesting that without regular exposure to HIV antigens (through sex work, in these cases), the protective cellular immune responses might not be maintained. Yet Letvin believes that the vaccinated monkeys in his study might have fared even better if they had been challenged six months after the last immunization. "The longer the period between immunizations, the more likely you are to a get maximum CTL response," Letvin explained. In fact, he thinks it may be beneficial to spread out the immunizations, but adds that the only way to know for sure is to do

the studies. As for whether the vaccine will provide protection 6 years after the last immunization, he said, "that may be too long. But you never know."

- Will the vaccine protect against diverse viral strains?
  The Harvard researchers used the identical SHIV strain to produce both the vaccine and the challenge virus. This "homologous" challenge is much easier to protect against than a "heterologous" challenge that utilizes a different SHIV strain in the challenge. Given HIV's enormous genetic variability and the multitude of HIV strains circulating throughout the world, the question of whether a vaccine will protect against diverse strains of the virus is critically important. Studies to see how the DNA IL-2/Ig vaccine works against different challenges are now underway, says Letvin. While no one knows for sure what level of protection will be seen, he suggests that "if indeed it is a CTL response that is protecting these monkeys, the breadth of the protection should be substantial."

- How does this vaccine compare with other vaccines in development?
  A number of other vaccine approaches have demonstrated some ability to "blunt" disease in the SIV/SHIV monkey model. These include viral vectors such as modified vaccinia Ankara (MVA), MVA used with a DNA prime, Venezuelan equine encephalitis virus, Semliki forest virus and adenovirus. "There are now a lot of ways to make good CTL responses," says Letvin. And he told The Wall Street Journal on 20 October that "at least 3 or 4 other vaccines have achieved similar results in monkeys." Moreover, the Science paper concludes by noting that "the cytokine administration should be readily applicable to other vaccine modalities and for immunotherapeutic purposes."

  But it is difficult to directly compare this DNA vaccine/IL-2/Ig regimen to other approaches in terms of its ability to generate immune responses and protect against disease. Comparative data barely exists because researchers generally do not use standardized animal models, immunization schedules or challenge regimens. Thus, it is still problematic to prioritize promising approaches.

- What are the regulatory hurdles to testing a combination of an HIV DNA vaccine and IL-2/Ig in humans?
  At least three different teams have tested HIV DNA vaccines in humans, so the DNA component should face few hurdles in moving into human studies. However, using IL-2 in healthy people will entail more significant regulatory considerations. The cytokine (which is naturally produced by the body) is currently approved as a treatment for certain types of cancer but can, at times, cause significant side effects. It is also being studied as a treatment in HIV-infected individuals on HAART. In Letvin's study he compared an IL-2/Ig protein to a plasmid expressing IL-2/Ig genes. The plasmid may present more safety concerns than the protein, since the protein is likely to disappear in the body, while the plasmid may continue to express IL-2 genes (with unknown long-term effects).

  To further evaluate the impact of IL-2 on responses to the DNA vaccine, some researchers have suggested including another control arm in any further studies: IL-2 plasmid without vaccine. After challenge, would the IL-2/Ig give any protection, or even accelerate disease? Clearly, it is important to learn more about the potential biological effects of this cytokine.

  Other research teams are also looking at testing cytokine-augmented HIV DNA vaccines. David Weiner at the University of Pennsylvania reports that his group, working with researchers from Wyeth Lederle Vaccines, hopes to move a second-generation HIV DNA vaccine administered with IL-2 into human studies.

  With the intellectual property controlled by a number of different parties, will anyone take the lead in developing this vaccine and moving it into humans? In news reports about the study, Merck officials appeared to be lukewarm about prospects for this particular vaccine. Safety and regulatory concerns are clearly a concern, and the company is known to be developing other candidate HIV vaccines. Another complication is that intellectual property rights to the vaccine components are owned by several different parties. Merck itself controls the DNA vaccine

technology (licensed from Vical, the San Diego-based biotech company); the Chiron Corp. controls rights to IL-2; Genentech reportedly holds some rights to the use of Ig in a vaccine and Letvin's own team has patented some rights to the overall approach. While multiple patent rights often get sorted out in the end (as they did with the hepatitis B vaccine), such negotiations often take a lot of time.

On 26 October, an advisory committee of the NIAID AIDS vaccine program discussed how NIH can help move Letvin's approach into human studies. The NIH's newly created Vaccine Research Center (VRC) could be ideally suited to produce the vaccine for Phase I trials. The clinical trials could be conducted at the VRC or within NIAID's new HIV Vaccine Trials Network. It is unclear whether this can happen, and if so, how quickly. But, assuming safety issues can be adequately addressed, the field will benefit enormously if a clinical study can be initiated as fast as possible.

- Might the vaccine work as a therapeutic vaccine in HIV-infected individuals?
  A growing number of researchers are interested in testing HIV vaccines as therapies in HIV-infected individuals. In fact, on the day the paper was published, Merck representatives informed U.S. activists that the company had begun human trials of its HIV DNA and live vector vaccine (separately) in HIV-infected individuals.

  Given the potent cellular immune response generated by the cytokine-augmented DNA vaccine, it would make sense to test the vaccine as an immune therapy, both in SIV-infected monkeys and HIV-infected individuals. Letvin himself supports the idea of such studies, but says he may be unable to do so himself. Yet there is clearly interest from the outside in seeing the therapeutic approach pursued: TAG has already written to Letvin to request that the vaccine approach be moved quickly into therapeutic trials.

  On the whole, there is no question that Harvard study will have an impact on AIDS vaccine development. It also begins to show how the newer, more precise methods of quantifying T-cell responses will assist researchers in evaluating candidate HIV vaccines. These tests - known as tetramer binding and ELISPOT assays - will hopefully enable researchers to evaluate and compare a new generation of more potent vaccines, including cytokine-augmented HIV DNA vaccines in human studies.

  "The study represents a major advance toward making a vaccine that really works," says Neal Nathanson, the former director of the U.S. NIH's Office of AIDS Research. And, he predicts, "it will help energize the whole field." ¤

#4 Early indications of what 'the accidental president' might do for AIDS:

- In a letter in response to questions posed by the International Association of Physicians in AIDS Care, Bush said that the primary effort of his administration to fight this "urgent health problem" would be to "support significant government-funded research aimed at conquering" AIDS. He has "proposed doubling NIH's budget" to increase AIDS research and supports prevention campaigns and "programs like the Ryan White CARE Act" that address the epidemic (Kaiser Daily HIV/AIDS Report, 10/12).

- In another letter to Numedx, a quarterly HIV medical journal and Internet guide, Bush "promis[ed] to do [his] part" to fight AIDS if elected, and indicated his support for a "permanent extension of the research and development tax credit for pharmaceutical companies who are currently conducting research and development on drugs to combat AIDS." Bush also stated that he supported "increasing the funding to southern Africa to improve their ability to combat HIV, with certain safeguards to ensure the money the U.S. sends actually helps those in need" (Bush letter, 2000).

- An inquiry from the AIDS Foundation of Chicago prompted Bush to respond with a letter in which he states that he "do[es] not favor needle exchange programs and other so-called 'harm reduction' strategies to combat drug use." Stating that he does support "prevention, education, treatment, law enforcement and supply interdiction" to stop drug use, he wrote that needle-

exchange programs "signal nothing but abdication." He also noted that he supports medical privacy legislation, saying that "every American should have absolute control over their personal information, particularly their highly sensitive medical, genetic and financial information" (Bush letter, October/2000).

- Early in the campaign, according to Time magazine, Bush promised he would allocate $135 million—the same amount the government now spends on contraception programs—to "elevate abstinence education from an afterthought to an urgent priority." As governor of Texas, Bush "poured" $6 million into abstinence education programs (Morse, Time, 10/18/99).

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