FOIA Number: 2018-0758-F

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Issues - Vaccines

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Carole Heilman (Division of AIDS at the National Institutes of Allergy and Infectious Diseases) and David Baltimore (President of the California Institute of Technology) review current research efforts toward developing anti-HIV vaccines. While recognizing the extraordinary challenges involved in developing a vaccine, Heilman and Baltimore stress that important steps have been taken and that as such there is room for optimism.

HIV vaccines—where are we going?

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Despite the often voiced frustration that HIV vaccine research and development is static, a closer look at this area of research suggests that not only is recent technology and research impacting vaccine products currently under clinical development, but novel approaches are beginning to emerge. This review charts the impact of recent research findings that are influencing HIV vaccine design.

The humoral response

HIV vaccine products fall into two general categories, those that stimulate the humoral immune system and those that elicit a cellular immune response. With a focus on maximizing neutralizing antibody responses, the surface protein of HIV (Env) has been the main target of an antibody-based vaccine approach for two important reasons: First, it is the principal viral determinant that interacts with the host receptors; second, it is the major antigenic determinant to which neutralizing antibodies are directed. Although the tremendous variability among HIV isolates was a known problem with regard to developing an antibody based vaccine strategy, the main concern was the lack of cross-reactivity among the different HIV sequence based subsets (clades). The potential impact of other variations, such as HIV Env conformation, had not been fully appreciated until relatively recently. Opportunities to study the impact of Env conformation on HIV variation emerged shortly after the identification of a second host receptor, required for the binding and entry of HIV into host cells. CXCR4 and CCR5, two members of the chemokine receptor family, were identified as the prototypic second receptors.

HIV primary isolates are capable of infecting T cells and macrophages. Whereas, T cell line-adapted laboratory isolates (TCLA) use the CXCR4 receptor, isolates capable of infecting macrophages (M-tropic) use CCR5 (ref. 1). (The new nomenclature for these viruses are based on co-receptor usage. R5 viruses use CCR5 but not CXCR4; X4 viruses use CXCR4 but not CCR5; and R5X4 viruses can use both co-receptors.) The possible relevance of this finding to HIV vaccine design became apparent when considered in the context of two points: The vast majority of HIV isolated from patients with primary infection, infected macrophages (R5) (ref. 2); and X4, rather than R5, Env had been used to develop the various Env based vaccines. The use of X4 HIV isolates as Env vaccine candidates had made sense because they could readily generate high levels of neutralizing antibodies[3]. On closer examination however, the antibodies generated were restricted in their neutralizing activity to a small subset of viral isolates closely related to the vaccine virus[4]. Of even more concern was the lack of neutralizing cross reactivity with viruses isolated from patients. Now, by probing the HIV surface structure with monoclonal antibodies (mAbs), the inaccessibility of crucial epitopes within the Env of R5 viruses compared to X4 viruses is becoming clearer.

The mature Env protein exists as a processed, mature trimer on the surface of HIV. This protein is initially made as individual glycoproteins (gp160), which are cleaved into gp120 and gp41 entities that non-covalently associate into the surface glycoprotein spikes[5]. Recent reports[6] further clarify the importance of the variable regions of gp120 in shielding the conserved binding regions from the immune system. Also shielding immunogenic epitopes from view is a complex of carbohydrates. In SIV (simian immunodeficiency virus)- infected rhesus monkeys the presence of these surface carbohydrates has been observed to directly impact the production of neutralizing antibodies. Infection with mutant forms of SIV lacking specific N-linked glycosylation sites resulted in markedly increased levels of neutralizing antibodies compared with the carbohydrate-sheltered native SIV[7].

The protective value of neutralizing antibodies generated by X4 Env-based vaccines has been hotly debated. The lack of relationship between neutralizing antibodies generated by X4 viruses and either containment of viral load in HIV-infected persons[8,9] or association with long-term non-progressors (LTNPs)[10] has been noted. On the other hand, neutralizing antibodies against R5 viruses, although difficult to detect in LTNPs, are often[11-13] but not always[14] found in these cohorts and are usually associated with subsets of LTNPs who have lower viral load[11].

Three human monoclonal antibodies (b12, 2G12 and 2F5) that broadly neutralize a panel of T- and M-tropic viruses have, however, been immortalized from the sera of infected patients. Each of these monoclonals can neutralize a genetically diverse range of R5 and X4 viruses from different clades (A–F) [15-17]. The importance of antibodies like these in preventing HIV infection or modulating disease course is still unclear. In passive transfer experiments, b12 administered at high doses to hu-PBL-SCID mice (severe combined immunodeficient mice populated with human peripheral blood mononuclear cells), completely protected these animals against R5 virus challenge.[18] However, such antibody had no impact at lower doses and could not affect the course of an ongoing infection. The rarity of antibodies that exhibit a cross clade response, has led some investigators to try to structurally define epitopic sites to which these antibodies are directed, with the hopes of developing a novel immunogen.

The ability to elicit high affinity, broadly reactive (that is, against multiple genetic variants) antibodies that can contain the virus, is a central theme in antibody-based vaccine design and development studies. For example, R5, gp120-based vaccines are being evaluated for their ability to elicit cross reacting neutralizing antibodies in Phase I studies. Unfortunately, a preliminary report[19] suggests that vaccination with an R5X4 gp120 vaccine did not broaden the neutralization response in vaccinees. The impact of conformation on directing the generation of protective antibodies is being addressed through development of gp140 (soluble oligomer containing gp120 and the ectodomain of gp41) and gp160 vaccine candidates (complete gp120 and gp41sequence). The impact of adjuvants in the presentation of oligomeric candidates is also being evaluated. Using the SHIV/macaque model system (SHIV is a chimera virus containing the internal genes of SIV and the external HIV proteins), oligomeric gp160 formulated with either Ras3C[8]

or polyphosphazene resulted in antibodies that neutralize a range of HIV isolates. Animals vaccinated with this immunogen and challenged with the homologous chimera (SHIV MN), were virus-free at four weeks post-challenge, whereas all non-vaccinated control animals were virus positive[20]. The importance of surface structure and presentation is also being considered through the development of pseudovirions, VLPs (viral-like particles), whole killed and other novel antigen display vehicles (for example, poliovirus, VEE and VSV vectors, as well as replicons—see Liu, page 515). Finally, consideration is being given to replicating a stable conformation, allowing for maximal expression of neutralizable epitopes based on the tertiary structure of the gp120-CD4-CCR5 interface.

The cellular response

Targeting the other arm of the immune system, cellular immunity, has always been and continues to be a major focus of HIV vaccine development. Various parts of the HIV genome have been expressed using live viral vectors such as vaccinia and avipox. With these vaccines, both non-human primates and humans have developed cytotoxic T lymphocytes (CTL) against the HIV encoded proteins and a recently developed method, the tetramer assay, is providing the technology to easily characterize the phenotypic specificity of the T cell response[21].

In humans, one of the most studied vectors has been a canarypox vector containing HIV $Env_{120\ \&\ TM}$+Gag+Pro+Pol sequences (vCP205). A CTL response, which usually ranges from approximately 20–45% at any single time point during a study, with 40–60% of volunteers mounting some response, can be demonstrated. Additionally, the duration of the CTL response in the majority of CTL-positive volunteers is at least 15 months after the last vaccination. The generation of CTLs by vCP125 containing Env gp160 vaccinated volunteers is of particular interest in that some were also capable of lysing autologous $CD4^+$ cells infected with HIV clade A–F isolates, suggesting a broad CTL response was induced[22].

In order to predict potential CTL cross-reactivity, amino acid sequences from HIV isolates of different clades have been compared with the sequence of functionally recognized clade B CTL epitopes. Over 65% of such clade B CTL epitopes are either identical or have a one amino acid difference with respect to the corresponding sequences in over 40 viruses from clades A, C, D, F, G or H, or interclade recombinants. Evaluation of CTLs from clade B infected individuals has shown cross-recognition among other clades[23–25]. In general, one amino acid difference from the primary peptide did not preclude recognition and often even two differences were tolerated. As expected, most of the differences across clades lie in gp160 (only ~ 45% of the gp160 CTL epitopes are identical or have one amino acid difference). Similar observations have been made when comparing T-cell help epitopes identified from clade B infections with corresponding sequences of other viruses. This analysis supports the concept that a 'monovalent' HIV vaccine might induce CTL activity (and T-cell help) against non-clade B viruses, a concept beginning to emerge from vaccine studies in Caucasian volunteers[22].

The critical question is whether CTL epitopes in a vaccine representing a given clade would be recognized by individuals of a different genetic background who were exposed to viruses of different clades. Such a concept will soon be tested in Uganda, where the vCP205 will be tested for its ability to induce CTL activity against other HIV clades.

More recently, two new vectors containing either $Env_{120\ \&\ TM}$+Gag+Pro+Pol and Nef CTL epitopes (vCP 1433) or vCP 1452—which contains $Env_{120\ \&\ TM}$+Gag+Pro+Pol and Nef CTL epitopes plus two vaccinia coding sequences (E31 and K31, which enhance, *in vitro*, the efficiency of HIV mRNA translation)—are planned for evaluation in Phase I trials, with expansion of the breadth and duration of the HIV specific CTL response, the obvious goal. Alternative HIV vaccine approaches for inducing CTL responses continue to be explored. Although lone peptides do not elicit a strong CTL response, approaches focused on presenting an array of HIV peptide, as branched-chain multimers or in combination with various adjuvants, for example, are being pursued for potential CTL boost strategies. Still under refinement for maximal expression and presentation, HIV DNA vaccines have shown tremendous promise as a way to induce strong CTL responses in animal model systems[26,27].

The combined approach

A third approach, receiving much attention, is to combine both humoral and cellular responses. The 'prime-boost strategy', which includes the administration of live recombinant and envelope based vaccines, in combination or in sequence, does not interfere with the individual responses seen when either vaccine is given alone. Indeed, the effects from the two vaccines appear to be additive when other components of immune responsiveness are measured. For example, vCP205 in combination with SF2gp 120 (from R4 virus) resulted in increased antibody dependent cellular cytotoxicity (ADCC) and T-cell help activities when compared to vCP205 given alone. Evidence for the possible role of ADCC and T-cell help in protection against HIV disease is only now emerging. HIV specific antibodies that mediate ADCC are found very early in acute infection and correlate well with declines in plasma virus[28,29]. Now, the importance of maintaining $CD4^+$ T-cell help during the containment of viral replication is emerging as a strong *in vivo* correlate[30]. Recent evaluation of a well-defined cohort with wide ranges of HIV viral loads and CD4 lymphoproliferative responses demonstrated that the ability to maintain strong CTL responses and control plasma viremia was directly correlated to the presence of p24 specific $CD4^+$ helper cells[31].

Another approach that appears to broadly target the immune system and has also received much attention, is the live, attenuated HIV vaccine. Studies of an SIV model with nef deletions have shown impressive protection[32]. Using a systematic approach for deleting regions of SIV, a series of potential SIV vaccines have been generated and evaluated in rhesus macaques. Evaluation of a highly attenuated version devoid of nef, vpr and upstream sequences in U3, SIV delta 3, demonstrated the presence of measurable CTLs, and increasing levels of SIV-neutralizing antibodies. More importantly, the animals were protected against intravenous challenge[32]. Evaluation of an HIV-infected Australian Blood Bank cohort described six individuals with a common source of infection, all of whom had remained disease-free for 10–14 years[33]. The virus isolated from each of these people showed a deletion in nef and a portion of the LTR, suggesting a naturally occurring attenuation.

Although the immune basis of the protective response of this approach is still not clear, the effectiveness of the approach has been proven in other infectious disease models. The Sabin polio vaccine, vaccinia, rubella, mumps and measles vaccines and more recently varicella, rotavirus and cold-adapted influenza vaccines all work by mimicking the natural infection process without inducing concomitant disease. Based on using a weakened strain of virus obtained by host restriction, selective mutations or deletions, or natural adaptation under restrictive growth conditions, these vaccines have all been found to be effective (see Hilleman, page 507). Lingering concerns about potential reversion to pathogenic strains

has made the question of safety paramount and is probably behind the lack of aggressive development of attenuated HIV for use in humans. Dose-related pathogenicity was reported in neonatal monkeys vaccinated with SIV delta 3 nef[34,35]. More recently, long-term safety concerns have been raised as early clinical symptoms of AIDS have begun to be identified in monkeys vaccinated with attenuated SIV strains more than two years ago. Alternative live attenuated non-human lentivirus approaches are also being evaluated. Shibata and colleagues recently described the cross-protective response of attenuated SIV by challenging rhesus macaques with SHIV. Despite the absence of neutralizing antibodies, animals were protected against the chimera expressing human Env + Gag, suggesting the possibility that a non-human primate lentivirus may be a candidate vaccine for humans[36].

Better models

Parallel to the development of new HIV vaccines, opportunities to more rapidly evaluate their potential value are being explored. To date, the most used model for evaluating candidate vaccines is the SIV/macaque model. Although only 3–4 macaques per group have been used in most experiments, this model has provided valuable information regarding the potential success of various vaccine strategies. In general, protection against challenge by SIV strains that are poorly pathogenic has been achieved with a number of vaccines. However, protection against highly pathogenic SIV strains has only been seen in animals receiving live, attenuated SIV vaccines. This does not mean that other vaccine designs are doomed to fail but rather points to the paucity of SIV vaccines available for detailed evaluation and the evolving knowledge on the use of the SIV/macaque model. The recent generation of SHIV chimeras (that allow HIV-based envelope vaccines to be evaluated in an SIV model) and the development of corresponding pathogenic challenge viruses, is now providing an opportunity to evaluate in more detail a variety of HIV-based vaccines in macaques.

The recent development of smaller and less expensive animal models for the testing of HIV vaccines is interesting. Most intriguing are transgenic mice and rabbits expressing human CD4 and the relevant chemokine receptors. The rabbit model is unique in that it supports the replication of HIV, albeit at low levels[37,38], and preliminary reports (Speck and colleagues) suggest that replication levels can be increased through the expression of appropriate chemokine receptors.

There is a reason for optimism. The science discussed here is both exhilarating and sobering and the complexities of host/virus interactions present remarkable challenges. However, these are being addressed. We believe that expanded commitments from both government and the scientific community will hasten that pace.

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Last year, President Clinton made clear the urgent need for an effective HIV vaccine and suggested that it should be possible to create one within ten years. The authors agree. Although recent progress should not be underestimated, many obstacles remain—some technical, others not. Here, Dennis Burton (Scripps Research Institute) and John Moore (Aaron Diamond AIDS Research Center) outline their views on the state of development of an HIV vaccine and the areas in which more effort should be focused.

Why do we not have an HIV vaccine and how can we make one?

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The most fundamental question to ask about an HIV vaccine is: 'What evidence exists that protection against disease after exposure to HIV is possible?' The best evidence for successful protection against a virulent primate lentivirus such as HIV is that monkeys are almost always protected against challenge with pathogenic SIV_{mac} after vaccination with an attenuated (*nef*-deleted) SIV_{mac} strain[1]. Whether this particular observation can be directly or indirectly exploited for the development of an HIV vaccine for humans is an important issue, to which we return below.

There is evidence that neutralizing antibodies can protect against HIV infection in certain animal models[2]. However, the antibody concentrations required are high and the specificities of effective antibodies are uncommon. The overwhelming majority of antibodies to envelope immunogens produced during natural infection or vaccination are probably elicited and affinity matured against envelope proteins in conformations different from that present on the virion surface. Most of these antibodies then bind weakly or not at all to virions and are functionally ineffective. Very few antibodies capable of binding to and neutralizing a broad spectrum of representative primary viruses have been generated during natural infection[3], none yet by vaccination. A fundamental problem is the poor immunogenicity of the mature oligomeric glycoprotein complex that constitutes the surface spikes of HIV. The limited accessibility of the critical neutralizing antibody epitopes on the virion also means that antibody binding is relatively inefficient[2,4]. Even the best HIV-neutralizing antibodies are at least an order of magnitude less effective than the best neutralizing antibodies to polio virus, for example. Although it will not be easy to induce antibodies of the right quality in sufficient quantity by vaccination, this must be an important goal.

Although there is no direct evidence that cytotoxic T lymphocytes (CTL) protect against challenge with HIV or its simian counterparts, there is a wealth of data showing a correlation between the appearance of CTL activity and the containment of viral infection[5–7]. For example, the early CTL response in one HIV-infected person was focused on a highly immunodominant epitope of gp160, leading to the rapid elimination of the initially dominant strain (transmitted virus)[8]. The selection pressure of the CTL response was even sufficient to drive the emergence of a CTL escape mutant. That CTL (but not antibody) responses can be detected in certain very highly exposed, yet HIV-uninfected, African prostitutes also argues for the protective effect of cellular immunity; these individuals may have been naturally vaccinated against HIV by a mechanism that is unknown, but obviously important to determine[9]. Thus, the induction of a strong CTL response is also on most peoples' vaccine wish list.

Overall, we believe that both antibody and CTL responses will need to be induced for an HIV vaccine to be effective. The view that both arms of the immune system are required is also supported by studies in mice challenged with retroviruses and other RNA viruses[10–12]. By reducing the infectivity of the initial viral inoculum, neutralizing antibodies provide the CTL response time to mature and clear those cells which do become infected. $CD4^+$ T-cell help is essential for both humoral and cellular immune responses to work effectively[10]; interference with T-helper cell functions is probably one of the ways by which HIV prevents the immune system from clearing the virus during natural infection[13]. Vaccine priming of T-cell help may buy the immune system time in the critical, initial race between HIV replication and immune-mediated viral clearance[10]. Whether other, less well characterized innate or immune responses might also be advantageous to an HIV vaccine is unclear, but they are certainly worth exploring.

There has been a surprising paradigm shift in HIV vaccine research during the past few years: It used to be the perception that making a significant, vaccine-induced antibody response to HIV was easy, whereas it would be extremely difficult to make an effective CTL response. Now, however, CTL responses can be induced fairly efficiently by some immunogens (at least in mice), but a meaningful neutralizing antibody response remains elusive. This problem must be overcome, urgently.

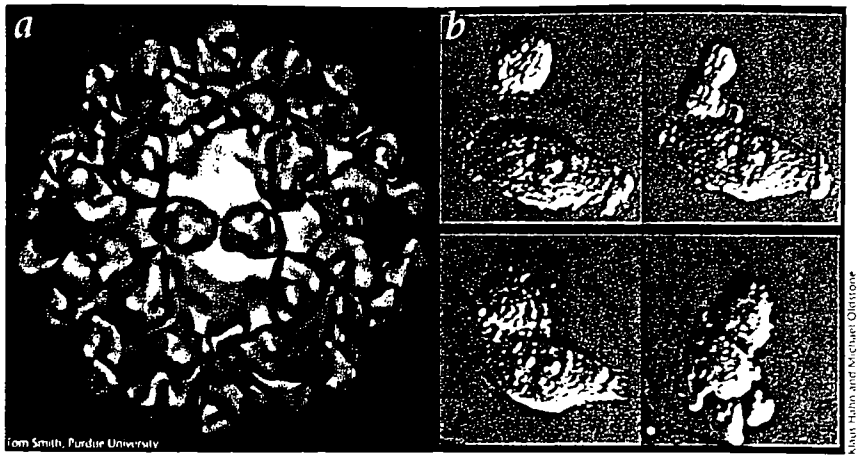
The current strategies

Historically, most successful vaccines have been made of attenuated virus or killed virus. However, both of these approaches are problematic for HIV. Although attenuated viruses are likely to be quite effective, there are genuine safety concerns, as emphasized by recent reports[14] of morbidity in monkeys after vaccination with attenuated (*nef*-deleted) SIV_{mac}. Whether this would necessarily be so with HIV in humans is uncertain; trials are necessary to prove safety, but there is a reluctance to approve trials because of the perceived safety concerns—an unfortunate Catch 22. Whether additional attenuation of SIV (and by analogy HIV-1) would retain its protective potential while further reducing virulence is an important area of investigation and one where there are already encouraging signs of progress.

Irrespective of the continued debate about human studies, research on attenuated SIV_{mac} in monkeys remains essential because of the power of the induced protection. Understanding its cause is of the utmost importance for HIV vaccine development, for the mechanism is still sadly unclear. Critical roles have been alternatively proposed and refuted for both humoral (neutralizing antibodies) and cellular (CTL) immunity[15]. A 'viral interference' model has also been invoked, in which the attenuated virus occupies all the available 'niches' and thereby prevents a virulent virus from gaining a foothold[16]. Cross-protection studies involving SHIVs[17], and other studies, indicate that neutralizing antibodies are probably not all that important for protection by attenuated viruses, which is not to say that antibodies are unimportant for vaccine design in general. If cellular immunity

indeed dominates the protection achieved by attenuated viruses, a central, perplexing riddle is: How does the vaccine strain prevent an incoming virus from becoming established, yet not eliminate itself? Likewise, humans naturally infected with a *nef*-deleted virus have not eradicated this virus from their bodies[18]. Why not?

The major problem associated with a killed HIV vaccine involves inactivating the virus without losing or destroying the fragile envelope glycoproteins. Because killed vaccines work by inducing neutralizing antibodies, there is little to be gained by using an immunogen that lacks the antigens which induce them, either prophylactically or post-infection. A further substantial obstacle is the sheer difficulty of producing useful quantities of primary isolate virions. These problems, although very significant, are at least visible for attack.



Vaccines generally aim to elicit neutralizing antibodies and cytotoxic T lymphocytes (CTLs). Neutralizing antibodies bind to virus and prevent entry. Fig. 1*a* shows neutralizing antibody (Fab fragment) coating the surface of rhinovirus. CTLs kill infected cells. Fig. 1*b* shows stages in the CTL (smaller cell) killing of a target cell.

Subunit envelope vaccines using recombinant forms of the HIV envelope glycoproteins (particularly gp120) are safe, but have been disappointing[19]. To date, these proteins (or derived peptides) have not elicited significant neutralizing antibody responses to representative primary viruses[20], almost certainly because epitope exposure differs between recombinant proteins and the mature oligomer found on the virus[2-4]. Nor do soluble proteins elicit strong $CD8^+$ CTL responses. Current attempts to make recombinant gp120s induce CTLs by the use of experimental adjuvants, run the risk of denaturing the protein and thereby destroying any chance of evoking a relevant antibody response[21]. It would seem prudent to focus on the potential strength of the recombinant protein in generating antibodies and leave CTL induction to other vaccine constructs. For recombinant envelope glycoproteins to be able to make a meaningful contribution to a vaccine cocktail, however, much needs to be done to increase the immunogenicity of the present generation of proteins, both by changing their antigenic structure and by developing better methods of presenting them exogenously. Ideally, a useful recombinant protein should improve on the qualities of the mature oligomer, as found on the virion surface, although this does not necessarily mean that oligomeric proteins *per se* are the answer to the problem. Much more effort is needed to understand the HIV envelope glycoproteins and to exploit them as immunogens.

Live recombinant vectors (such as avipox, canarypox or vaccinia) that include HIV antigens, and naked DNA vectors which also express these proteins, are important approaches still at a relatively early stage of what one hopes will be a highly successful evolution[22-25]. DNA vectors, which include multiple HIV antigens, seem more promising than ones which focus on a single antigen (for example, gp160). Expression of the encoded antigens in humans and monkeys also needs to be optimized by the evaluation of different promoters and the improvement of delivery systems; this is an especially important function of non-human primate models. However, neither live viral vectors nor DNA has so far induced worthwhile antibody responses to the HIV envelope glycoproteins—their strength lies in their ability to stimulate cellular immune responses, particularly CTLs. Additional antibody responses can be induced by 'boosting' the live vector- or DNA-primed immune system with soluble recombinant gp120. However, these are the same proteins that have performed poorly as sole immunogens and there is little evidence that they are working any better as part of a more complex vaccine—indeed, there are few reasons why they should. The CTL-inductive powers of live virus vectors and DNA need to be supplemented by a greatly improved series of antibody-inducing recombinant proteins.

Why is an HIV vaccine so difficult?

Many hypotheses have been proposed to explain the difficulties in generating a vaccine to HIV when vaccines against other viruses have been successful. These include a rapid replication rate for HIV, viral variation and the importance for immunity of the $CD4^+$ target cell that HIV infects and destroys. Whereas such factors are clearly significant for the development of disease, it is not readily apparent why alone they should create insurmountable obstacles to a vaccine. The replication rate of HIV is not remarkable compared to other viruses for which vaccines exist. Influenza is highly variable, but vaccines against individual influenza strains are readily developed whereas protecting against molecular clones of HIV (SIV) has proven very difficult. Measles virus infects cells of the immune system and produces immunosuppression but a vaccine can still prevent measles infection.

We believe the most important distinguishing features of HIV are the nature of the virus envelope and the ability of a retrovirus to integrate into host DNA. As noted above, the properties of the mature envelope glycoprotein complex on the viral surface render the virus 'stealth-like' with respect to the humoral immune system. It is extremely difficult to present the envelope glycoproteins in a way that stimulates a significant antibody response or memory. The integration capability of HIV means that, unless sterilizing immunity is achieved, some of the infecting virus will remain invisible to humoral and cellular immune responses. Activation will release infectious virus until sufficient diversity is generated to nullify the efficacy of vaccine-induced immunity.

The great action debate

There is an ongoing debate between those who favor emphasizing large trials of candidate HIV vaccines in humans to determine efficacy, and those who believe more basic knowledge must be attained before large trials would be warranted. The empirical approach has worked in the past for other pathogens and so naturally attracts much support. However this approach has ap-

peared unlikely to generate an HIV vaccine due to some of the complexities discussed above. Some argue that there is no harm in testing many different vaccine candidates, however weak the underlying scientific justification or preliminary data. We do not accept this argument, except at the Phase I level where we partially endorse it (see below). First, funding for HIV vaccine research is not unlimited: resources allocated to large trials of inadequate vaccines could be better spent in developing a stronger vaccine. Second, the patient cohorts needed for Phase III trials are a precious resource that should be called upon with great care. Third, there is a social and political price to be paid for failed vaccines: losing the support of the public for a health measure as important as an HIV vaccine would be a disaster. Whatever the external pressure 'to be seen to be doing something,' large vaccine trials must be based on good science and a reasonable chance of achieving something worthwhile, and not just on the availability of an immunogen.

An empirical approach can teach but it is not true that one always learns from failure. An efficacy trial of a gp120 subunit vaccine based on a lab. strain (as is pending approval by the FDA) will not tell us that no gp120-based recombinant protein could ever work, only that the particular product is inadequate, something which is already clear enough from Phase I/II trials[19,24]. There is a disturbing tendency in HIV vaccine research to dress up failure as success, or to design the conditions of the experiment to improve the likelihood of an *apparent* success. For example, primary viruses have a spectrum of antibody neutralization sensitivity. There are even some primary viruses which are almost as easy to neutralize as the lab. strains (for example, IIIB and MN), that so misled the vaccine field for many years, but they are not representative. Choosing neutralization-sensitive viruses to give apparently positive results has obvious short-term appeal, but in the long term, it is a practice that will not facilitate the development of an effective HIV vaccine. Similarly, some groups focus on avirulent and/or readily neutralized viruses. These viruses can be valuable for eliminating a concept from further consideration—failure to protect against, for example, SHIV-IIIB in macaques would be a most discouraging sign—but success against such viruses should not be overemphasized in the way it so often is. Arguably the most misleading of the easy protection models is the HIV-1 SF-2 challenged chimpanzee. Here HIV-1 replication is so weak and protection so easy to achieve that any positive conclusions drawn about the prospects of vaccinating humans against virulent HIV-1 strains should attract considerable skepticism.

Despite the problems associated with the poor humoral immune responses to the live recombinant vector-prime/gp120-boost vaccines, there is considerable pressure to move these vaccines rapidly from limited Phase II trials into Phase III trials. Is this justified? Results from the first generation of vaccinia-prime/gp120-boost vaccines have been disappointing in terms of the breadth and duration of the CTL response[25]. Because induction of a CTL response is the theoretical strength of the prime-boost approach, major improvements to the first generation of immunogens are clearly required prior to conducting Phase III trials. An additional point to consider is that a CTL-based vaccine is unlikely to induce sterilizing immunity. It is then difficult to judge vaccine efficacy in trials carried out in developed countries because ethical requirements will surely mandate that any individuals infected during a vaccine trial will be immediately treated with antiretroviral drugs, as noted recently by Barry Bloom[26]. Whatever decision is taken about efficacy trials of the present prime-boost vaccines, it would be prudent to assume that these vaccines, in their current form, will fail and to plan accordingly.

Table 1 Status of current HIV-1 vaccine strategies

Candidate Vaccine	*safety concerns*	*potency of elicited immune response*		*other undefined protective mechanisms*
		Neutralizing antibody	*CTL*	
Attenuated virus	Yes	Poor	Emerging evidence	Some evidence
Killed virus	Limited	Poor	Negligible	No evidence
Envelope subunits	None	Poor	Negligible	No evidence
Vaccinia or avipox prime/boost	None	Poor	Weak	No evidence
DNA prime/boost	Limited	Poor	Weak	No evidence

Government-directed and investigator-initiated research

Should the AIDS vaccine effort in the United States be strongly directed by the National Institutes of Health (NIH) and other federal agencies, or carried out via a myriad of investigator-initiated projects? The answer is both. HIV vaccine development requires the kind of leaps forward classically made by individuals with insight and drive who work in intramural and extramural research laboratories. Yet, it could also greatly benefit from direction that introduced standardization. For example, simian models have a crucial role to play in HIV vaccine development[1], but there are too many individual models. The number and variety of different challenge stocks, animal species and experimental protocols strongly mitigate against comparisons of different concepts tested in different research laboratories. And no single laboratory has the resources to conduct satisfactory experimentation on more than one or two concepts. How can anyone possibly judge whether a DNA vaccine tested in a rhesus macaque challenged with SIVmac-251 is superior to a gp120-subunit tested in a nemestrina macaque challenged with HIV-2 or to a prime-boost vaccine in cynomolgus monkeys challenged with SIV delta70? This morass needs urgent resolution by simplification and consolidation worldwide. This was accomplished because of financial necessity in Europe, with benefits that are now clear.

It is a general premise that the less a challenge stock replicates in a host, the easier it is to protect against it. A rational strategy for animal models would involve the convergence of the field around two well-tested models at opposite ends of the pathogenicity-protection spectrum, and perhaps one in the middle of the spectrum. The 'easy' model can be used to eliminate concepts, as noted above, the 'hard' one to explore the limits of their potential. These 'approved' models would be used for strictly comparative evaluations of vaccine concepts, to refine and improve their performance along with similar studies in humans, where challenge experiments are obviously not possible.

Thus we urge a more centralized direction to human and animal trials aimed at HIV vaccine development. This needs to go hand-in-hand with investigator-initiated research. To quote Gustav Nossal[27]: '... in the early years of the new millennium, ... the third golden age of immunology (will help create) a panoply of new vaccines'. However, some areas of vaccine development are so expensive and complex that they are beyond the financial

and administrative scope of individual investigators. It is here that central direction is most needed. In the USA, this should be provided by the NIH and in particular by the NIH's AIDS Vaccine Research Committee working closely with the directors of those institutes most involved in HIV vaccine research.

The role of biopharmaceutical companies

The experience of biopharmaceutical companies in the HIV vaccine area has not been a happy one. Creation of an HIV vaccine has been seen too much as product development, too little as experimental science. Companies and their academic collaborators have been reluctant to acknowledge the failure of their favored HIV vaccine—there seem to be many trials, few errors. Instead, interpretive loopholes are ruthlessly exploited to breathe life into a corpse, as is now occurring with the subunit gp120 vaccines. To reverse this trend, we urge the NIH and its principal advisors to play a primary role in selecting immunogens for comparative evaluation in multiple Phase I trials. The financial responsibility for making and testing a range of immunogens for these early clinical trials could be carried by the NIH under the contract mechanism; this might properly be viewed as experimentation, rather than product development *per se*. Comparative immunogenicity studies in humans could be supported by challenge experiments using analogous SHIVs in monkeys, if the concept under evaluation is suitable for this model. The emphasis of Phase I human trials must be squarely on the rejection of poorly performing concepts before too many resources are devoted to them. Clearly, this is alien to corporate practice, and quite beyond the financial capability of smaller companies, which is why alternative funding mechanisms must be developed. Only the more promising immunogens should be advanced to Phase II and beyond, and it is at this stage that corporate experience in vaccine development will be essential. Ultimately, it is the larger biopharmaceutical companies that will produce an HIV vaccine on a large scale and bring it to the public. Their continued involvement is crucial.

Conclusions

Why do we not have an HIV vaccine? We attribute this to the 'stealth-like' qualities of the viral envelope glycoproteins with respect to the humoral immune system, combined with the ability of the virus to integrate into host cells to emerge later, diversify and escape CTL control. How can we make an HIV vaccine? Understanding the mechanisms for the protection afforded by attenuated viruses is vital. Both CTL and antibody responses are likely to be necessary. Significant progress has been made in eliciting CTL responses, although much remains to be done in primates. To induce good antibody responses, enhancing the immunogenicity and antigenicity of the HIV envelope are crucial steps. Animal models need rationalizing, but remain of central importance. Human clinical trials must be guided by the wealth of knowledge accumulating from basic studies of immunology and virology, with the immediate emphasis on experimentation at the Phase I level rather than on product development. The NIH should commission immunogens designed under the direction of the AIDS Vaccine Research Committee. Judgment, and not absolute certainty, will be necessary to evaluate Phase I (and II) studies; this can also be provided by the same committee. The need for independent evaluation of trials is highlighted by the very different conclusions reached from the same clinical trial of a gp120 subunit vaccine[19,24,28]. Central direction by the AIDS Vaccine Research Committee, working with senior figures in the institutes it advises, could hasten the pace of vaccine research in the United States. The powers of this committee should be strengthened in the coming months and its performance must only be judged over a period measured in years. There will be no 'quick fix' to the HIV vaccine problem: none should be expected.

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New vaccines are aimed at the rich says UNICEF

Speaking at the World Bank meeting on vaccine development and delivery this March in Washington D.C., the Executive Director of United Nations Children's Fund (UNICEF) Carol Bellamy, criticized current vaccine R&D programs for targeting diseases that occur in rich countries.

Carol Bellamy

Bellamy complained that even efforts to develop an HIV vaccine are focusing on variants of the virus that affect people in Europe and North America rather than Africa and Asia. Although she recognized that significant advances have been made in the last few decades to broaden access to vaccines, Bellamy stressed that half of the children in sub-Saharan Africa have never been immunized and around 12 million children still die every year from preventable diseases such as measles, pneumonia, diarrhea and malaria.

Despite this censure, Bellamy said that UNICEF and the World Health Organization (WHO) were "excited" by the breakthroughs in science and biotechnology that are making new vaccines possible: "today, there are predictions that as many as 20–30 additional vaccines may come on line over the next two decades."

She singled out two vaccines that have recently received marketing approval—against rotavirus and pneuomococcus—as having the potential to prevent around 2 million infant deaths per year. "But before they can be used on a wide scale, their effectiveness must be carefully assessed in clinical trials in developing countries," Bellamy continued, "WHO is prepared to conduct these assessments within the next three years—a job that will require about $20 million." Development of vaccines against diseases such as malaria will need greater public investment in the order of $250 million over the next decade, "and these vaccines will not reach their final development stage without the active support of WHO in coordinating clinical trials in affected countries," she warned.

Bellamy also made an appeal for the children of the 47 poorest countries (Band A—see Batson, page 487) to receive vaccines free of charge. Although nearly 80 percent of the 130 million children born worldwide each year now receive vaccinations against diphtheria, tetanus, whooping cough, polio, measles and tuberculosis—thanks largely to the Expanded Program on Immunization (EPI) campaign launched by WHO in 1974—the cost of coverage against these diseases as well as hepatitis B and yellow fever for children in Band A is $70 million. Adding *Haemophilus influenzae* type b (Hib)and rotavirus vaccine coverage raises the cost to $225 million and pneumococcal vaccination further increases the price tag to $381 million.

UNICEF is committed to raising funds for Band A immunization and Bellamy asked that the private sector keeps prices at affordable levels. She commended the tiered pricing system, which enables the poorest countries to receive vaccines at prices they can afford, as being the cornerstone of private-public partnership in vaccines.

Bellamy listed 90 percent worldwide coverage with four EPI vaccines (diphtheria, polio, measles and tuberculosis) as one of four UNICEF targets for 2000, in addition to eliminating neonatal tetanus, eradicating poliomyelitis and achieving a 95 percent reduction in measles mortality. Goals for 2010 include reducing deaths due to Hib pneumonia and meningitis by 80 percent and introducing vaccines against malaria and, hopefully, HIV.

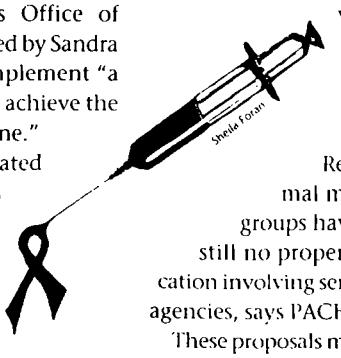
Bellamy concluded her speech by calling on the scientific community and the private sector to join UNICEF and WHO in ensuring that "all children enjoy the practical health benefits made possible by existing vaccines, vaccines under development and vaccines of the future."

KAREN BIRMINGHAM, NEW YORK

Panel recommends White House coordinates AIDS vaccine development

Twelve months ago, President Clinton declared the US government's commitment to producing an AIDS vaccine within ten years. His statement was based, in large part, on the recommendations of the Presidential Advisory Council on HIV/AIDS (PACHA)—a 33 member panel made up of government, academic and advocacy representatives—charged with advising the President on the direction of AIDS research. But after one year with what some regard to be little progress—few vaccine candidates in the pipeline, no Phase III clinical trials, no director of the new NIH Vaccine Research Laboratory and no one to replace William Paul as NIH AIDS coordinator—some PACHA members have become restless and doubt that the goal will be met.

Consequently, the council has passed a new resolution calling for tighter control of the AIDS vaccine development process through the White House's Office of National AIDS Policy (ONAP) led by Sandra Thurman and for ONAP to implement "a comprehensive federal plan to achieve the goal of an effective AIDS vaccine."



Moreover, PACHA has repeated its belief that if the President's goal is to be met, other agencies in addition to the NIH must be involved. The council states that the Centers for Disease Control and Prevention, Department of Defense and the United States Agency for International Development have "extensive experience and expertise in the area of vaccine development, field epidemiology, surveillance and the conduct of vaccine efficacy trials," and should be more involved in the AIDS vaccine program. Despite interagency cooperation also being advocated by the 1996 Levine Report, so far only informal meetings between these groups have taken place. There is still no proper process of communication involving senior leadership from the agencies, says PACHA.

These proposals mark a return to draft recommendations made by PACHA prior to the President's May 1997 speech, and are certain to protract the discord between those that favor an empirical route to an

AIDS vaccine and basic scientists (see Burton & Moore, page 495; and Heilman & Baltimore, page 532).

Many basic scientists oppose any weakening of the NIH role on this issue. They argue that the Baltimore Committee, established as a result of the Levine Report, has to be given time and space to do their work and its performance must be assessed over a period of years, not months. They believe that a "comprehensive federal plan" already exists and is presently being overseen by the Baltimore Committee in association with NIH Institute Directors.

The appointment of a full-time Director to the NIH Vaccine Research Center was to have been a primary action resulting from the President's AIDS vaccine speech and PACHA chose its words carefully in discussing the inability of NIH so far to employ a suitable director: "the Council is very concerned that recent progress has been slowed substantially by the failure to appoint this individual, who must be at the highest level of expertise."

Jonathan Mann, Dean of Public Health at Allegheny University and Founding Director of the World Health Organization's Global Program on AIDS, who addressed the council, was less gracious. "The people who have been placed in charge of AIDS vaccine development in this country have no experience in developing vaccines and come from the stream of science that only has one view," accused Mann, "the names of David Baltimore and Harold Varmus come right at the top of the list."

One point on which both sides agree is that the pharmaceutical industry must become more actively involved in the process. PACHA stressed the need to find a way of overcoming existing financial disincentives to industry and suggested subsidies for pilot manufacture of vaccine approaches that are not commercially attractive, support for Phase III trials, tax rebates and patent extensions. It also proposed other aspects of commercial development that must be given special attention, such as intellectual property rights and liability issues. But such appeals are not novel and they have met with little response in the past.

Overall, basic scientists do not believe that responsibility for AIDS vaccine development will be transferred to the White House despite PACHA's latest recommendations. Time will tell. PACHA will request a response from the President before it meets again in June.

KAREN BIRMINGHAM & MYRNA E. WATANABE, NEW YORK

Deal emphasizes the importance of DNA vaccines

There is perhaps no better single illustration of the commerical importance of vaccines as medicines for the next century than the deal signed between the two British companies, PowderJect Pharmaceuticals and Glaxo Wellcome (GW). With a potential total value of around $300 million, the agreement is the second biggest pharmaceutical/biotech. R&D deal to date and represents Glaxo's serious reentry into the vaccine business.

Cells containing gold carrier particles.

The deal centers on one of the currently most advanced technologies in the vaccine field. Rather than using live attenuated pathogenic material, or protein subunits of pathogens to stimulate an immune response, PowderJect's technology is based on DNA vaccines. DNA from a pathogen is adhered to gold particles to increase its mass before being injected through the skin using a helium-driven gun that accelerates the particles to up to three times the speed of sound. The DNA is incorporated into the skin's antigen presenting cells, which produce corresponding antigenic proteins that in turn illicit an immune response. The gold is inert in the body and separates from the DNA once injected.

GW made a $20 million equity investment in PowderJect and paid $4 million in license and option fees for PowderJect's hepatitis B prophylactic DNA vaccine, which is currently undergoing Phase I clinical trials at the University of Maryland's Center for Vaccine Development in the US. GW has an option to develop ten more DNA vaccines.

Other DNA vaccines in early clinical trials include the Apollon/Wyeth-Lederle vaccine against genital herpes and an influenza virus vaccine being developed by Merck & Co, using technology licensed from Vical. None of the companies involved in DNA vaccine development has so far released data on the safety or efficacy of the technique in humans.

MYRNA E. WATANABE, NEW YORK

Reactions to MMR immunization scare

In February, Andrew Wakefield of the Royal Free Hospital in London published a paper in the Lancet linking immunization with the combination measles/mumps/rubella (MMR) vaccine to the development of bowel disease and autism in 12 children (*Lancet* 1998, 351; 637–41).

Writing in the same issue of the Lancet, Robert Chen and Frank DeStefano of the US Centers for Disease Control and Prevention (CDC) national immunization program, presented evidence that Wakefield's methodology was flawed and that the adverse events are coincidental rather than causal (see *Nature Med.* 4, 371, 1998). Britain's Chief medical Officer, Sir Kenneth Calman, also made public statements aimed at dispelling fears about the vaccine and a review by the WHO listed substantial evidence against an association. Despite these efforts to put Wakefield's data into perspective—over 90 percent of all children receive the vaccination in the UK and chance alone predicts some overlap with those that go on to develop autism—his study has already had many repercussions.

Wakefield's suggestion that it might be safer to give the vaccine in separate doses to reduce viral load, led to shortages of each individual vaccine in the UK and French vaccine manufacturer, Pasteur Merieux, reported that it could no longer keep pace with demand for single vaccines. A special panel of 37 doctors and scientists was convened by the Medical Research Council in London to review Wakefield's data. The panel declared that there was no proof of any link between MMR and the subsequent development of these disorders and urged that vaccination policies should not be altered.

The alarm also spread across the Atlantic, causing parent groups and policymakers in the US to clash over MMR vaccination. The CDC and the American Academy of Pediatrics attempted to discredit the study, prompting allegations that they were "threatening independent scientific research and the public health." Autism advocate groups called for an investigation into the link to be funded from the one billion dollars appropriated annually to the department of Health and Human Services to purchase and develop vaccines.

Chen and DeStefano have wisely proposed that the UK and other countries set up a surveillance system similar to that established in the US in 1991, which uses information from four selected Health Maintenance Organizations as "sentinel"

Questions & Answers - AIDS Vaccine Status
Research Subcommittee, PACHA
December, 1997

The Current State of AIDS Vaccine Research

1) Q: How many different AIDS vaccines have already been tested in human volunteers?
A: Over 20 different vaccines have been tested in Phase I clinical trials. Three of these have gone on to more extensive testing in Phase II trials of several hundred volunteers. None have been tested in large scale efficacy trials.

2) Q: Do any of the vaccines thus far tested confer protection against HIV?
A: No one knows. Candidate vaccines have only been taken through Phase II trials, not enough to know for certain if there is any protection.

3) Q: What approach seems the best?
A: Live attenuated viruses - viruses that have been genetically weakened by cutting out some of their key genes - can reproducibly protect monkeys against infection and death from AIDS viruses (SIV).

4) Q: If live attenuated viruses work in monkeys, why isn't this approach being tested in humans?
A: Although genetically altered "live attenuated" viruses are definitely weakened, and definitely do protect most animals, they may not be completely safe. A small fraction of monkeys have developed AIDS-like illnesses from these viruses.

5) Q: Are there any safe vaccines that confer protection?
A: No one knows for sure. Some apparently safe immunization strategies have been reported to protect monkeys or other animals against inoculation. However, not everyone is convinced by these experiments.

6) Q: If results from animal model protection experiments are not clear, and if there is no reliable blood test for protective immunity to HIV, how is it possible to know if any particular candidate vaccine is a good or a bad prospect?
A: Currently the only way to know for sure if a given vaccine candidate will protect humans against HIV is if it is tested in a large scale Phase III trial involving thousands of at risk persons.

7) Q: If large scale Phase III trials are the only way to obtain definitive answers, why aren't they being done?
A: In 1994 the proposal was made that two leading candidate vaccines, the genetically engineered envelop protein vaccines from Chiron and Genentech, should be advanced to Phase III trials. However, the NIH decided that there were insufficient reason to

proceed.

8) Q: Are there alternatives to Phase III trials in order to get definitive answers?
A: Many scientists believe that there is insufficient evidence that any of the available candidate vaccines will confer protection, and that Phase III testing of these candidate vaccines would be a waste of time and money. They believe that we need more basic research on HIV molecular biology and immunology before any candidate vaccine will come along that merits Phase III trials.

9) Q: How is the scientific research community divided on the question of whether to proceed to Phase III trials now with best available vaccines (the "empiric approach"), or to await new scientific discoveries ("horizon approach")?
A: It's about evenly divided. The empiricists are becoming more vocal about the urgent need for definitive answers that can only come from clinical trials.

The US Government AIDS Vaccine Effort

10) Q: How is AIDS vaccine research organized in the US Government?
A: The National Institutes of Health in Bethesda, Maryland is the lead agency for all kinds of HIV/AIDS research, including vaccines. Other federal agencies, like the CDC and the Walter Reed Army Institute of Research, also have smaller AIDS vaccine programs.

11) Q: Where does a vaccine fit in the priority scheme of the Federal AIDS research efforts?
A: AIDS vaccine work is the fourth priority for the NIH, behind pathogeneses, chemotherapy, and opportunistic infection research. About 13% of NIH AIDS annual research funding goes towards vaccines.

12) Q: Who is in charge of AIDS vaccine research at the NIH?
A: No one person is in charge. Responsibility is vested in the Director of the NIH, the Director of the OAR, the Director of the NIAID, and the Director of the NCI. The highest ranking full time official responsible for AIDS vaccines at the NIH is in the Division of AIDS of the NIAID, 3 reporting levels below the Director of the NIH.

13) Q: What about other Federal agencies?
A: Vaccine work is the top DOD AIDS research priority, at approximately 70% of their AIDS research budget, but the total amount ($30 million per year) is much less than the NIH program. The AIDS vaccine budgets of the CDC and other Federal agencies are even smaller..

14) Q: What is CDC's experience in vaccine research and development?
A: An ongoing history has documented over 100 projects and studies in all phases of vaccine research and development over the 50 year history of the CDC. These range

from basic science work to attenuate organisms and define antigens for use as vaccines, laboratory animal studies to test vaccine designs, through human clinical and field trials with both domestic and developing country collaborators. CDC scientists have run or been involved in field efficacy (Phase III) trials of vaccines for Haemophilus influenzae type b, hepatitis B, meningococcal meningitis, measles, pertussis, and polio, among other diseases.

15) Q: Has there been any planning on the Federal level that has used a comprehensive process among Federal agencies, the private sector, and the international community?
A: In 1996 there was an effort to provide some guidance by producing **The Federal Biomedical Research Plan and Budget for HIV and AIDS.** One section of the report focused on vaccines. The NIH, DOD, CDC, VA and FDA developed objectives and strategies for each of their agencies. The private sector, and the international community were not included. Coordination and collaboration strategies were not addressed in the report. Also product development issues, such as those outlined in PACHA's report were not addressed. Prioritization and leadership issues were not addressed.

16) Q: Has there been any coordination of the AIDS vaccine efforts of the NIH with those of other Federal agencies?
A: There is no formal mechanism for coordination of HIV/AIDS work between the various Departments of the Federal government. Nonetheless, there are good working informal relationships at the investigator level.

17) Q: What other institutions in the USA are important players in AIDS vaccine research?
A: University based physicians and scientists conduct the majority of AIDS vaccine research in the USA; most are funded through grants from the NIH. Small biotech companies, many of which are affiliated with universities, are also important players. The large established pharmaceutical companies and vaccine manufacturers have the full range of capabilities for research, development, testing, and production.

18) Q: Is the government vaccine effort coordinated with these other institutions?
A: Because they derive most of their funding from the NIH, university based researchers are closely affiliated with the NIH. Small biotech companies very in their relationship with the NIH; large pharmaceutical companies set their own agendas.

19) Q: If industry's effort is independent from that of the NIH, does this mean that there is no communication?
A: Industry keeps a close watch on new scientific finds generated through the Federal effort, but large industry tends to keep much of its privately financed R&D effort confidential. Since the 1994 decision, interactions between the US government and industry are minimal with regard to AIDS vaccine research.

20) Q: Why is industry important to the national effort?
A: Industry is an essential partner at several steps. First, pilot lots of candidate vaccines for even Phase I trials must be produced under Good Manufacturing Practices, and industry has the best facilities and expertise for this work. Second, large quantities are needed for efficacy testing and industry is best suited for this work. And last, if a vaccine is shown to be protective, only industry has the production plant capacity that will be needed to insure the supply of vaccine. Such production facilities and expertise are rare outside industry. Only industry has the production plant capacity that will be needed to insure the supply of vaccine. Small biotech firms don't have the facilities or the resources to produce material under GMP for human studies.

21) Q: What is the role of the WHO, or UNAIDS, in funding and coordinating AIDS vaccine research?
A: UNAIDS in Geneva is the lead agency for all United Nations HIV/AIDS activities. However, the total AIDS vaccine research budget of UNAIDS is only $2 million per year. UNAIDS plays an important convening and consensus building role between industrialized and developing countries, but UNAIDS has neither the budget nor the staff to fund or coordinate research.

November 14, 1997

TO: Sandy Thurman
CC: Scott Hitt
Alexandra Levine

FROM: Helen Miramontes

RE: Participants for Preliminary Meeting on PACHA's Vaccine Report/Recommendations

This is a follow up memo of our discussion this week on the tentative meeting with DHHS representatives and representatives from outside the Federal government to discuss PACHA's vaccine report and recommendations from the December meeting. Per our discussion we will limit the meeting participants to approximately 20 people.

External:
1) Don Francis - Vaxigen
2) Don Burke - John Hopkins
3) Pasteur - Stanley Plotkin
4) Seth Berkley - IAVI
5) Mary Lou Clements-Mann - John Hopkins
6) Bob Belshe - St. Louis University
7) Cathy Wilfert - Duke (or her husband Sam Katz - but she is the one that has been working on AIDS)
8) Jerald Sadoff - Merck
9) Max Essex - Harvard

Internal:
1) DOD - Deborah Birx
2) FDA - Karen Goldenthal
3) CDC - Bill Haywood
4) CDC - Patricia Fass, M.D., Ph.D.
5) NIH - Jack Whitescarver

Bill Snow
David Baltimore

ONAP:
1) Sandra Thurman

PACHA:
1) Helen Miramontes
2) Daniel Montoya
3) Alexandra Levine ?
4) Scott Hitt ?

November 14, 1997

TO: Daniel Montoya
CC: R. Scott Hitt
Alexandra Levine

FROM: Helen Miramontes

RE: Vaccine Report Draft #11

Per our conversation this memo is met to clarify the Vice President's role/responsibilities that are being requested in the above report.

The Research Committee of PACHA is asking the Vice President to initiate the Vaccine Comprehensive Planning Process as outlined in the draft report by:

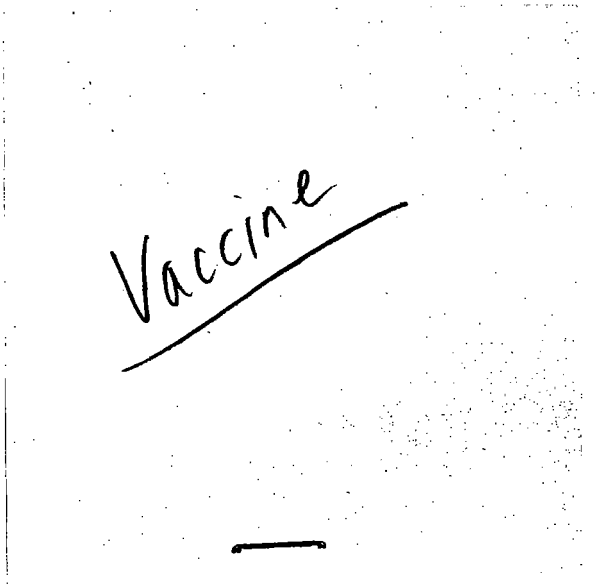
1) Appointing a Chairperson to be responsible for implementing the planning process, establishing meeting dates, overseeing the work of the various committees, and reporting back to the Vice President on the progress of the planning process.

2) The organizing and operationalizing of the planning process, including the lists of participants would be assigned to the Office of National AIDS Policy (ONAP). PACHA would participate in this process as needed and in areas of interest as mutually identified with ONAP. ONAP would keep the Vice President informed as to the progress of the planning process.

3) Funding sources would need to be identified for the implementation of the comprehensive planning process. This identification of funding sources would be assigned to ONAP.

4) It is requested that at the first meeting of the comprehensive planning group that the Vice President would offer greetings and charge the committee as to expected outcomes.

5) Organization of the goals and objectives of the comprehensive planning process would be the responsibility of ONAP in collaboration with PACHA.


Vaccine

Achieving an HIV vaccine:

The need for an accelerated national campaign

Richard Marlink, MD

Last spring, when President Clinton called for "a new national goal for science"—that we develop an HIV vaccine within the next 10 years—I learned that yet another close friend had been diagnosed with HIV. In this new era of treatment, combination drug therapies offer hope to HIV-infected people who, like my friend, can afford them. Yet not all infected Americans can afford or even tolerate these therapies, and the drugs cannot prevent the more than 100 new infections that occur in this country each day. Moreover, in the developing world, where more than 90 percent of people with HIV live, the situation is dramatically worse. There, the expense of the new therapies is prohibitive. There, an estimated 8000 to 9000 people become infected each day. Worldwide, an AIDS vaccine is our only solution.

Most AIDS scientists, especially vaccinologists, agree with the President that it is no longer a question of whether we can develop an AIDS vaccine—it is simply a question of when. It is incumbent upon us, therefore, to develop an AIDS vaccine as quickly as possible. The President's leadership on this issue, this fiscal year's increased AIDS vaccine budget, and the concentration of National Institutes of Health (NIH) researchers in a special Washington facility may indeed catalyze an expanded national effort to obtain the obtainable: a truly effective HIV vaccine for worldwide use.

Yet with this expanded effort must come a sharpening of resolve. Our efforts must extend beyond laboratories and animal research facilities. To reach the President's goal, we must learn from the past and reorganize our effort in three major ways: (1) dramatically expand human testing of the safe vaccine preparations that already exist; (2) launch a national campaign whose organizational structure follows those with proven track records in achieving specific goals and in delivering tangible products; and (3) vastly expand our international vaccine trials.

Lessons from the vaccinologists

Twice a year, the Harvard AIDS Institute convenes vaccinologists from government, industry, and academia to participate in intensive workshops aimed at determining how to make an AIDS vaccine for worldwide use. These senior vaccinologists come from all over the world and represent a significant proportion of our planet's expertise in developing successful vaccines against such killers as polio, cholera, smallpox, and hepatitis.

During those workshops, the vaccinologists repeatedly return to two major lessons from

A vaccine is the only solution to the global AIDS epidemic. But how should research proceed? The author argues for expanded human testing of the safe vaccines that already exist, development of a new national organization similar to those with track records in achieving specific goals and in delivering tangible products, and expansion of international vaccine trials.

the history of vaccine development. First, for half of the vaccines now in human use, we had no clear understanding of how or even if they would work before demonstrating success in human vaccine trials. For some vaccines that ultimately proved successful in humans, such as the meningococcus vaccine, animal models had actually predicted failure. For other vaccines, such as the typhoid vaccine, the initial challenge testing in humans did not accurately predict the later effectiveness in large population studies.

Louis Pasteur's rabies vaccine—it has become clear that only one animal can reliably predict a vaccine's success in people: the human animal.

Lessons from the polio vaccine

In the early 1980s, after the discovery of HIV and methods to grow the virus in test tubes, a vaccine was expected to appear soon. But thirteen years after the isolation of HIV in the laboratory, the NIH has been unable to bring a single candidate AIDS vaccine into field trials to determine if it

The polio vaccine

1. Do not let a better vaccine of the future preclude a potentially lifesaving one now.

2. And if existing research organizations cannot respond quickly and effectively, do not hesitate to create a new one that can.

Second, for many of the successful vaccines we now have in use, we still do not understand the basic biological mechanisms that confer protection. We can and should infer which vaccine preparation might better offer protection by correlates of immunity, but these correlates commonly help guide our best access. We should remember that our limited understanding of how vaccines actually protect us has not prevented us from developing successful vaccines against numerous infectious agents.

These lessons led the vaccinologists to draft a Call for Action, which urges active pursuit of the many safe AIDS vaccine preparations under consideration [see table]. Their Call for Action goes on to state that we should not wait until we fully understand laboratory parameters that may or may not predict protection. Nor should we wait for an animal model to show us the clear, safe path. From the beginning of vaccine science—with William Jenner's smallpox vaccine and even works. In response to a critical review late last year, the agency restructured its AIDS vaccine program by appointing a part-time committee of external scientists to guide the effort. Although welcome, this reform is unlikely to overcome the fundamental handicaps of the agency itself.

The history of the polio vaccine teaches us that a different kind of entity would be better suited to manage an expedited vaccine program in the face of a public health emergency. In the early 1950s, frightening polio epidemics were sweeping the United States, each year killing up to 3000 and crippling 20,000 more. In 1949, John Enders and his colleagues had grown the polio virus in test tubes, a critical step in vaccine development. Then Jonas Salk applied this discovery by developing a killed whole-virus vaccine.

At that time, orthodox science dictated that ideal vaccines for viral diseases required living but weakened virus strains. Many scientists criticized Salk's product for lacking sufficient scientific rationale, suspecting that it would either not work, or not work as well as future live vaccines.

Polio research was then funded by the March of Dimes campaign, whose director, Basil O'Connor, was undeterred by the lack of consensus among scientists. Motivated by the fears and concerns of parents, he was committed to widespread public distribution of the vaccine, even if it proved to be only 25 percent effective. Thus, Salk's vaccine was tested in over half a million children before the summer polio season of 1954.

In April 1955, the vaccine was declared successful. The rate of paralysis was found to be 72 percent lower among vaccine recipients than among children who had received placebo shots. A better vaccine—Sabin's oral vaccine—was not introduced for another seven years. In that time, Salk's vaccine saved tens of thousands of lives

Table 1. Favorability rating for types of HIV vaccine preparations

Formulation	*Example*	*Immunogenecity*	*Cost*	*Safety*	*Adjuvant needed?*	*CTL response*
Protein subunit	gp120/160	moderate	low	high	yes	no
Synthetic peptides	V3	low	moderate	high	yes	no
Whole killed	env preserved	moderate	moderate	moderate	yes	yes
Bacterial vector	BCG	low/moderate	high	moderate	no	no
Viral vector	Pox	moderate	moderate	moderate	no	yes
Naked DNA	*env* plasmid	moderate	moderate	moderate	no	yes
Live-attenuated	*nef* deletion	high	moderate	low	no	yes

CTL: Cytotoxic T-lymphocytes

and prevented hundreds of thousands of lifelong disabilities. The polio vaccine thus provides us with an additional critical lesson: Do not let a better vaccine of the future preclude a potentially lifesaving one now.

The polio saga also illustrates the tension between academic basic science and empirical applied research. The former scrupulously pursues knowledge and elegant solutions, while the latter seeks rapid answers to urgent public health problems. The struggle between these complementary approaches is one of the impediments to rapid AIDS vaccine development. That is, although the NIH is the world's premier biomedical research agency and is run by sincere and devoted scientists, its principal mission is to advance basic scientific knowledge and to nurture academic research—not to develop products like vaccines. Its bureaucracy hinders efforts to respond quickly to epidemics. In addition, despite Clinton's revamping, there still will be no senior, full-time official whose sole responsibility is to produce an AIDS vaccine as soon as possible and who has the vaccinology background, budgetary resources, and contracting authority to do so.

The current impasse in vaccine development arose in June 1994, when the NIH halted plans to conduct field trials of the first generation of bioengineered AIDS vaccines, overruling its own vaccine advisory panel and mid-level staff scientists. These vaccines were called envelope products because they mimic the outer coat of the virus and thus generate antibodies that could potentially cover the virus surface and block infection.

During eight years of research and development, enormous investments of private capital and federal funding were expended for laboratory and animal studies and preliminary human testing of safety and immune response. The new products were found to be successful in protecting chimpanzees from HIV. Had these entities been approved, the human trials could have begun in 1994, costing some $20 million annually over three years. And had the vaccines worked in people, the entire expense of the trials would have been recouped by the first 500 cases of AIDS prevented.

All who analyzed the data agreed the envelope vaccines appeared to be safe. Proponents of the field trials said they would accelerate vaccine development by determining definitively if and how well the products worked and perhaps reveal why. Opponents criticized the vaccines according to an unproven theory for predicting whether an AIDS vaccine would work. But vaccinology is a trial-and-error science in which progress sometimes requires the courage to conduct careful and expensive human trials to test theory and revise vaccine designs accordingly. Although some experimental vaccines provide clues for efficacy, such as blocking infection in animal models, most do not. As Jonas Salk once said, "You have no chance of success unless you are willing to fail."

Had the first generation of AIDS vaccines been approved, human trials could have begun in 1994, costing some $20 million annually over three years. And had the vaccines worked in people, the expense of the trials would have been recouped by the first 500 cases of AIDS prevented.

We should also learn from organizational structures with proven track records in delivering successful products. Consider the successful development of the US space program: The mission was given to a newly created NASA, not to the existing, yet grant-making, National Science Foundation. The March of Dimes gave us both the Salk and Sabin polio vaccines. And finally, our own military's applied research system has developed dozens of vaccines—from flu to measles, plague, and typhoid—sometimes in record time to meet war needs.

The mandate for developing an AIDS vaccine, therefore, should go to a goal-oriented, rapidly acting, streamlined, and semi-independent campaign or agency to pursue all possible strategies systematically and simultaneously. This entity should propose legislation to overcome economic and legal disincentives for private investment and should work closely with industry and other nations to shepherd vaccine products through field trials and FDA approval. The campaign's director should be full-time, report to the White House, and be an accomplished vaccinologist or pharmaceutical research manager. Most importantly, the campaign or agency should be well-funded—far beyond the $117 million budgeted for this year's NIH effort.

Lessons from the epidemic

Now for the hard part. Our nation's new effort would mean human experimentation on a large scale, particularly as part of an increased effort at international collaboration with developing countries—those hardest hit by the epidemic.

As long as the stringent ethical and safety standards followed in the United States are used in international vaccine trials, the reasons for vastly increasing our international collaborations are threefold. First, it is simply the right thing to do. Millions of lives will be saved. Second, a vaccine preparation will more rapidly and economically be tested among populations with high rates of new infections. Those regions lie mostly outside our borders. If the AIDS epidemic has taught us one thing, it is that this is a worldwide epidemic requiring that we operate globally. Third, the HIV epidemic actually comprises at least ten epidemics of different subtypes, each with its own distinct geographic distribution and even distinct biological features. In the United States, only one subtype predominates at present. With the evolution and expansion of other subtype epidemics, our efforts at testing a worldwide AIDS vaccine only in the United States may be like testing last year's flu vaccine during this year's flu season. We will need to ensure from the outset that AIDS vaccine preparations can protect against all subtypes of HIV. Again, we will only know this by testing preparations in humans.

The consensus among scientists today is that an effective AIDS vaccine is possible. In a time of disillusionment over Sputnik, President Kennedy galvanized the nation by setting a deadline to reach the moon. In May of this year, President Clinton declared a goal of protecting the world's population with an AIDS vaccine within the next ten years. Reinventing the federal AIDS vaccine effort will be an essential step toward such an urgent and inspiring achievement. ■

Richard Marlink, MD, is executive director of the Harvard AIDS Institute.

Sandra Thurman 03/21/98 03:09:05 PM

Record Type: Record

To: Wendyw @ nih.gov @ inet

cc:
Subject: From Todd - Dr. Jonathan Mann's prepared text

---------- Forwarded by Sandra Thurman/OPD/EOP on 03/21/98 03:10 PM ----------

Dear Fellow PACHA members,

FYI, below is the prepared text I just received from Jonathan Mann from his presentation before the International Committee this week. He has also faxed this to Drs. Varmus, Baltimore, and Fauci.

I hope the focus of discussion and debate will be on the important issues raised, and not on his extemporaneous personalizing of responsibility, as quoted by the press present at our discussion on Sunday. It was quite obvious to those of us in attendance that he feels quite strongly about this subject.

Best regards,

Bruce

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Paralysis in AIDS Vaccine Development Violates Ethical Principles and Human Rights

Jonathan M. Mann, MD, MPH
Dean and Professor, School of Public Health
Allegheny University of the Health Sciences
Philadelphia, Pennsylvania
Founding Director, Global Program on AIDS,
World Health Organization
March 20, 1998

There is increasing worldwide consensus that a preventive vaccine will be essential for controlling the expanding and intensifying global HIV/AIDS epidemic.

There are several AIDS vaccine candidates which have been shown to be safe in humans, and some produce a variety of immune responses, including those possibly associated with protection against HIV, in a majority of recipients. If the process of vaccine development was proceeding normally - traditionally - this would lead to prompt initiation of field trials to determine protective efficacy of vaccine candidates. Yet years later, field trials of AIDS vaccine candidates are still not underway.

Three reasons have been put forward to explain this unusual deviation from standard vaccine development practice. First, it has been alleged that special ethical problems exist regarding conduct of AIDS vaccine field trials. While important, none of these ethical issues are insurmountable. Secondly, the fear has been expressed that if the first vaccine trial is not highly successful, it would be impossible to conduct further trials; the global urgency and need for an AIDS vaccine make this fear groundless.

The third issue involves disagreement within the scientific community about whether current candidate vaccines will protect. This controversy, inherent in development of all vaccines, has been allowed unreasonably to paralyze progress towards AIDS vaccine development. Something has gone wrong with the process, because the history of successful vaccine development, including recent vaccines such as against rotavirus and whooping cough (pertussis) unequivocally shows that the immune correlates of protection are very often unknown, both prior to field testing and even after approval for licensure.

Some vaccines (such as against Lyme disease) have been found to be highly effective in field trials without identifying a human correlate of immunity. And smallpox was eradicated using a vaccine whose exact mode of action and protection was unknown!

This raises a series of ethical and human rights issues. For the failure to proceed expeditiously with field trials of available AIDS vaccine candidates constitutes unethical practice and violates human rights of Americans.

The key ethical concept of concern is the duty to help people in need, and the central human rights violations involve the right "to share in scientific advancement and its benefits", and the rights to non-discrimination and to life.

The ethical duty to help involves a balance of benefits to another and the risk to self. For example, if you do not know how to swim and you see a person being swept away in a

raging river, failure to jump in and try to save the person is not unethical. However, if you are a trained lifeguard and see someone drowning in a calm lake, you have an ethical duty to help.

The failure to mount field trials of available AIDS vaccine candidates, in a manner consistent with traditional and current good vaccine development practice, violates the duty to help and is patently unethical. Requiring certainty about immune correlates of protection before starting field trials of AIDS vaccine candidates is unethical because it creates an unreasonable barrier to progress.

To illustrate: the immune correlates of protection against rotavirus, a major cause of death in childhood worldwide, were unclear when field trials of candidate rotavirus vaccines were initiated. Field trials were started once candidate rotavirus vaccines were shown to be safe and to induce some immune responses. In a series of field trials, rotavirus vaccine proved its effectiveness and today, even while the vaccine was recently approved by the FDA advisory committee and recommended for universal childhood immunization by the federal government's Advisory Committee on Immunization Practices, the immune correlates of protection are still unknown. Proceeding to field tests of rotavirus vaccine was highly ethical, while delaying testing until all the scientific answers were available would have been unethical, and detrimental to public health.

It is unrealistic and illusory to wait for universal consensus within the scientific community about when a vaccine candidate is ready for field trials. There has never been universal consensus about vaccines: to cite just one example, the names of those prominent scientists who declamed vigorously against polio vaccine testing have been forgotten, while Enders, Salk and Sabin made public health history. The decision about how and when to proceed to field trials, bearing its own burden of responsibility and accountability, is best placed in the hands of those experienced with vaccine development, including its public health dimensions.

Human rights are also particularly relevant because the US government has invested so heavily and several of its institutions, including NIH, the Department of Defense, CDC and FDA, are involved in AIDS vaccine research and development. In this context, federal governmental failure to proceed to AIDS vaccine field trials, while contributing institutionally and financially to field trials of other vaccines which met essentially similar criteria vaccine development criteria (human safety and immunogenicity without clear knowledge about correlates of immunity) represents a clear violation of the human rights of American citizens.

This human rights violation is underscored by the fact that the vulnerable population for HIV infection in the United States, the estimated 40,000 new HIV infections in 1998, will occur predominantly in already marginalized populations, thereby exacerbating pre-existing patterns of societal discrimination. It is as if the US government had decided that the AIDS epidemic could be controlled in this country without a vaccine. In contrast, progress towards Lyme vaccine development, to protect against a disease affecting middle and upper-class populations in this country, has proceeded rapidly. Very simply, if 40,000 college students were becoming HIV infected each year, it is obvious that field trials of AIDS vaccine candidates would have long been underway.

Thus, the failure to proceed to field trials, in the context not of an ideal world but in the real world of successful vaccine development, is unethical and violates human rights. The failure to act, like silence, has moral consequences.

At an institutional level, this failure stems from decisions and recommendations made by NIH and its AIDS vaccine advisory committee, both of which are headed by notable scientists who nevertheless lack experience with vaccine development and public health. This is not a plea for AIDS as a special case; no special dispensation is required. What is needed is to develop AIDS vaccine candidates according to procedures and mile-stone driven strategies which have produced highly successful vaccines which save millions of lives from diseases like polio, whooping cough and measles. It is unethical and violative of human rights to hold AIDS vaccine development hostage to a requirement for scientific exactitude which is unreasonable and may well be unattainable.

Science is an instrument of public health. The larger responsibility, central to the moral authority and legitimacy of our government, is protection of the public health. The program for AIDS vaccine must be lifted above institutional defensiveness and parochial interests. The health of America and the world needs leadership - "can do" American leadership - to develop AIDS vaccines. Failing to proceed is unethical and violates basic human rights.

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HIV/AIDS VACCINE AWARENESS DAY

May 18, 1998, will be the first HIV/AIDS Vaccine Awareness Day. A national event sponsored by a variety of groups involved in testing, developing and advocating for HIV/AIDS vaccines, HIV/AIDS Vaccine Awareness Day is an opportunity for people around the country to understand:

- Why the world needs a vaccine to stop the spread of HIV and halt the global growth of the AIDS epidemic;
- What such a vaccine would mean to their local communities;
- What it will take to develop and test an HIV/AIDS vaccine;
- How ordinary people can be a part of the international effort to find an HIV/AIDS vaccine.

Preventive vaccines have been immensely successful in global efforts to stop other diseases. Smallpox has become extinct in the natural world, and other diseases are becoming more and more rare, as the direct result of international vaccination efforts. In the 1950s, when Jonas Salk made the vaccine to stop polio, church bells rang and banner headlines trumpeted the good news. Salk's vaccine was the direct result of ordinary people's commitment to the cause. Many scientists and activists now believe that a vaccine to stop HIV is possible. As part of the March of Dimes, the public sent dimes to the White House to help fund a polio vaccine; today, public involvement, from national politics to community education, is just as important in the effort to find an HIV/AIDS vaccine.

On May 18 of last year, President Clinton challenged the nation and the world to find a vaccine to stop the AIDS epidemic: "If the twenty-first century is to be the era of biology," Clinton said, "let an AIDS vaccine be its first triumph." This year's HIV/AIDS Vaccine Awareness Day is a chance for people to learn more about the long and unpredictable road ahead--towards the day the church bells ring with the joy of a new vaccine.

Many challenges lie ahead. Not only must we find a vaccine which works tomorrow, we must not give up our efforts to stop HIV today, with condoms, clean needles, and other proven HIV prevention strategies. Not only must we find a vaccine which works, we also must continue to work towards finding better and more accessible treatments for HIV disease. Not only must we find a vaccine which works, we must ensure that vaccine trials benefit the communities in which they take place. Not only must we find a vaccine which works, but we must also ensure that once such a vaccine arrives, it is accessible and widely promoted all over the world.

Accomplishing all of these goals will require the concerted efforts of a wide range of Americans and people around the world. You can be an important part of this HIV/AIDS Vaccine Awareness Day:

- Educate others about efforts to find a vaccine
- Honor HIV/AIDS vaccine trial volunteers
- Highlight the importance of a vaccine to other countries around the world
- Take part in commemorative efforts locally and nationally
- Support vaccine-related policy initiatives
- Speak to the media about HIV/AIDS vaccines

For more information on HIV/AIDS Vaccine Awareness Day activities contact:

HIV Network for Prevention Trials (HIVNET)

Joy Workman, National Community Education Coordinator, ABT Associates
Email: joy_workman@abtassoc.com
Phone: 301-718-3103

New York, NY

Paul Teixeira, Community Relations Coordinator, Project ACHIEVE
Email: pteixeira@nybc.org
Phone: 212-388-0008, ext. 18

Bronx, NY

Denise Goodman, Community Relations Coordinator, Project ACHIEVE
E-mail: dgoodman@nybc.org
Phone: 718-588-8900

Chicago, IL

Fred Swanson, Community Education Coordinator, Chicago Prevention Research Project, Howard Brown Health Center

Email: FredS@howardbrown.org
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San Francisco, CA

Joe Wright, Community Educator, San Francisco Department of Public Health AIDS Office
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Seattle, WA

Ellen Blackstone, Seattle AVEU Community Relations Coordinator
Email: vaccine@u.washington.edu
Phone: 206-667-2300

Dennis I. Torres, Seattle HIVNET Community Education Coordinator
Email: ditorres@u.washington.edu
Phone: 206-521-5821

For more information on HIV vaccines:

Johns Hopkins University AIDS Vaccine Evaluation Unit
http://ih1.sph.jhu.edu/cir

ACTIS HIV Vaccine Information Page
http://www.actis.org/vaccine.html

Vaccine Advocates
http://www.vaccineadvocates.org

International AIDS Vaccine Initiative
http://www.iavi.org/

The AIDS Vaccine Clinical Trials Network
http://www.emmes.com/avctn/index.html

AIDS Vaccine Evaluation Units

University of Washington AVEU Seattle, Washington
http://weber.u.washington.edu/~vaccine/

Vanderbilt University AVEU Nashville, TN
http://www.mc.vanderbilt.edu/adl/aids_project/vac/

University of Rochester AVEU Rochester, NY
http://www.urmc.rochester.edu/urmc/aidsvacc/aidsvacc.htm

Return to Clearinghouse Home Page

Achieving an HIV vaccine:

The need for an accelerated national campaign

Richard Marlink, MD

Last spring, when President Clinton called for "a new national goal for science"—that we develop an HIV vaccine within the next 10 years—I learned that yet another close friend had been diagnosed with HIV. In this new era of treatment, combination drug therapies offer hope to HIV-infected people who, like my friend, can afford them. Yet not all infected Americans can afford or even tolerate these therapies, and the drugs cannot prevent the more than 100 new infections that occur in this country each day. Moreover, in the developing world, where more than 90 percent of people with HIV live, the situation is dramatically worse. There, the expense of the new therapies is prohibitive. There, an estimated 8000 to 9000 people become infected each day. Worldwide, an AIDS vaccine is our only solution.

Most AIDS scientists, especially vaccinologists, agree with the President that it is no longer a question of whether we can develop an AIDS vaccine—it is simply a question of when. It is incumbent upon us, therefore, to develop an AIDS vaccine as quickly as possible. The President's leadership on this issue, this fiscal year's increased AIDS vaccine budget, and the concentration of National Institutes of Health (NIH) researchers in a special Washington facility may indeed catalyze an expanded national effort to obtain the obtainable: a truly effective HIV vaccine for worldwide use.

Yet with this expanded effort must come a sharpening of resolve. Our efforts must extend beyond laboratories and animal research facilities. To reach the President's goal, we must learn from the past and reorganize our effort in three major ways: (1) dramatically expand human testing of the safe vaccine preparations that already exist; (2) launch a national campaign whose organizational structure follows those with proven track records in achieving specific goals and in delivering tangible products; and (3) vastly expand our international vaccine trials.

Lessons from the vaccinologists

Twice a year, the Harvard AIDS Institute convenes vaccinologists from government, industry, and academia to participate in intensive workshops aimed at determining how to make an AIDS vaccine for worldwide use. These senior vaccinologists come from all over the world and represent a significant proportion of our planet's expertise in developing successful vaccines against such killers as polio, cholera, smallpox, and hepatitis.

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Louis Pasteur's rabies vaccine—it has become clear that only one animal can reliably predict a vaccine's success in people: the human animal.

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At that time, orthodox science dictated that ideal vaccines for viral diseases required living but weakened virus strains. Many scientists criticized Salk's product for lacking sufficient scientific rationale, suspecting that it would either not work, or not work as well as future live vaccines.

Polio research was then funded by the March of Dimes campaign, whose director, Basil O'Connor, was undeterred by the lack of consensus among scientists. Motivated by the fears and concerns of parents, he was committed to widespread public distribution of the vaccine, even if it proved to be only 25 percent effective. Thus, Salk's vaccine was tested in over half a million children before the summer polio season of 1954.

In April 1955, the vaccine was declared successful. The rate of paralysis was found to be 72 percent lower among vaccine recipients than among children who had received placebo shots. A better vaccine—Sabin's oral vaccine—was not introduced for another seven years. In that time, Salk's vaccine saved tens of thousands of lives

The polio vaccine

1. Do not let a better vaccine of the future preclude a potentially lifesaving one now.

2. And if existing research organizations cannot respond quickly and effectively, do not hesitate to create a new one that can.

Second, for many of the successful vaccines we now have in use, we still do not understand the basic biological mechanisms that confer protection. We can and should infer which vaccine preparation might better offer protection by correlates of immunity, but these correlates commonly help guide our best access. We should remember that our limited understanding of how vaccines actually protect us has not prevented us from developing successful vaccines against numerous infectious agents.

These lessons led the vaccinologists to draft a Call for Action, which urges active pursuit of the many safe AIDS vaccine preparations under consideration [see table]. Their Call for Action goes on to state that we should not wait until we fully understand laboratory parameters that may or may not predict protection. Nor should we wait for an animal model to show us the clear, safe path. From the beginning of vaccine science—with William Jenner's smallpox vaccine and

Table 1. Favorability rating for types of HIV vaccine preparations

Formulation	*Example*	*Immunogenecity*	*Cost*	*Safety*	*Adjuvant needed?*	*CTL response*
Protein subunit	gp120/160	moderate	low	high	yes	no
Synthetic peptides	V3	low	moderate	high	yes	no
Whole killed	env preserved	moderate	moderate	moderate	yes	yes
Bacterial vector	BCG	low/moderate	high	moderate	no	no
Viral vector	Pox	moderate	moderate	moderate	no	yes
Naked DNA	*env* plasmid	moderate	moderate	moderate	no	yes
Live-attenuated	*nef* deletion	high	moderate	low	no	yes

CTL: Cytotoxic T-lymphocytes

and prevented hundreds of thousands of lifelong disabilities. The polio vaccine thus provides us with an additional critical lesson: Do not let a better vaccine of the future preclude a potentially lifesaving one now.

The polio saga also illustrates the tension between academic basic science and empirical applied research. The former scrupulously pursues knowledge and elegant solutions, while the latter seeks rapid answers to urgent public health problems. The struggle between these complementary approaches is one of the impediments to rapid AIDS vaccine development. That is, although the NIH is the world's premier biomedical research agency and is run by sincere and devoted scientists, its principal mission is to advance basic scientific knowledge and to nurture academic research—not to develop products like vaccines. Its bureaucracy hinders efforts to respond quickly to epidemics. In addition, despite Clinton's revamping, there still will be no senior, full-time official whose sole responsibility is to produce an AIDS vaccine as soon as possible and who has the vaccinology background, budgetary resources, and contracting authority to do so.

The current impasse in vaccine development arose in June 1994, when the NIH halted plans to conduct field trials of the first generation of bioengineered AIDS vaccines, overruling its own vaccine advisory panel and mid-level staff scientists. These vaccines were called envelope products because they mimic the outer coat of the virus and thus generate antibodies that could potentially cover the virus surface and block infection.

During eight years of research and development, enormous investments of private capital and federal funding were expended for laboratory and animal studies and preliminary human testing of safety and immune response. The new products were found to be successful in protecting chimpanzees from HIV. Had these entities been approved, the human trials could have begun in 1994, costing some $20 million annually over three years. And had the vaccines worked in people, the entire expense of the trials would have been recouped by the first 500 cases of AIDS prevented.

All who analyzed the data agreed the envelope vaccines appeared to be safe. Proponents of the field trials said they would accelerate vaccine development by determining definitively if and how well the products worked and perhaps reveal why. Opponents criticized the vaccines according to an unproven theory for predicting whether an AIDS vaccine would work. But vaccinology is a trial-and-error science in which progress sometimes requires the courage to conduct careful and expensive human trials to test theory and revise vaccine designs accordingly. Although some experimental vaccines provide clues for efficacy, such as blocking infection in animal models, most do not. As Jonas Salk once said, "You have no chance of success unless you are willing to fail."

Had the first generation of AIDS vaccines been approved, human trials could have begun in 1994, costing some $20 million annually over three years. And had the vaccines worked in people, the expense of the trials would have been recouped by the first 500 cases of AIDS prevented.

We should also learn from organizational structures with proven track records in delivering successful products. Consider the successful development of the US space program: The mission was given to a newly created NASA, not to the existing, yet grant-making, National Science Foundation. The March of Dimes gave us both the Salk and Sabin polio vaccines. And finally, our own military's applied research system has developed dozens of vaccines—from flu to measles, plague, and typhoid—sometimes in record time to meet war needs.

The mandate for developing an AIDS vaccine, therefore, should go to a goal-oriented, rapidly acting, streamlined, and semi-independent campaign or agency to pursue all possible strategies systematically and simultaneously. This entity should propose legislation to overcome economic and legal disincentives for private investment and should work closely with industry and other nations to shepherd vaccine products through field trials and FDA approval. The campaign's director should be full-time, report to the White House, and be an accomplished vaccinologist or pharmaceutical research manager. Most importantly, the campaign or agency should be well-funded—far beyond the $117 million budgeted for this year's NIH effort.

Lessons from the epidemic

Now for the hard part. Our nation's new effort would mean human experimentation on a large scale, particularly as part of an increased effort at international collaboration with developing countries—those hardest hit by the epidemic.

As long as the stringent ethical and safety standards followed in the United States are used in international vaccine trials, the reasons for vastly increasing our international collaborations are threefold. First, it is simply the right thing to do. Millions of lives will be saved. Second, a vaccine preparation will more rapidly and economically be tested among populations with high rates of new infections. Those regions lie mostly outside our borders. If the AIDS epidemic has taught us one thing, it is that this is a worldwide epidemic requiring that we operate globally. Third, the HIV epidemic actually comprises at least ten epidemics of different subtypes, each with its own distinct geographic distribution and even distinct biological features. In the United States, only one subtype predominates at present. With the evolution and expansion of other subtype epidemics, our efforts at testing a worldwide AIDS vaccine only in the United States may be like testing last year's flu vaccine during this year's flu season. We will need to ensure from the outset that AIDS vaccine preparations can protect against all subtypes of HIV. Again, we will only know this by testing preparations in humans.

The consensus among scientists today is that an effective AIDS vaccine is possible. In a time of disillusionment over Sputnik, President Kennedy galvanized the nation by setting a deadline to reach the moon. In May of this year, President Clinton declared a goal of protecting the world's population with an AIDS vaccine within the next ten years. Reinventing the federal AIDS vaccine effort will be an essential step toward such an urgent and inspiring achievement. ■

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Greetings!

From the desk of...

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"To let oneself be bound by a duty from the moment you see it approaching is part of the integrity that alone justifies responsibility." – Dag Hammarskjöld

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Saturday, January 31, 1998

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4-DRUG REGIMEN SELECTED AS BACK-UP IN PROPOSED IAPAC HIV VACCINE TRIAL

IAPAC applauds commitment made by four companies to provide lifetime supply of AIDS drugs, viral load testing in unlikely event any volunteer requires HIV/AIDS care

CHICAGO – The International Association of Physicians in AIDS Care (IAPAC) today announced the selection of a four-drug antiviral combination therapy as the recommended treatment option in the unlikely event any of the initial volunteers for a live attenuated HIV vaccine human safety trial requires HIV/AIDS care. The selected combination consists of Abbott Laboratories' ritonavir (Norvir); Hoffmann-La Roche's saquinavir (Fortovase), Glaxo-Wellcome's lamivudine (Epivir), and Bristol-Myers Squibb's stavudine (Zerit).

In IAPAC's ongoing efforts to mitigate any potential harm to trial volunteers, it has secured commitments from Abbott Laboratories, Bristol-Myers Squibb, and Hoffmann-La Roche to provide lifetime supplies of ritonavir, stavudine, and saquinavir, respectively, should the need arise. Glaxo-Wellcome officials said that IAPAC's request for lamivudine is under scientific review.

IAPAC has selected the Roche AMPLICOR HIV-1 MONITOR Test as the preferred technology for measuring the amount of HIV-1 RNA in the blood (viral load) of the initial trial volunteers. Should the need arise, the monitor test would also assess viral response to antiretroviral treatment. Roche Diagnostics Systems has committed to provide the test for use in the initial group of volunteers involved in the delta-4 vaccine human safety trial.

"There is a growing amount of data indicating that a combination of two protease inhibitors and two nucleoside analogues may be the most promising option for initial treatment of antiviral naive patients with HIV," said Charles Farthing, MD, chair of IAPAC's Live Attenuated HIV Vaccine Subcommittee. Farthing is one of hundreds of physicians and healthcare professionals worldwide who are volunteers for the first human trial of a live attenuated HIV vaccine.

"We believe it is unlikely that there will be a need to provide this four-drug combination therapy to our trial volunteers. However, thanks to the generosity of some members of the pharmaceutical and diagnostics industry, we are living up to our longstanding commitment to safeguard the well-being of those registered as volunteers for this critical human trial," Farthing concluded.

–MORE–

In the coming month, IAPAC hopes to submit to the US Food and Drug Administration (FDA) a provisional protocol for the clinical trial of the HIV-1 delta-4 vaccine strain. This action is pending word from the FDA on a manufacturing plan submitted to the agency in late December by Therion Biologics Corp. The delta-4 vaccine strain was developed by Ron Desrosiers, PhD, of Harvard Medical School's New England Regional Primate Center.

"IAPAC and our cadre of trial volunteers and advocates from around the globe are anxious to move forward with a human safety trial of the delta-4 vaccine," said José Zuniga, IAPAC's deputy director and a trial volunteer. "With 16,000 new HIV infections a day globally, we can ill afford not to explore every possible avenue of HIV vaccine research and development."

Pharmaceutical and diagnostic company donation of drug products and viral load technology does not necessarily represent an endorsement by that company of IAPAC's live attenuated HIV vaccine trial.

###

The International Association of Physicians in AIDS Care (IAPAC) is devoted to developing and implementing global strategies to better the quality of life of all people affected by HIV and AIDS. IAPAC has 5,500 members in 42 countries. In the United States, IAPAC's member physicians care for the majority of Americans living with HIV and AIDS.

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New Technique for Vaccines

■ BOSTON—Scientists have developed a new technique for creating vaccines to combat cancer and viral infections such as AIDS, according to a study to be published in today's Proceedings of the National Academy of Sciences.

Richard Young and colleagues at the Whitehead Institute for Biomedical Research and the Massachusetts Institute of Technology fused together a heat-shock protein and a protein called ovalbumin. They then injected the results into mice.

The animals mounted an immune response against ovalbumin and developed immunity against cancer cells that make ovalbumin. Usually ovalbumin-producing cancer cells kill mice.

Young and his colleagues last month began testing the technique on macaques to try to find out if it is effective in combating Simian Immunodeficiency Virus—an essential step in the road to finding a vaccine for Human Immunodeficiency Virus, which causes AIDS.

He estimated it would take at least two years to complete the SIV study.

—Reuters

HIV VACCINE UPDATE

S10 Alerte Quarterly TB & HIV No 14 Mar-May, 1997

W. Rutter, Chiron's chairman : HIV vaccine development necessary for humanity

In the course of the VACCINE 2000 conference organized in Toronto last fall by Pasteur Mérieux Connaught, the founder and chairman of Chiron Corporation, William Rutter put in the balance the benefits of anti-HIV vaccines, with the present treatment oriented effort against HIV. During an interview with members of the press, including the editor of "TB & HIV", Rutter expressed concern that developing countries populations were "forgotten" in the present day emphasis on multitherapies. He characterized antivirals as a high price and long term type of treatment that would remain totally out of reach for developing countries.

Rutter spoke on the benefits of vaccine investments in general and HIV vaccine research in particular, «because only vaccines could ensure the future well being of humanity, whereas short term financial considerations tend to disregard vaccines today, focusing only on treatments, and short term money returns».

The US pharmaceutical industry is not at all concerned about developing countries' needs, added Rutter, and, worldwide, investments in biotechnology are not focusing on vaccines since "the latter only represent 2% of all investments".

"The first objective of-medicine is not to cure but to prevent, and as such vaccines

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Industry Investment in HIV Vaccine Research

Chris Collins
AIDS Vaccine Advocacy Coalition,
2215 Market Street, #501,
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In December 1996 the AIDS Vaccine Advocacy Coalition published a report on private industry investment in HIV vaccine research. The report followed from interviews the group did with pharmaceutical and biotech company representatives in several countries. Following is the executive summary from the AVAC report.

EXECUTIVE SUMMARY

A safe, effective and affordable vaccine is the best hope to bring the AIDS epidemic under control. There is widespread belief among scientists that development of such a vaccine is possible. Yet, fifteen years into the epidemic, the AIDS vaccine research effort faces extraordinary hurdles. These include: inadequate funding, insufficient focus on the scientific roadblocks, lagging industry investment, few candidate vaccines in the pipeline, little urgency among affected communities and a lack of leadership in the overall effort.

A series of interviews with industry scientists and leaders were conducted by the community-based AIDS Vaccine Advocacy Coalition (AVAC). In total, researchers and leaders from 23 companies with active or once-active HIV vaccine programs were interviewed. The interviews, conducted in confidence, attempted to examine the major incentives

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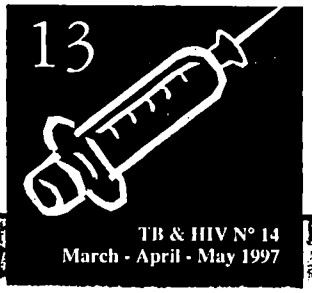


TB & HIV N° 14
March - April - May 1997

W. Rutter, Chiron's chairman : HIV vaccine development is necessary for humanity

Continued from page 13.

Research Focus In The Advanced Technology Industry 1996

	Venture Companies (236)		Macro Companies (40)	
Research Orientation	Number	Market Capitalization ($ billion)	Biotechnology	Pharmaceutical
rDNA Proteins	47	6.97	6	26
Vaccines	11	1.66	1	4
Diagnostics :				
• Immunodiagnostics	25	3.06		3
• Biosensors	2	0.29	1	
• DNA Probes	3	0.22	1	6
Cell Therapy	18	2.30		2
Chemistry :				
• Structural	3	0.89	1	21
• Synthetic	59	8.92		28
• Combinatorial	26	0.80	1	13
• Antisense	3	1.55	1	4
Drug Delivery	30	4.49	2	2
Gene Therapy	15	0.80	2	8
Genomics	7	1.71	1	15
Total Market Capitalization ($ billion)		**34**	**33**	**800**

Data is current as of October 1996 and is in part from Recombinant Capital

Vaccines represent a small fraction of pharma/biotech industry value and committment

Company Type	Number	Estimated Market Cap ($ billion)	Number of Companies in Vaccines	1996 Estimated Vaccine Revenues ($billion)	Estimated Market Value* ($billion)	Market value as Subset of total Industry Sector (%)
Pharmaceutical	34	800	4	3.0	15.0	1.9
Large Biotechnology	6	33	1	0.3	1.5	5.0
Small Biotechnology	236	34	11	0.1	1.7	5.0
TOTALS	**276**	**867**	**16**	**3.4**	**18.2**	**2.1**

**Estimated Market Value = Either Market Cap or Product revenues x 5*
Data is current as of October 1996 and is in Part from Recombinant Capital and Pharma Projects

Consolidation in the Vaccine industry

Withdrawals	Mergers & Acquisitions
Dow	Praxis
Eli Lily	Lederle
Richardson Merrell	Pasteur Vaccine
Miles	Merieux
Parke Davis	Connaught
Pfizer	Evans
Wellcome	S.S.W.
Glaxo	Sclavo-Behring

The Vaccine Landscape

Major Companies (Widespread Distribution)

- **Pasteur/Merieux/Connaught**
- **Merck & Co.**
- **SmithKline Beecham**
- **American Home Products (Lederle, Wyeth, Praxis)**
- **Chiron (S.p.A., Behring)**
- Commonwealth Serum Labs
- Medeva
- Swiss Serum Institute
- North American Vaccines
- Immuno (Baxter)

are the cornerstones of public health», but, at the same time, we must make sure that, under no circumstances, the fabrication or distribution of mediocre or second rate vaccines for developing countries populations be tolerated".

Vaccines against diseases such as AIDS, hepatitis and cancer are coming on line, but health industries are spending too little on prevention today. "If investors and major pharmaceutical industries are not interested in prevention, that is because they think, as financial analysts do, that we are destroying the market". Investors and companies like therapies for chronic diseases which bring a high and long lasting return on investments, and vaccines are much less fashionable because they are expensive to develop in terms of R&D investments, and they are more risky.

Most large pharmaceutical companies have totally pulled out of the vaccine sector, and today vaccines only represent 2% of pharmaceutical and biotechnological industries' investments.

Labs are weary about the lack of protection for industrial property in developing countries : to them it means that if you provide access to technologies for DCs, the latter will hit you back with competition. For example, by manufacturing cheap "second rate" vaccines, as has already occurred in a number of cases.

At the same time, a company can get blamed by a zealous US administrator who discovers that you put a vaccine product on a poor country's market at a low price compared to the price you are selling at for the home health sector.

Another problem is the lack of public awareness regarding vaccines. The public tends to pay a very high price for antibiotics and all sorts of treatments, and has become accustomed to that, but people think that vaccines are owed to them, and they don't want to pay. If you consider the tremendous benefits of vaccines in terms of years of lives and years of sickness saved, it is incomparably more expensive to treat even common ailments than to pay for a vaccine.

The analysts at the conference (such as Hambrecht & Quist biotechnology) argued that vaccines were not attractive to investors because the financial risk benefits were not so obvious to them.

Rutter's polemics in favor of vaccine development, were in line with his thinking as a successful "scientist-investor" whose company likes to pride itself for its advanced view of the HIV problem.

At the end of the discussion, Rutter indicated he was very proud of Chiron's invention of bDNA measurement of viral load, an instrument without which the multiple therapies of today could not have been evaluated, the key to care management being the capacity to measure what is the outcome of different drugs on viral production.

(Tables from slides shown in Toronto)

Industry Investment in HIV Vaccine Research • *Chris Collins*

Continued from page 13.

and disincentives to private investment in HIV vaccine development.

Overall, according to the industry scientists, the current HIV vaccine effort is a patchwork of efforts, not the aggressive, well-funded and coordinated international strategy that is required.

Though the current picture is discouraging, it need not remain so. A number of particularly urgent needs were identified. These include: providing more resources for HIV vaccine research, focusing on the key scientific roadblocks, actively encouraging investment by large pharmaceutical companies, insuring effective and accountable leadership in the HIV vaccine effort, and increasing commitment to the HIV vaccine effort by community-based organizations.

STATE OF INDUSTRY RESEARCH AND DEVELOPMENT

On a worldwide basis, private industry investment in HIV vaccine development is extremely limited. Biotech and pharmaceutical company interest in HIV vaccine development is extremely low. Private financing favors surer investments. The U.S. government, which carries the weight of facilitating and financing the worldwide effort, has centered its research in one division of one institute of the NIH. The Executive Branch and Congress provide relatively little support. Opportunities for expanded private/public partnerships and inter-company collaboration are being overlooked. In terms of the number of companies with active programs, the actual funds and staff being devoted, and the number of approaches being pursued, the overall picture is quite discouraging. Only a handful of companies have reasonably secure programs of any size. In fact, of the five leading global vaccine manufacturers, only two (Pasteur-Merieux-Connaught and Chiron) have broad based HIV vaccine programs that are pursuing a number of approaches. Merck & Co. has what appears to be a substantial program, but, after earlier discouragement, it is currently focused on only a single approach. The remaining two companies (SmithKline Beecham and Wyeth Lederle) have insignificant HIV vaccine programs. The smaller biotech companies have programs that are largely limited to a single scientific approach. While these programs must be actively supported, there is no reason to believe they will continue if the approach being pursued proves unsuccessful.

In short, very few companies are making a sustained, comprehensive investment in HIV vaccine development.

To date, industry investment has focused largely on the subunit approach -gp160, gp120 or other HIV proteins. Other approaches being pursued include DNA vaccines (also known genetic immunization), live vector strategies and peptide vaccines. Overall, HIV DNA vaccines appear to be the single approach which has attracted significant private investment capital. A few HIV vaccine approaches are being studied in combination. One notable example is the ALVAC canary pox vaccine, manufactured by Pasteur-Mérieux Connaught, used in combination with a gp120 vaccine, produced by Chiron, as a boost. Unfortunately, this NIAID-facilitated collaborative effort is the exception rather than the rule.

OBSTACLES TO PRIVATE SECTOR INVESTMENT

Questions about the scientific feasibility of making an HIV vaccine, given current knowledge, emerged as by far the most important reason for limited private sector investment in the field. Defining and addressing such questions must be a responsibility of both government and industry. In addition to its traditional role as funder of exploratory science, government must support research that seeks to answer specific scientific questions which, when answered, will nourish private sector efforts. Other commonly noted reasons for limited industry involvement include liability concerns and the opportunity costs of HIV vaccine research compared to development of other products with a shorter and more certain development timeline. Interestingly, smaller biotech companies viewed liability concerns as a significantly greater worry than large pharmaceutical companies. The threat of price controls and concerns about market size did not emerge as major constraints.

INCENTIVES TO PRIVATE SECTOR INVESTMENT

Direct funding from government to stimulate HIV vaccine research efforts was the most widely supported potential strategy to increase private sector scientific

Continued page 20

Copies of the full AVAC report may be ordered for $9.50 each. Please send a check to: AVAC, 2215R Market Street, #501, San Francisco, CA 94114, USA.

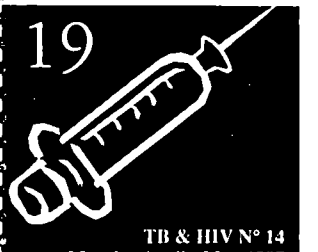
Vaccine advocate worries about too little emphasis on anti-HIV vaccine by governments

UNAIDS' new budget, as adopted by the governements sitting on the PCB, the management body, has no specific mention of "vaccines". Instead, vaccines come under the general label of 'strategies for the prevention of HIV', according to a vaccine specialist in Geneva. «To put vaccines in the same bin as microbicides - for example- is to me worrisome, he said.» «Furthermore, if international AIDS research did put a lot of emphasis on microbicides, notably in the USA, and more often than not, considered it "politically correct" to treat it as if it were a sort of "vaccine", latest data indicate that not many hopes should be placed on those preventive technologies. We know today that the data on microbicides is really NOT encouraging.»

Nonoxynol 9 doesn't work to prevent HIV. Cameroon N-9 Film Study

The Cameroon Nonoxynol-9 (N-9) Film Study was a randomized, controlled clinical trial to evaluate the safety and effectiveness of an N-9 containing film when applied vaginally for the prevention of HIV in female sex workers

Continued page 20



(prostitutes) in Cameroon. Women who consented to be enrolled into the study were given either the N-9 containing film or a placebo (no N-9) film. All volunteers were periodically counseled on safe sex practices and supplied with condoms. The volunteers maintained coital logs of how often they had sex, with whom, and whether condoms and/or film was used. The volunteers and study staff were blinded as to whether the N-9 film or placebo film was being used. The target sample size was 1000 women (500 each group). This would provide a 90% power to detect whether the film was 50% effective in preventing HIV infection. The study endpoints were HIV infection and vaginal lesions, which were determined by HIV antibody tests and vaginal colposcopic exams at monthly intervals, respectively. Transmission rates were based on crude rate ratios and Kaplan-Meier estimates.
After screening for HIV infection, pregnancy and other disqualifying factors, 1292 women were enrolled in the study and were eligible for analysis. Of these, 941 completed 12 months of follow-up and 351 (27%) did not. (...)
Conclusion :
The N-9 film was not effective in preventing HIV transmission in this group of female sex workers in Cameroon. There was a non-statistically significant increase in the rate of genital lesions which was not associated with an increase in HIV transmission. The N-9 film had no effect on preventing transmission of gonorrhea or chlamydia.

Industry Investment in HIV Vaccine Research • *Chris Collins*

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research. Faced with difficulty in obtaining private financing and significant scientific uncertainty, it is not surprising that direct contracting from government is attractive to industry. This idea has appeal because it would allow government to identify gaps in research and strategically fill those gaps by utilizing private sector expertise as well as investigator initiated research. It is also a model which has some precedent in the United States and abroad.
Other potential government actions receiving broad support from industry leaders and researchers were: tax deductions and credits for HIV vaccine development costs, better coordination of research efforts, assistance in securing animal models, and guaranteed purchase of approved vaccines. The need for leadership in the overall HIV vaccine research effort was consistently cited by industry researchers. An increase in the priority given to the development of an HIV vaccine by government and the public at large was proposed as a potential influence on internal company funding decisions, even in the absence of other incentives.
This report and the recommendations that follow are an attempt to fully engage private sector resources in the effort to develop an HIV vaccine. Working in partnership, industry, government, community based organizations, and the public has the potential here and now to save literally tens of millions of lives.

"HIV-Resistant Kenyans Spur Vaccine Hopes"

Washington Times (02/14/97) P. A13; Orr, David

A group of about 40 prostitutes in Majengo, Kenya, who are apparently resistant to HIV infection, are providing clues to researchers hoping to develop an AIDS vaccine. Researchers from the University of Nairobi, the University of Washington, the University of Manitoba in Canada, and Oxford University are collaborating to map the women's genes in an attempt to uncover what offers them protection from the virus. "We are taking blood from the HIV-negative women and their relatives, as well as from some women who have tested positive," says Dr. Ephantus Njagi of Majengo's clinic for sex workers.

"High-Powered Support for AIDS Vaccine"

Science (02/21/97) Vol. 275, No. 5303, P. 1055

The National Institutes of Health's new vaccine committee, chaired by Nobel laureate David Baltimore, met for the first time on Feb. 17 to discuss topics ranging from the 1998 budget to the possibility of creating an AIDS vaccine institute. The 11-member committee was joined by NIH director Harold Varmus; Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases; and Richard Klausner, who heads the National Cancer Institute. Baltimore noted that by appearing at the meeting, the directors demonstrated "great interest in seeing the vaccines move to a very prominent position in the AIDS program."

Immunologist Barry Bloom, of the Albert Einstein College of Medicine, noted that it is important for Baltimore to "persuade industry that it [a vaccine] is important enough to work on. He has to work with Congress and the regulatory agencies to find appropriate incentives for industry to do what they do best, without losing money for their shareholders."

Source: CDC Daily Summary

"Opinion : Clearing the Way for an AIDS Vaccine"

The recent appointment of Nobel laureate Dr. David Baltimore to head the United States' AIDS vaccine effort is not likely to solve the problems stalling this program, claim Bruce G. Weniger and Max Essex in a New York Times commentary. Weniger sits on the Presidential Advisory Council on HIV and AIDS, and Essex is chairman of the Harvard AIDS Institute. The authors point out that AIDS vaccine research receives less than 10 percent of the National Institutes of Health's AIDS budget and that the vaccine effort lacks an experienced senior official whose job is dedicated to vaccine development. Furthermore, they claim that the government's decision not to conduct human vaccine trials in 1994, despite approval from the NIH's vaccine advisory panel and $100 million of industry investment over eight years, virtually halted vaccine research in the industry. A single-purpose organization, led by an experienced vaccine scientist in close contact with industry, should lead the vaccine effort, Weniger and Essex contend.

Source: CDC Daily Summary

TB & HIV

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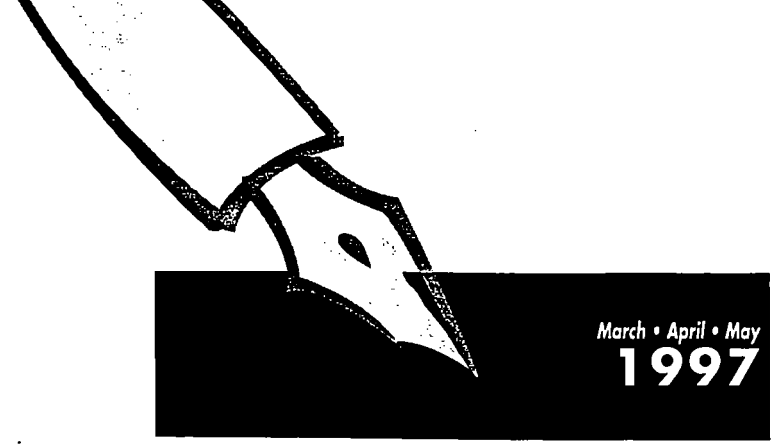
ISSN 1157 - 5042 - Commission paritaire 76 128 GC
TB & HIV is a quarterly
published in English by SidAlerte Internationale



Clinton Presidential Records
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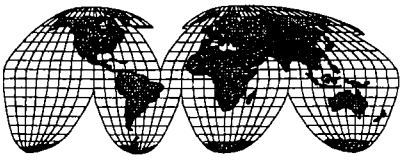
Publications have not been scanned in their entirety for the purpose of digitization. To see the full publication please search online or visit the Clinton Presidential Library's Research Room.

NCIH National Council for International Health



AIDSLink

A new global priority

Mobilizing for an AIDS Vaccine

By Sam Avrett, International AIDS Vaccine Initiative

In February 1997, in the United States "State of the Union" address, US President Bill Clinton referred to a national priority of making the U.S National Institutes of Health (NIH) a "powerful discovery engine" for a preventive HIV vaccine. On May 18, at the Morgan State University Commencement Address, President Clinton expanded this promise by announcing a new AIDS vaccine research center at the NIH and pledging to further mobilize the US pharmaceutical industry and, through the G7 Summit, other national governments to this effort.

This increased focus in the United States follows increasing international attention to the need for preventive HIV vaccines, heard at the XI International Conference on AIDS in Vancouver and through organizations such as the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the International AIDS Vaccine Initiative (IAVI).

What does this increased attention and effort toward HIV vaccine development really mean? Should developing an effective HIV vaccine be an international priority? What are the specific actions that need to be taken? And what are the implications for governments, industry, non-governmental health organizations, and affected communities?

The reason that HIV vaccine research and development must be an international priority for all governments, non-governmental agencies, and communities is that an HIV vaccine is both possible and necessary, and will not happen without international collaboration.

Scientific data is promising

Scientific evidence, including protection of vaccinated monkeys from SIV, the examples of control or clearance of HIV from newborns, long-term nonprogressors, and exposed-but-uninfected individuals, and the immune responses seen by current HIV vaccine candidates, all suggests that an HIV vaccine is possible. The recent successes of protease inhibitors show that even very difficult scientific challenges can be overcome with sufficient resources and talent.

Worldwide, more than 8500 people become infected with HIV every day, 90% of whom live in developing countries. Studies in several countries have shown that behavior change interventions, condoms, and access to clean needles can dramatically reduce HIV infection rates. But these methods are far from perfect; even with high quality counseling and access to prevention interventions, infection rates often remain above 2 per 100 people per year in research cohorts in Asia, Africa, and the Americas. Furthermore, many people may never have access to such counseling and interventions. A vaccine must be added as a tool for prevention.

HIV vaccine research and development can best be accomplished through a vast collaboration of researchers at universities, companies, government laboratories and community-based trial sites throughout the world. Much of the worlds current effort is funded from the U.S. National Institutes of Health and a few multinational pharmaceutical companies. Smaller sources of support

Continued on page 6

In this issue . . .

NCIH Global AIDS Network Newsletter #45

May/June 1997

11/8/97

Vaccine Basic Science

- live attenuated
- whole inactivated
- toxin-based
- subunit

Possible outcomes of vaccine

- complete blocking
- initial infection, then stop
- allow chronic infection, but forestall AIDS

Basic Research	Pre-Clinical Research	Clinical
Test Tubes	small animals	phases 1, 2, 3
Cells	non-human primates	
	~~	
	safe	
	immunogenic	
	protect?	

Immune Response

cellular immunity & CTL (killer T cells)
neutralizing

Vaccine (2)
11/8/97

conformational epitopes

adjuvants – enhance immune response to vaccine

Timeline

PreClinical	3-5 years
Clinical	7-10 years
Overall	10-15 years

$100-200 Million

Stark – '92 – no-fault vaccine bill – never made it out of committee

HIVNET			
Site	**Location**	**Studies**	**Study Population(s)**
Bronx-Lebanon Hospital	New York, NY	Vaccine Preparedness Study	IDU, WAHR
Denver Department of Public Health	Denver, CO	Phase II Vaccine Trial Behavioral Intervention Trial for MSM - Project EXPLORE	MSM
Fenway Community Health Center	Boston, MA Providence, RI	Phase II Vaccine Trial Behavioral Intervention Trial for MSM - Project EXPLORE Expedited Post-Exposure Chemoprophylaxis (PEP)	WAHR, MSM
Howard Brown Health Center	Chicago, IL	Phase II Vaccine Trial Behavioral Intervention Trial for MSM - Project EXPLORE Expedited Post-Exposure Chemoprophylaxis (PEP)	WAHR, MSM
Johns Hopkins University	Baltimore, MD	Vaccine Preparedness Study	IDU
Health Research Association	Los Angeles, CA	Vaccine Preparedness Study	MSM, WAHR
New York Blood Center	New York, NY	Phase II Vaccine Trial Behavioral Intervention Trial for MSM - Project EXPLORE Expedited Post-Exposure Chemoprophylaxis (PEP)	MSM, WAHR
New York University Medical Center	New York, NY	Phase II Vaccine Trial	IDU
San Francisco AIDS Office	San Francisco, CA	Phase II Vaccine Trial Behavioral Intervention Trial for MSM - Project EXPLORE Expedited Post-Exposure Chemoprophylaxis (PEP)	MSM
University of Pennsylvania	Philadelphia, PA	Phase II Vaccine Trial	IDU
University of Washington	Seattle, WA	Phase II Vaccine Trial Behavioral Intervention Trial for MSM - Project EXPLORE Expedited Post-Exposure Chemoprophylaxis (PEP)	MSM

[1] MSM = Men who have sex with men
WAHR = Women at heterosexual risk
IDU = Injection drug users

The AIDS Vaccine Advocates Forum

Community Education

Presented by

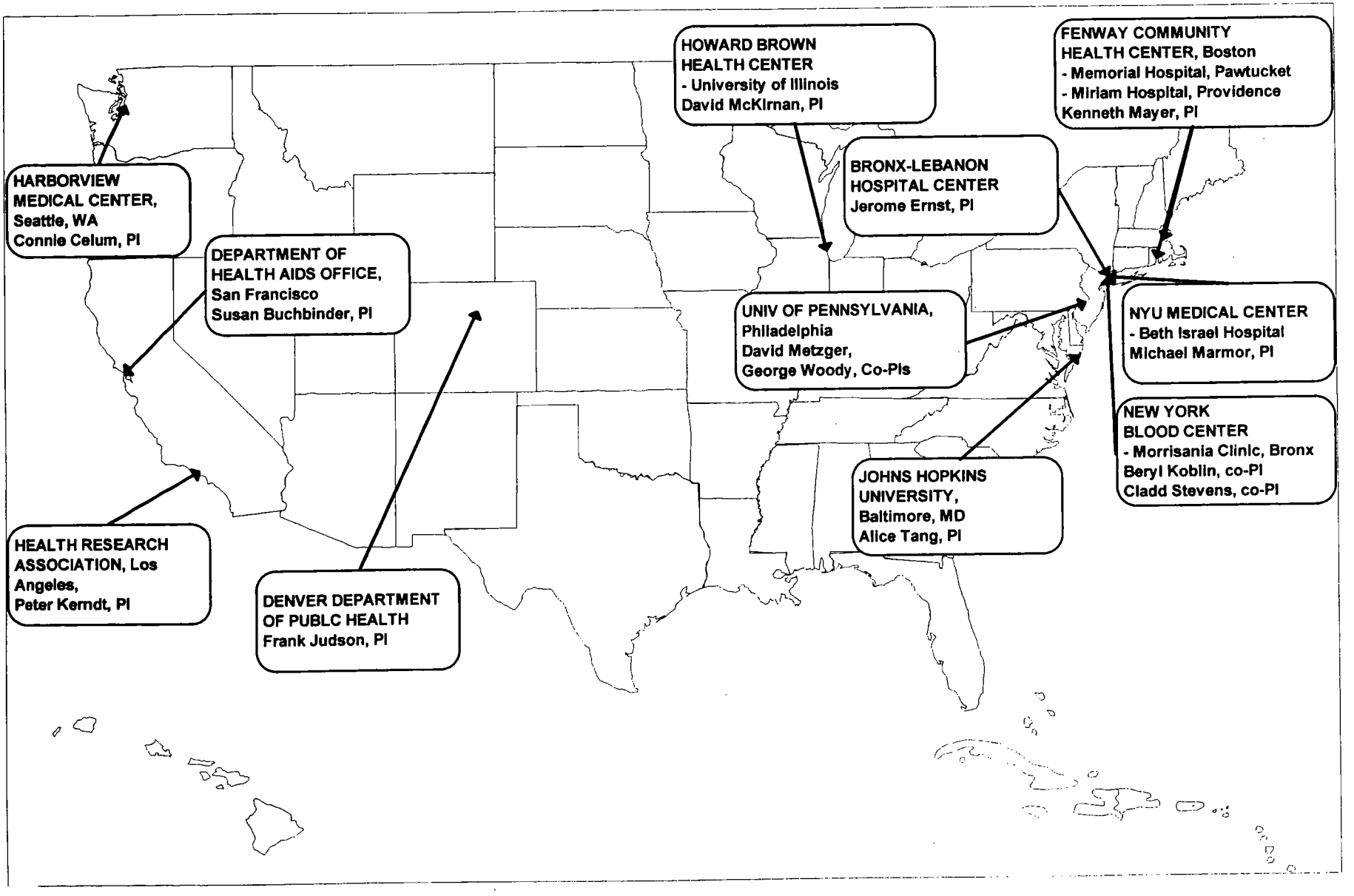
Joy Workman
National Community Education Coordinator
HIV Network for Prevention Trials (HIVNET)
Abt Associates Inc.

November 8, 1997
Handlery Hotel
San Diego, CA

HIV Network for Prevention Trials
HIVNET

A network of research study sites established to evaluate the safety and efficacy of multiple HIV prevention strategies.

HIVNET Domestic Field Sites



HIVNET Structure and Governance

HIVNET was established by a group of related contracts with the Division of AIDS of the National Institute of Allergy and Infectious Diseases. There are five "prime contractors" that perform the work of managing HIVNET.

- The Domestic Master Contractor is Abt Associates Inc. All of the study sites in the United States are subcontractors to Abt Associates Inc., and Abt oversees their participation to ensure consistency and quality of the research.
- The International Master Contractor is Family Health International, which subcontracts with study sites outside the United States and oversees their participation.
- The Statistical Center is operated by the Fred Hutchinson Cancer Research Center and the University of Washington. This center is responsible for collecting and analyzing the information obtained from HIVNET research, and helps coordinate the research at the sites.
- The Central Laboratory is operated by the Viral and Rickettsial Disease Laboratory of the California Department of Health Services, and provides medical testing services for HIVNET sites.
- The Repository Contractor is Biomedical Research, Inc., which provides very low temperature storage for biological specimens collected for HIVNET studies.

All five contractors, all of the subcontract study sites, and national and local CAB representatives work closely with staff from the Division of AIDS in the overall operation of HIVNET. Each of these groups is represented on the HIVNET Scientific Steering Committee, which provides scientific management of HIVNET. In addition to the Steering Committee, there are research teams that:

- propose, develop, and evaluate ideas for new research studies;
- regularly review the information obtained from ongoing studies to ensure the safety of participants and evaluate the progress of the studies; and
- prepare the information obtained from studies for publication in medical and scientific journals.

Membership on these teams is mostly determined by the function of the team. CAB representatives are involved in all facets of HIVNET governance, and are closely involved in the development of new research studies and in the review of information from ongoing studies. CAB representatives also serve as liaisons to the community for information exchange about HIVNET studies.

Representatives of relevant, local communities should be full participants in planning, implementing, and overseeing vaccine efficacy trials. Vaccine design and implementation must take into account both individual and community concerns, and must acknowledge the differential impact of HIV disease on certain communities.

— AIDS Action Foundation
HIV Preventive Vaccines: Social, Ethical, and Political Considerations for Domestic Efficacy Trials

Investigators and trial sponsors must forge links with community-based organizations (CBOs), at the national and local levels that serve or represent members of target populations.

— AIDS Action Foundation
HIV Preventive Vaccines: Social, Ethical, and Political Considerations for Domestic Efficacy Trials

Public fora should be held to discuss the ethical, scientific, and social issues of HIV vaccine trials.

— AIDS Action Foundation
HIV Preventive Vaccines: Social, Ethical, and Political Considerations for Domestic Efficacy Trials

Mission Statement
Community Educators' Group (CEG)

The mission of the community educators' group is to support the responsible and effective conduct of community-based HIV prevention trials. The ongoing task of the CEG is to develop and implement community education strategies designed to address community relations, increase community awareness, and facilitate community participation in the design and development of vaccine research. To accomplish this, the CEG ensures that key constituency groups are informed about HIV prevention vaccine research, new movements and trends in HIV prevention, scientific concerns in the design of clinical trials, and the overall efforts of the HIV Network for Prevention Trials (HIVNET).

Community Education Framework

collaboration

Awareness ➡

- Build knowledge about HIV prevention
- Build knowledge about research/clinical trials
- Build knowledge about vaccines and vaccine research

collaboration

Willingness ➡

- Build willingness to hear messages
- Build willingness to participate (training, workshops, seminars presentations, and forums, etc.)
- Build motivation to advocate and move messages (constituency conferences, etc.)
- Build framework for community informed consent

collaboration

Readiness/Preparedness

- Empowered community engagement
- Readiness for large scale phase III trial (recruitment/enrollment)
- Individual and community advocates

A p p r o a c h

Challenges at each stage:

- Social/Political climate
- Economic resources
- Leadership
- Time

Abt HEALTHWATCH

SUMMER
1996
VOLUME 1
NUMBER 4

A Quarterly Publication of the Health Research and Consulting Practices of Abt Associates Inc.

PREVENTIVE HIV VACCINE TRIALS: INITIAL FINDINGS FROM THE FIELD

During the July 1996 International AIDS Conference in Vancouver, Abt researchers and their colleagues presented an array of new findings from studies fielded to prepare for large-scale trials of vaccines and other interventions designed to prevent transmission of HIV. To help guide planning for such trials, these findings profile current risk behaviors among some of the US populations at greatest risk of infection with HIV and assess prospective participants' interest in joining trials of HIV preventive vaccines and other biomedical interventions.

Abt Associates — under contract with the National Institute of Allergy and Infectious Diseases (NIAID) — managed the selection process for eight domestic clinical trial sites and now monitors their performance as part of the HIV Network for Prevention Trials (HIVNET), the platform to be used to test HIV vaccine efficacy when such vaccines are available for testing. Components of HIVNET, other than Abt and its clinical sites are: Family Health International and its nine international sites, a Statistical and Clinical Coordinating Center at the Fred Hutchinson Cancer Research Center in Seattle, and a Central Laboratory at the California Department of Health Viral and Rickettsial Diseases Laboratory in Berkeley.

While early phases of clinical vaccine research proceed, preparatory studies are providing information that will be essential in recruiting and retaining suitable high-risk cohorts, while at the same time providing a framework for controlled trials of non-vaccine prevention interventions, should the next generation of candidate vaccines fail to live up to current expectations. At this time, promising candidate vaccines furthest along in development are slated for trials in 1998.

Within six months, the field sites exceeded their combined recruitment target of 4,800 participants (a remarkable achievement for a new multi-site clinical trial network); six months of follow-up has been completed for the entire cohort, with a retention rate close to 95 percent. Approximately two-thirds of the participants are gay/bisexual men, one-fourth male and female injection users, and the remaining 10 percent are women at risk of exposure through heterosexual intercourse. Nearly 40% are non-white.

These cohorts will be followed for a total of 18 months, at which time they may be invited to participate in one or more HIV prevention trials, including a possible vaccine efficacy trial. Although the brief duration of follow-up makes any estimate of the rate of new HIV infections very uncertain, the observed rate thus far approaches two per 100 person-years, or two percent per year. This rate would make feasible the implementation and timely completion of field trials of the efficacy of HIV vaccines or other prevention interventions where the outcome criterion is a measurable impact on the rate of new HIV infections among high risk populations.

With regard to cohort risk behavior in the six months prior to enrollment, Abt presentations at the Vancouver meeting reported that:

- Among men who have sex with men, one-fifth acknowledged that, when they were the receptive partner for anal intercourse, their partner never used condoms. Seventeen percent of men who used condoms cited at least one episode of failure (breakage, slippage or both).

PREVENTIVE HIV *continued on page 2*

- Among drug injectors, half reported at least two injections of heroin per week in the six months prior to enrollment, and almost one-fourth reported at least daily heroin injection. More than one-third said they shared needles, and more than half said they usually shoot up with others. Although 62 percent said they used needle exchange programs, 57 percent continued to obtain needles on the street.
- Among women at risk through heterosexual contact, half reported having had multiple partners.

A key question about these high risk populations is whether they would enroll in clinical trials of vaccines and other HIV prevention interventions. Participants were recruited without assurance that they would be enrolled in field trials of vaccines or any other HIV prevention interventions. Nevertheless, irrespective of risk group, approximately three-fourths of volunteers indicated they would probably (50%) or definitely (27%) be willing to participate. The most important motivators, cited by almost three-fourths of study participants, were to help find a vaccine or stop the epidemic.

Despite the high level of interest in vaccine trials, this cohort revealed a need for substantial education related to HIV vaccines and clinical trial methods. On a 14-item knowledge assessment focused on fundamental concepts a volunteer would need to understand, less than 10 percent scored 80 percent or higher. Even before these data became available, investigators began working on a model informed consent form and protocol, and a strategy for evaluating its impact. Abt staff provided substantial leadership in the development of the model consent document and the design of procedures for explaining vaccines and vaccine trial concepts to a heterogeneous population, among whom one-third had no formal education beyond high school. When participants in this mock informed consent procedure were re-evaluated on a more demanding 23-item knowledge assessment, more than 40 percent achieved scores of 80 percent or above.

The clear conclusion — that a volunteer spirit is strong but a substantial effort must be made to broaden the knowledge base regarding vaccines and clinical trial concepts — has been underscored by feedback Abt staff have received during extensive interactions with members of Community Advisory Boards (CABs) established at each site. In forthcoming months, this mission will become an increasingly important element in preparation for future HIV prevention trials.

Please submit requests for more information via email to michael_gross @abtassoc.com.

SELECTED HIV/AIDS PUBLICATIONS BY Abt STAFF

Amato D. The Design and Analysis of Equivalence Trials. In: AIDS Clinical Trials, eds. Finkelstein M and Schoenfield D. John Wiley and Sons, Inc. p155-176. 1995.

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Hammett T. HIV/AIDS in Prisons and Jails: The U.S. Experience. In: AIDS in Prisons, ed. Thomas P. Dartmouth Press, Aldershot England, 1994.

Leighton C. Direct and Indirect Costs of HIV/AIDS. In: AIDS in Kenya: Socio-Economic Impacts and Policy Implications. AIDSCAP, Family Health International. p65-84. June 1996.

Epstein A, **Seage G**. Weissman J, Cleary P. Costs of Medical Care and Out-of-Pocket Expenditures for Persons With AIDS in the Boston Health Study. Inquiry 32(2): 211-221. Summer 1995.

For more information contact Liz_arriaza@abtassoc.com.

DOMESTIC CLINICAL SITES	AT RISK POPULATION(S)
Denver Department of Public Health	Men who have sex with men
Fenway Community Health Center, Boston Memorial/Miriam Hospitals, Rhode Island	Men who have sex with men Women at risk through heterosexual contact
Howard Brown Health Center, Chicago Cook County Hospital / University of Illinois at Chicago	Men who have sex with men Women at risk through heterosexual contact
New York Blood Center (Manhattan, Brooklyn) Morrissania STD Clinic (Bronx)	Men who have sex with men Women at risk through heterosexual contact
New York University Medical Center	Injection drug users
San Francisco Department of Public Health	Men who have sex with men
University of Pennsylvania, Philadelphia	Injection drug users Women at risk through heterosexual contact
University of Washington, Seattle	Men who have sex with men

The HIV Vaccine Advocates Forum

Saturday, November 8, 1997 - Handlery Hotel, San Diego, CA

Sponsored by the AIDS Vaccine Advocacy Coalition (AVAC)
as a satellite forum to the National AIDS Treatment Advocates Forum (NATAF)
and supported by
Until There's A Cure Foundation ♦ International AIDS Vaccine Initiative ♦ American Foundation for AIDS Research

The goal of this meeting is to allow community advocates to become more informed and updated about HIV vaccine research and development, connect with other advocates, and incorporate vaccine research issues into ongoing advocacy and community education efforts. This meeting will run from 9:00am to 5:00pm.

Agenda

Saturday, November 8

9:00 - 9:30am	*COFFEE (plus breakfast buffet and sign-in)*
9:30 - 10:00	**Introduction** Helen Miramontes, UCSF Bill Snow, AVAC
10:00 - 11:00	**Vaccine Basic Science** Mary Allen, DAIDS Gregg Gonsalves, TAG Jane Silver, AmFAR DISCUSSION - supporting basic research and targeted research
11:00 - 12:00	**Product Development** David Gold, Moderator Sam Avrett, IAVI Lori Hansen, Chiron Vaccines Adrian Marinovich, AVAC DISCUSSION - supporting development of candidate HIV vaccines
12:00 - 1:00pm	*LUNCH (provided by AVAC)*
1:00 - 2:20	**Testing HIV Vaccines** - a review of on-going and planned vaccine trials Karen Charron, Abt Associates Debbie Birx, WRAIR **Testing HIV Vaccines** - perspectives from research participants "We All Have Our Reasons" video DISCUSSION - US and international issues regarding clinical trials
2:20 - 2:40	*BREAK*
2:40 - 4:00	**Community Education** Steve Wakefield, AVAC Joy Workman, Abt Associates Andrew Fullem, FHI **CABs and Role of Community** Pamela Brown-Peterside, Bronx HIVNET Site Chris Collins, AVAC DISCUSSION- supporting community involvement and education
4:00 - 5:00	**Wrap-Up Session** - planning community advocacy for HIV vaccines
after 5:00	Registration for the National AIDS Treatment Advocacy Forum (NATAF)

Forum Evaluation

NATIONAL AIDS VACCINE ADVOCATES FORUM

Please take a couple of minutes to tell us about your overall conference experience. Your feedback will greatly assist us in our future conference planning.

Please rate each conference criteria by circling a number from 1 to 5 where:
1 = Poor 2 = Fair 3 = Good 4 = Excellent 5 = Outstanding

OVERALL EVALUATION	Poor	Fair	Good	Excellent	Outstanding
1. Overall Learning Experience	1	2	3	4	5
2. Overall Networking Experience	1	2	3	4	5
3. NATAF Program Format	1	2	3	4	5
4. Expertise of Presenters (overall rating)	1	2	3	4	5
5. Registration Procedures	1	2	3	4	5
6. NATAF Staff	1	2	3	4	5
7. NATAF Program Book	1	2	3	4	5
8. Exhibit Area	1	2	3	4	5
SPECIFIC EVENTS/SESSIONS					
9. Welcome Luncheon	1	2	3	4	5
10. Networking Reception	1	2	3	4	5

GENERAL COMMENTS

11. How well did the conference meet your professional needs? _____

_____

_____

12. Would you recommend this conference to your colleagues? Yes No
13. Will you attend the 1997 conference? Yes No
14. What aspects of the conference were particularly beneficial? _____

_____

_____

15. What aspects of the conference would you change? _____

_____

16. Can we quote you? Yes No
17. Should NATAF except pharmaceutical industry funding? (We have not in the past.) Yes No Why/Why Not? _____

_____

18. Additional comments (use other side if necessary):

_____

(OPTIONAL)

Name _____ Affiliation _____

Please return the completed evaluation form to the registration area or fax to NATAF at 202-483-1135 by November 21, 1997

THANK YOU FOR YOUR COOPERATION

helenmm @ itsa.ucsf.edu
08/26/97 02:47:00 PM

Record Type: Record

To: Daniel C. Montoya, Sandra Thurman

cc:
Subject: Vaccines - 3rd Draft

Disregard the first email - It wasn't complete - this is the 3rd draft

DRAFT #3
8/26/97

PACHA RECOMMENDATIONS FOR ACHIEVING THE AIDS VACCINE GOAL

1. BASIC SCIENCE

As the world's premier biomedical research agency, it is appropriate for NIH to continue its essential role in promoting the basic research in virology, immunology, and related sciences which provides the knowledge base for vaccine development.

NIH plans to establish a dedicated AIDS Vaccine Center are commendable. It is unclear, however, whether its new director will have the requisite experience in vaccine product development and the necessary resources and authority. The bulk of designated "AIDS vaccine" funds may remain under existing structures and mechanisms which are diffuse and unaccountable in identifying responsibility for achieving the AIDS vaccine goal. Therefore:

* The director of the new NIH Vaccine Research Center should be an accomplished scientist with experience in developing vaccines.

* The director should have full responsibility, in consultation with appropriate advisory bodies, to manage, allocate, and prioritize all NIH funding that is designated "AIDS vaccine" research.

* The NIH must substantially increase the proportion of its total AIDS research funds allocated to vaccines.

2. PRODUCT DEVELOPMENT

Product development must be differentiated from basic scientific research. Product development is the translation of promising concepts from laboratory and animal experiments to actual vaccine products approved by the FDA for human testing. There is a serious lack of candidate AIDS vaccines in the "pipeline" to test in clinical trials, and it is imperative to overcome this bottleneck. Product development may require the government to subsidize private industry, to commission targeted applied research, and to address a host of related issues, such as intellectual property rights, financial incentives for the government vaccine purchase market, international vaccine development and purchase funds, tax rebates, patent extensions, and liability issues. The existing system of basic scientific research within NIH is not structured to address these issues. Therefore:

* The Vice President should meet privately with interested biotechnology and pharmaceutical firms - to hear their candid assessments of obstacles to their investment in AIDS vaccine product development and discuss suggestions as to how the government can assist the effort.

* The White House should oversee the preparation and implementation of a comprehensive plan to address AIDS vaccine product development. This plan should address: (1) relationships with and roles for other major industrialized nations (e.g., the G-7), UNAIDS, and non-governmental organizations such as IAVI; (2) funding and financial incentives; (3) management controls; (4) regulatory issues; (5) intellectual property rights; (7) liability issues, and (8) government-sponsored product field testing through expanded involvement of all appropriate government agencies (e.g., NIH, DOD, CDC).

3. PRELIMINARY CLINICAL TRIALS

The NIH has an effective domestic network to conduct small-scale, clinic-and hospital-based preliminary (phase I and II) human trials of candidate AIDS vaccines for safety and immunogenecity, and has successfully tested a number of such products. These sites, however, have been underutilized due to the lack of candidate AIDS vaccines.

* NIH should continue to maintain its capacity to conduct the early clinical phase I and II trials of AIDS vaccines.

4. LARGE SCALE FIELD TRIALS

Candidate vaccines which have completed phase I and II trials are not advancing to the definitive large-scale (phase III) field trials to determine potential efficacy. To achieve the vaccine goal, multiple, simultaneous field trials of various candidate vaccines should be conducted

concurrently, not waiting for the results of one before starting others. Many such trials will likely occur in developing countries, where the incidence of new infection is much higher, and where governments cannot afford expensive drug treatments after infection occurs.

It is widely acknowledged that no single agency has the expertise, capacity, and resources to do everything - conduct the necessary basic research, work with industry to develop many vaccine candidates, and evaluate multiple vaccines in large scale community-based field trials, both nationally and internationally. In addition to NIH, other agencies such as the CDC, DOD, and USAID have extensive experience and expertise in field epidemiology, surveillance, the conduct of vaccine efficacy trials, especially in developing countries. Although all agencies have a common goal of HIV prevention, each has its own "comparative advantage" due to their unique mission, strengths, and opportunities provided by their collaborating institutions. In addition, DOD and CDC currently have several long-term overseas field research infrastructures operating under government-to-government agreements with foreign Ministries of Health and institutions. These ongoing field research stations would provide tremendous capacity for the long and repeated international vaccine trials which may extend over decades. Therefore, as we proceed to large scale field efficacy trials, it is imperative that the following recommendations are implemented:

* All three agencies, NIH, DOD, and CDC, must be involved in conducting large scale Phase III AIDS vaccine field efficacy trials, working with diverse vaccine manufacturers. This task will require interagency collaboration which will be essential in achieving the mandate of an AIDS vaccine.

* The White House should convene a meeting of relevant federal agencies (1) to inventory and present their institutional expertise, capabilities, and resources for applied vaccine research and product development (basic research should not be the focus of this meeting); (2) to obtain commitments of priority and resource allocation to help achieve the President's AIDS vaccine goal; and (3) to establish mechanisms of communication, cooperation, and collaboration among the various agencies.

* The White House should convene a meeting of the leadership of relevant federal agencies and representatives from the international community involved in AIDS vaccine development, to include UNAIDS, IAVI, and the World Bank. The purpose of this meeting would be to establish mechanisms of communication, cooperation, and collaboration between our own efforts and those of the international community in terms of AIDS vaccine development and testing.

THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

FEB 13 1997

MEMORANDUM FOR THE PRESIDENT

ISSUE:

Whether to issue a Presidential message on the Government's responsibility for the Tuskegee Syphilis Study to the surviving participants, their families, and the African American community.

BACKGROUND:

In 1932, Federal, State, and local officials, working with the Tuskegee Institute, began a long-term study of untreated syphilis in African-American males in Macon County, Alabama. The Study was established after surveys revealed a high prevalence of syphilis, particularly in rural areas of the South, and a high rate of untreated syphilis in African-American men. The Study was intended to justify a syphilis treatment program for African-Americans. Instead, it has become known as a classic case of medical research gone wrong.

That is because researchers enrolled about 400 African-American men with non-infectious syphilis and about 200 men without syphilis (the latter group for control purposes) in the Study and told them they were being treated for "bad blood" -- a local term used to describe a number of conditions, including syphilis. Men with infectious, early stage syphilis were treated and excluded from the Study; however, those with late term, non-infectious syphilis received no treatment and none was available at the time the Study was begun. Researchers actually were observing the natural progression of untreated syphilis in their bodies.

The project was scheduled to last for only six months, but it continued for 40 years -- even after penicillin became recognized as the standard of care for treating syphilis by the late 1940s. The Study was not ended until 1972, when a front-page story in the New York Times led to a public outcry and the government convened an advisory panel that declared the Study to be "ethically unjustified."

The Federal Government has tried to mitigate the damage since the study was ended. In 1973, HEW Secretary Weinberger directed the Public Health Service to provide Study participants and certain members of their families with comprehensive medical care for the

rest of their lives. Also, in 1973, a class-action lawsuit was settled for $9 million. And, beginning in 1974, regulations for review and approval of experiments on human subjects were instituted to ensure that studies such as Tuskegee do not happen again:

- Since 1974, we have better instituted in research on human beings the practice of obtaining their voluntary informed consent.

- Also since 1974, all Federal studies using human subjects must be reviewed by Institutional Review Boards (IRBs) that are diverse and sensitive to community attitudes.

- In 1995, you created a National Bioethics Advisory Commission to review regulations and procedures, and to provide all possible safeguards for research volunteers.

- A 1996 meeting sponsored by the Centers for Disease Control and Prevention and HHS led to the establishment of the Tuskegee Syphilis Study Legacy Committee, which studied ways to preserve the memory of the Study and to transform the legacy into renewed efforts to bridge the gap between the health conditions of African-Americans and white Americans.

Even so, the Federal Government has never adequately expressed its responsibility for failure to inform Study participants and their families when treatment became available. Many commentators believe that the government's failure to make such an acknowledgment has helped to perpetuate feelings of widespread distrust among African-Americans toward government health-related initiatives. For example, African-Americans are far less likely than any other ethnic group to receive influenza vaccines (33.1 percent in 1993, compared to 50.4 percent for the total population). Similar low participation rates among African-Americans also are evident in research trials, organ donation, accessing simple medical care, and accepting advice from public health officials regarding the prevention of diseases such as AIDS. Even though there are many complex reasons for these low participation rates, the Tuskegee Study is cited as one significant contributing reason.

CURRENT ACTIVITIES INVOLVING THE TUSKEGEE STUDY

The Tuskegee Syphilis Study Legacy Committee has urged you to make an apology, and has issued a number of recommendations that would help assure the nation that research like the Tuskegee Study would not be duplicated.

You received last week a letter from two members of the Congressional Black Caucus -- Representative Louis Stokes, the Chairman of the Congressional Black Caucus Health Braintrust, and Representative Maxine Waters, Chairwoman of the Caucus -- requesting that you issue a formal apology on behalf of the United States for the Tuskegee Study, similar to the apology you issued to the so-called "atomic veterans." They note that Black History Month would be "a most appropriate time" to issue such a statement.

Home Box Office has produced a movie about the Tuskegee Study, entitled "Miss Evers' Boys," that is expected to receive substantial attention throughout the month of February, which is National African American History Month. Between February 11 and February 18, public screenings of "Miss Evers Boys" will be held in seven cities across the country -- Washington, New York, New Orleans, Los Angeles, Atlanta, Stamford, and San Francisco. The screenings and ensuing panel discussions will be attended by prominent African-American officials, including United Negro College Fund President William H. Gray III, Charles Drew University President Reed Tuckson, Former HHS Secretary Louis Sullivan, Emory School of Public Health Dean James Curran, Atlanta Journal-Constitution Editor Cynthia Tucker, "Our Common Welfare" Director Fay Brown-Sperling, and CDC Director David Satcher M.D. After the public screenings have been held, HBO will air the movie nationally on February 22.

There are eight participants of the Tuskegee Study still surviving, as well as 23 wives or widows, 15 children and two grandchildren.

RECOMMENDATIONS:

I recommend that you issue a statement similar to the one you made to atomic veterans -- one made on behalf of leaders from another time and era. You could either issue this statement as a written statement, or preferably, you could deliver it in person at an event coordinated to address participants and their families as well as African-American leaders.

In doing so, you would send a positive message that could help shift perceptions within the African-American community about medical research. You could add to your statement an announcement of additional steps you will take to further protect all human participants in research studies. Those steps would be as follows:

- Have HHS work with academic institutions and schools of public health to expand bioethics training, paying particular attention to minority perspectives and the needs of minority communities.

- Have HHS offer fellowships to postgraduate students for training in bioethics, with the goal of creating a national cadre of individuals -- especially minorities -- who would serve as experts in the conduct of research involving human subjects and as future leaders in the field of bioethics.

- Extend for two years the charter of the National Bioethics Advisory Commission, which you created, and ask it to explore ways in which communities -- particularly minority communities -- can become more involved in the development, implementation, and analysis of medical research. (There are other reasons currently under consideration for extending the Charter for two additional years).

DECISIONS

- Issue a Presidential message on the Government's responsibility for the Tuskegee Study to the surviving participants, their families, and the African American community.

  Approve_____ Disapprove_____ Other_____

- Additional steps could be taken with academic insitutions and schools of public health, researchers, and the National Bioethics Advisory Commission to further protect human participants in research studies:

  -- HHS would expand bioethics training that are diverse and sensitive to minority communities.

  -- HHS would offer fellowships to postgraduate students, including minorities, who would serve as experts in research involving human subjects and in the field of bioethics.

  -- Extend the charter of the National Bioethics Advisory Commission for two more years and ask it to explore ways to better involve minorities in the mechanics of medical rsearch.

Approve_____ Disapprove_____ Other_____

Donna E. Shalala

helenmm @ itsa.ucsf.edu
08/08/97 01:07:00 PM

Record Type: Record

To: Sandra Thurman

cc:
Subject: conversation with Bill Paul

I had a telephone conversation with Bill Paul, Director of OAR,NIH, this morning about the status of the AIDS Vaccine Center at NIH. This was just a preliminary exploration about what's going on and I asked him if he would be willing to speak later with the research committee. He suggested that the conversation take place after Congress returns and is back in session. That way we would have a better idea about the budget and also they (NIH) would be further along in the process of identifying a director for the vaccine center.

I'm going to briefly summarize our conversation.

BUDGET: The total NIH budget for an AIDS vaccine is 150 million - but most of that is distributed extramurally. The proposed 1997-98 budget has an overall increase for NIH and Congress may actually increase the % more then is in the Pres. budget (will know more later) so there would be an increase for vaccines. NIH does have the resources ($) for building the building for the Center. In the 1998 budget there will be up to 10 million to run the Center. Baltimore's group is the "over arching" group for the Center and will oversee use of those $.

The innovation grants (Fauci & Baltimore mentioned during April panel) - had 130 applications - expect that approx. 30 will be funded - will add resources if necessary.

Working on getting funds for FY99 in case they (NIH) decide to move ahead on the prime boost.

STRUCTURE: The vaccine center is the joint activity of NCI and NIAID. The Director of the vaccine center will report to Harold Varmus and the 2 Directors of NCI and NIAID. Supposedly the Center Director will have some autonomy. NIH AIDS vaccine efforts lacked coordination and the Center will address that lack. A steering committee of 6 NIH scientists has been established to set the agenda for the Center. The relationship of the Center to OAR is that the OAR will be providing the resources for the Center.

DIRECTOR: There is no list. A call has been put out. A search committee has been established and will meet next week to begin to identify potential candidates with appropriate expertise. Looking for a candidate with both vaccine research expertise and basic science expertise.

CONCEPTUAL: Center will take certain products and run through (push forward) (whatever that means). The simple paradigm of vaccine research not

working well for HIV. That simple paradigm is that inject something into the arm and something happens. Dr. Paul mentioned that this works for some diseases but not all. Considers this an old immunological idea. We have ignored advances in immunology.

STUDY SECTION; Issue not fully resolved as yet. Looking at whether to reflect all vaccine research or just AIDS vaccine research.

I believe that my summary reflects accurately the focus of our conversation. I'll be around if anyone has any questions or comments. Also I don't have email addresses for Debra or Ron Johnson, so I will FAX these comments to them.

take care,

helen

FAX TRANSMISSION

U.S. Department of Health and Human Services
Office of the Secretary

DATE: 9/26/97

TO: Daniel Montoya

FAX: 632-1090 **PHONE:** _____

FROM: **Victor Zonana**
Deputy Assistant Secretary for Public Affairs/Media
Phone: **(202) 690-6343**
Fax: **(202) 690-6247**

TOTAL NUMBER OF PAGES TRANSMITTED: 8

COMMENTS:

Vaccine awards — set up appt @ Johns Hopkins

File

Vaccine

HHS NEWS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOR IMMEDIATE RELEASE
Monday, Sept. 29, 1997

Contact: HHS Press Office
(202) 690-6343

HHS ASKS FOR COMMENTS ON RECOMMENDED DRUG TREATMENTS FOR INFANTS AND CHILDREN WITH HIV

HHS Secretary Donna E. Shalala today announced draft guidelines on tailoring the use of powerful antiretroviral drugs to treat infants, children, and adolescents with HIV. Developed by 64 specialists in pediatric HIV care, family members of HIV-infected children, and federal agency representatives, the proposed guidelines will be published in this week's *Federal Register* for a 30-day public comment period.

"These guidelines will fill an important gap in our knowledge by recognizing the unique treatment needs of infants, children and adolescents living with HIV," said Secretary Shalala. "With early testing and aggressive treatment, infected children will live longer, more normal lives." Last June, HHS and the Kaiser Family issued draft guidelines for antiviral treatments of adults with HIV. The final guidelines will be published shortly.

The guidelines were developed by the Working Group on Antiretroviral Therapy and Medical Management of HIV Infected Children, which was convened in July 1997 by the National Pediatric and Family HIV Resource Center.

The working group was co-chaired by Dr. James Oleske, University of Medicine and Dentistry of New Jersey, New Jersey

- More -

Medical School, and Dr. Gwendolyn Scott, University of Miami, Florida, and sponsored by the Health Resources and Services Administration (HRSA). HRSA is the Federal Agency responsible for providing access to HIV-related care through the Ryan White Comprehensive AIDS Resources Emergency (CARE) Act, a $1 billion a year program serving those who would otherwise be unable to receive treatment.

As most HIV infection in children is acquired by transmission of virus from mother to child, there are many unique issues for caring for children born to HIV-infected women. The majority of perinatal transmission occurs shortly before or during birth. The working group believes that by using sensitive viral tests, most infected newborns can be identified by one month of age, and virtually all by 6 months of age. HIV perinatal infection also occurs during the time that the infant's immune system is immature and developing. Consequently, how the disease manifests and progresses varies substantially from that of an adult. Disease progression appears more rapid among infected children than adults, and viral levels in the blood remain persistently elevated in many perinatally-infected children for prolonged periods. Therefore, most working group participants would initiate combination antiretroviral therapy in all HIV-infected infants under 12 months of age as soon as a confirmed diagnosis is established. The working group recommends that therapy be initiated with potent combination antiretroviral drug regimens similar to those recommended in infected adults. Two protease inhibitors (ritonavir and nelfinavir)

with pediatric formulations have recently been approved by the Food and Drug Administration for use in children.

According to Joseph F. O'Neill, M.D., M.P.H., Associate Administrator of HRSA's HIV/AIDS Bureau, an important concept in formulating these guidelines was that "appropriate treatment of HIV-infected infants depends upon the identification of HIV-exposed infants as soon as possible. Thus, it is critical to identify HIV-infected women before or during pregnancy, and it is critical that these women and their newborns receive care directed by health care providers with extensive experience in HIV care."

The panel also developed recommendations for treatment of older infants and children as well as adolescents. Group co-chair Dr. James Oleske emphasized, "adult guidelines are more appropriate for older adolescents, but youth in their growth spurt or younger may be more appropriately treated using the pediatric guidelines." Dr. Gwendolyn Scott, the second chair, explained that the group's intent is that the guidelines, when published in final form, "be regarded as flexible and not supplant the clinical judgement of experienced health care providers. As research continues, and our knowledge grows, these guidelines will need to be modified." The group also recommended that all antiretroviral drugs approved for treatment of HIV infection be available for use in children, irrespective of labeling notations.

Comments on the proposed guidelines must be received by HRSA on or before (XXXX) to ensure that all comments are considered in preparing the final guidelines. Submit written comments to: The HIV/AIDS Treatment Information Service, P.O. Box 6303, Rockville, MD 20849-6303. Only written comments will be accepted. After consideration of the comments, the final document will be published in the Centers for Disease Control and Prevention (CDC) *Morbidity and Mortality Weekly Report*.

Copies of the Guidelines are available from the National Aids Clearinghouse (1-800-458-5231), Website (http://www.cdcnac.org); and from the HIV/AIDS Treatment Information Service (1-800-448-0440; Fax: 301-519-6616; TTY: 1-800-243-7012), Website (http://www.hivatis.org).

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Note: HHS press releases are available on the World Wide Web at: http://www.dhhs.gov.

HHS NEWS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOR IMMEDIATE RELEASE
Monday, Sept. 29, 1997

Contact: Cheryl Parrott (NIAID)
(301) 402-1663
cparrott@nih.gov

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"President Clinton has challenged the nation to develop a vaccine against AIDS in the next ten years," said HHS Secretary Donna E. Shalala. "These grants will help to foster the kind of fresh, innovative thinking we need to achieve that goal."

"We are extremely pleased by the overwhelming response to this announcement. The 49 grants we are funding will explore creative approaches to vaccine design and involve many investigators new to AIDS research," commented NIAID Director Anthony S. Fauci, M.D.

NIAID awarded the 49 grants, totaling more than $11.8 million, after an exhaustive evaluation of more than one hundred applications. The grants will be for either one- or two-year funding periods. The grant recipients, 28 of whom are new to NIAID's extramural research program, will be conducting research within the following areas: understanding the structure and function of the HIV envelope protein; improving animal models for vaccines and studies on the causes and progression of disease; and understanding the mechanisms of antigen processing in living organisms to maximize the immune response.

NIAID created the INNOVATION Program to encourage novel ideas and approaches while stimulating interest from a new group of scientists, including those who had not been involved in HIV research. The AIDS Vaccine Research Committee (AVRC) chaired by David Baltimore, Ph.D., president-designate of the California Institute of Technology, endorsed the concept of the INNOVATION Program.

"Traditional killed vaccine or live attenuated vaccine development methods are being pursued, but may not be the most successful for HIV," said Dr. Baltimore. "To discover the best way to tame HIV infection, we need also to focus on the newer biomedical technologies and approaches that depart from the conventional."

- More -

The grant recipients will be conducting research to:

- Identify sites and mechanisms of viral and immune cell interactions once the virus has attached to a cell.
- Develop novel approaches to analyzing the structure of HIV. New knowledge of the biophysical characteristics of HIV's structure can bring to light additional sites for attacking it.
- Improve the immune-stimulating ability of HIV proteins.
- Study the impact of newly described or less studied cell types of the immune response to HIV. These studies may provide information on how to improve existing vaccine candidates or additional therapeutic targets.
- Explore the potential of new genetically engineered animal models.
- Study the mechanisms of action that may clarify the roles of HIV as it interacts with immune cell receptors during infection. Such studies may show researchers more opportunities to intervene in the infection and disease processes.
- Develop new vaccine formulations to improve ways in which the vaccine material is presented to the immune system. HIV is a quickly mutating virus. The chances for a vaccine interfering with the virus' progress are improved when scientists can identify better ways of alerting the immune system to potential danger.
- Develop new vectors and improve existing ones. Vectors, or carriers of vaccine materials and immune system stimulators, can greatly enhance a vaccine's effectiveness.

The grantees are:

- Christopher C. Broder, Ph.D., Henry M. Jackson Foundation for the Advancement of Military Medicine, Rockville, Md.
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- George J. Cianciolo, Ph.D., Duke University, Durham, N.C.
- Nancy L. Haigwood, Ph.D., Seattle Biomedical Research Institute
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NIAID, a component of the National Institutes of Health (NIH), conducts and supports research to prevent, diagnose and treat illnesses such as AIDS and other sexually transmitted diseases, tuberculosis and malaria, as well as asthma and allergies. NIH is an agency of the U.S. Department of Health and Human Services.

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Note: Press releases, fact sheets and other NIAID-related materials are available on the Internet via the NIAID home page at http://www.niaid.nih.gov.

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NCIH National Council for International Health

AIDSLink

A new global priority

Mobilizing for an AIDS Vaccine

By Sam Avrett, International AIDS Vaccine Initiative

In February 1997, in the United States "State of the Union" address, US President Bill Clinton referred to a national priority of making the U.S National Institutes of Health (NIH) a "powerful discovery engine" for a preventive HIV vaccine. On May 18, at the Morgan State University Commencement Address, President Clinton expanded this promise by announcing a new AIDS vaccine research center at the NIH and pledging to further mobilize the US pharmaceutical industry and, through the G7 Summit, other national governments to this effort.

This increased focus in the United States follows increasing international attention to the need for preventive HIV vaccines, heard at the XI International Conference on AIDS in Vancouver and through organizations such as the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the International AIDS Vaccine Initiative (IAVI).

What does this increased attention and effort toward HIV vaccine development really mean? Should developing an effective HIV vaccine be an international priority? What are the specific actions that need to be taken? And what are the implications for governments, industry, non-governmental health organizations, and affected communities?

The reason that HIV vaccine research and development must be an international priority for all governments, non-governmental agencies, and communities is that an HIV vaccine is both possible and necessary, and will not happen without international collaboration.

Scientific data is promising

Scientific evidence, including protection of vaccinated monkeys from SIV, the examples of control or clearance of HIV from newborns, long-term nonprogressors, and exposed-but-uninfected individuals, and the immune responses seen by current HIV vaccine candidates, all suggests that an HIV vaccine is possible. The recent successes of protease inhibitors show that even very difficult scientific challenges can be overcome with sufficient resources and talent.

Worldwide, more than 8500 people become infected with HIV every day, 90% of whom live in developing countries. Studies in several countries have shown that behavior change interventions, condoms, and access to clean needles can dramatically reduce HIV infection rates. But these methods are far from perfect; even with high quality counseling and access to prevention interventions, infection rates often remain above 2 per 100 people per year in research cohorts in Asia, Africa, and the Americas. Furthermore, many people may never have access to such counseling and interventions. A vaccine must be added as a tool for prevention.

HIV vaccine research and development can best be accomplished through a vast collaboration of researchers at universities, companies, government laboratories and community-based trial sites throughout the world. Much of the worlds current effort is funded from the U.S. National Institutes of Health and a few multinational pharmaceutical companies. Smaller sources of support

Continued on page 6

In this issue . . .

NCIH Global AIDS Network Newsletter #45

May/June 1997

HHS NEWS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOR IMMEDIATE RELEASE
Monday, Sept. 29, 1997

Contact: Cheryl Parrott (NIAID)
(301) 402-1663
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- More -

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White House Press Release

Commencement Address By The President At Morgan State University

The White House

Office of the Press Secretary

For Immediate Release May 18, 1997

Commencement Address By The President
At **Morgan State University**

Edward P. Hurt Gymnasium
Baltimore, Maryland

10:30 A.M. Edt

The President: Thank you. Dr. Richardson, Judge Cole, Governor Glendenning, Lieutenant Governor Kennedy-Townsend, Mr. Mayor, City Council President, other elected officials, Mr. Speaker, Senator Miller, Senator Sarbanes, Congressman Cardin and Congressman Cummings, my great partners, to the Board of Regents, to faculty, staff, to distinguished alumni, to the magnificent band and choir. I thought it was a great day when I got here, but I know it is now. Thank you very much. (Applause.)

To the members of the class of 1997, your family and your friends -- (applause) -- congratulations on this important day in your lives, the lives of your nation, and the life of this great institution.

Your diploma reflects a level of knowledge that will give you the chance to make the most of the rapidly unfolding new reality of the 21st century. It gives your country a better chance to lead the world toward a better place, and it reaffirms the historic mission of **Morgan State** and the other historically black colleges and **universities** of our great land.

When the doors of college were closed to all but white students, **Morgan State** and the nation's other historically black institutions of higher education gave young African Americans the education they deserved and the pride they needed to rise above cruelty and bigotry.

Today, these institutions still produce the lion's share of our black doctors and judges and business people, and **Morgan State** graduates most of the black engineers and scientists in the great **state** of Maryland. (Applause.)

I am here today not because **Morgan State** is just a great historically black **university**, it is a great American **university**. (Applause.) You have produced some of our nation's finest leaders. Your grads like Parren Mitchell, Kweisi Mfume and Earl Graves. (Applause.) Judicial leaders like Judge Bell and Judge Cole; public servants like **State** Treasurer Dixon and on a very personal note, my fine assistant, Terry Edmonds, Class of 1972, the first African American ever to serve as a speechwriter for the President of the United **States**. (Applause.) There he is.

Now, you're getting too much applause now, Terry. (Laughter.)

You graduate today into a world brimming with promise, enriched with opportunity. Our economy is the strongest in a generation, our unemployment the lowest in 24 years, with the largest decline in income inequality since the 1960s.

On Friday we finalized the details of an historic agreement with the leaders of Congress to balance the federal budget for the first time in nearly three decades, in a way that will keep our economy going and in balance with our values, caring for those in need, extending health care to 5 million more children, cleaning and preserving and restoring our environment, helping people to move from welfare to work, and, most important, funding the largest investment in education in a generation and the largest increase in higher education since the G.I. bill in 1945, more than 50 years ago. (Applause.)

It will open the doors of college to all, with the largest increase in Pell Grant scholarships in three decades, $35 billion in tax relief to help families pay for higher education, including tax deductions for the cost of all education after high school, and our Hope Scholarship tuition tax credits to make the first two years of college as **universal** by the year 2000 as a high school diploma is today. (Applause.)

And this agreement contains a major investment in science and technology, inspired in our administration by the leadership of Vice President Gore, to keep America on the cutting edge of positive change, to create the best jobs of tomorrow, to advance the quality of life of all Americans.

This is a magic moment, but like all moments it will not last forever. We must make the most of it. In commencement addresses across the nation this year, I will focus our attention on what we must do to prepare our nation for the next century, including how we can make sure that our rich diversity brings us together rather than driving us apart, and how we must meet our continuing obligation to lead the world away from the wars and Cold War of the 20th century through the present threats of terrorism and ethnic hatred, weapons proliferation and drug smuggling, to a more peaceful and free and prosperous 21st century.

But today here, I ask you simply to imagine that new century, full of its promise, molded by science, shaped by technology, powered by knowledge. These potent transforming forces can give us lives fuller and richer than we have ever known. They

can be used for good or ill.

If we are to make the most of this new century, we -- all of us, each and every one of us, regardless of our background --must work to master these forces with vision and wisdom and determination. The past half-century has seen mankind split the atom, splice genes, create the microchip, explore the heavens. We enter the next century propelled by new and stunning developments.

Just in the past year we saw the cloning of Dolly the sheep, the Hubble telescope bringing into focus dark corners of the cosmos never seen before, innovations in computer technology and communications, creating what Bill Gates calls "the world's new digital nervous system," and now cures for our most dreaded diseases -- diabetes, cystic fibrosis, repair for spinal cord injuries. These miracles actually seem within reach.

The sweep of it is truly humbling. Why, just last week we saw a computer named Deep Blue defeat the world's reigning chess champion. I really think there ought to be a limit to this. No computer should be allowed to learn to play golf. (Laughter.) But, seriously, my friends, in science, if the last 50 years were the age of physics, the next 50 years will be the age of biology. (Applause.)

We are now embarking on our most daring explorations, unraveling the mysteries of our inner world and charting new routes to the conquest of disease. We have not and we must not shrink from exploring the frontiers of science. But as we consider how to use the fruits of discovery, we must also never retreat from our commitment to human values, the good of society, our basic sense of right and wrong.

Science must continue to serve humanity, never the other way around. The stakes are very high. America's future -- indeed, the world's future -- will be more powerfully influenced by science and technology than ever before. Where once nations measured their strength by the size of their armies and arsenals, in the world of the future knowledge will matter most. Fully half the growth in economic productivity over the last half-century can be traced to research and technology.

But science is about more than material wealth or the acquisition of knowledge. Fundamentally, it is about our dreams. America is a nation always becoming, always defined by the great goals we set, the great dreams we dream. We are restless, questing people. We have always believed, with President Thomas Jefferson, that "freedom is the first born daughter of science." With that belief and with willpower, resources and great national effort, we have always reached our far horizons and set out for new ones.

Thirty-six years ago, President Kennedy looked to the heavens and proclaimed that the flag of peace and democracy, not war and tyranny, must be the first to be planted on the moon. He gave us a goal of reaching the moon, and we achieved it -- ahead of time.

Today, let us look within and step up to the challenge of our time, a challenge with consequences far more immediate for the life and death of millions around the world. Aids will soon overtake tuberculosis and malaria as the leading infectious killer in the world. More than 29 million people have been infected, 3 million in the last year alone, 95 percent of them in the poorest parts of our globe.

Here at home, we are grateful that new and effective

anti-Hiv strategies are available and bringing longer and better lives to those who are infected, but we dare not be complacent. Hiv is capable of mutating and becoming resistant to therapies, and could well become even more dangerous. Only a truly effective, preventive Hiv vaccine can limit and eventually eliminate the threat of Aids.

This year's budget contains increased funding of a third over two years ago to search for this vaccine. In the first four years, we have increased funding for Aids research, prevention and care by 50 percent, but it is not enough. So let us today set a new national goal for science in the age of biology. Today, let us commit ourselves to developing an Aids vaccine within the next decade. (Applause.) There are no guarantees. It will take energy and focus and demand great effort from our greatest minds. But with the strides of recent years it is not longer a question of whether we can develop an Aids vaccine, it is simply a question of when. And it cannot come a day too soon.

If America commits to find an Aids vaccine and we enlist others in our cause, we will do it. I am prepared to do all I can to make it happen. Our scientists at the National Institutes of Health and our research **universities** have been at the forefront of this battle.

Today, I'm pleased to announce the National Institutes of Health will establish a new Aids vaccine research center dedicated to this crusade. And next month at the Summit of the Industrialized Nations in Denver, I will enlist other nations to join us in a worldwide effort to find a vaccine to stop one of the world's greatest killers. We will challenge America's pharmaceutical industry, which leads the world in innovative research and development to work with us and to make the successful development of an Aids vaccine part of its basic mission.

My fellow Americans, if the 21st century is to be the century of biology, let us make an Aids vaccine its first great triumph. (Applause.)

Let us resolve further to work with other nations to deal with great problems like global climate change, to break our reliance on energy use destructive of our environment, to make giant strides to free ourselves and future generations from the tyranny of disease and hunger and ignorance that today still enslaves too many millions around the world. And let us also pledge to redouble our vigilance to make sure that the knowledge of the 21st century serves our most enduring human values.

Science often moves faster than our ability to understand its implications, leaving a maze of moral and ethical questions in its wake. The Internet can be a new town square or a new Tower of Babel. The same computer that can put the Library of Congress at our fingertips can also be used by purveyors of hate to spread blueprints for bombs. The same knowledge that is developing new life-saving drugs can be used to create poisons of mass destruction. Science can enable us to feed billions more people in comfort, in safety, and in harmony with our earth; or it can spark a war with weapons of mass destruction rooted in primitive hatreds.

Science has no soul of its own. It is up to us to determine whether it will be used as a force for good or evil. We must do nothing to stifle our basic quest for knowledge. After all, it has propelled from field to factory to cyberspace. But how we use the fruits of science and how we apply it to human endeavors is not properly the domain of science alone or of scientists alone. The answers to these questions require the application of ethical and

moral principles that have guided our great democracy toward a more perfect union for more than 200 years now. As such, they are the province of every American citizen.

We must decide together how to apply these principles to the dazzling new discoveries of science. Here are four guideposts. First, science and its benefits must be directed toward making life better for all Americans -- never just a privileged few. Their opportunities and benefits should be available to all. Science must not create a new line of separation between the haves and the have-nots, those with and those without the tools and understanding to learn and use technology.

In the 21st century a child in a school that does not have a link to the Internet or the student who does not have access to a computer will be like the 19th century child without school books. That is why we are ensuring that every child in every school, not matter how rich or poor, will have access to the same technology by connecting every classroom and library to the Internet by the year 2000. (Applause.)

Science must always respect the dignity of every American. Here at one of America's great black **universities** let me underscore something I said just a few days ago at the White House. We must never allow our citizens to be unwitting guinea pigs in scientific experiments that put them at risk without their consent and full knowledge. (Applause.)

Whether it is withholding a syphilis treatment from the black men of Tuskegee or the Cold War experiments that subjected some of our citizens to dangerous doses of radiation, we must never go back to those awful days in modern disguise. We have now apologized for the mistakes of the past; we must not repeat them -- never again. (Applause.)

Second, none of our discoveries should be used to label or discriminate against any group or individual. Increasing knowledge about the great diversity within the human species must not change the basic belief upon which our ethics, our government, our society are founded. All of us are created equal, entitled to equal treatment under the law. (Applause.)

With stunning speed, scientists are now moving to unlock the secrets of our genetic code. Genetic testing has the potential to identify hidden inherited tendencies toward disease and spur early treatment. But that information could also be used, for example, by insurance companies and others to discriminate against and stigmatize people.

We know that in the 1970s, some African Americans were denied health care coverage by insurers and jobs by employers because they were identified as sickle cell anemia carriers. We also know that one of the main reasons women refuse genetic testing for susceptibility to breast cancer is their fear that the insurance companies may either deny them coverage or raise their rates to unaffordable levels. No insurer should be able to use genetic data to underwrite or discriminate against any American seeking health insurance. This should not simply be a matter of principle, but a matter of law, period. (Applause.)

To that end, I urge the Congress to pass bipartisan legislation to prohibit insurance companies from using genetic screening information to determine the premium rates or eligibility of Americans for health insurance.

Third, technology should not be used to break down the wall of privacy and autonomy free citizens are guaranteed in a free society. The right to privacy is one of our most cherished freedoms. As society has grown more complex and people have become more interconnected in every way, we have had to work even harder to respect the privacy, the dignity, the autonomy of each individual.

Today, when marketers can follow every aspect of our lives, from the first phone call we make in the morning to the time our security system says we have left the house, to the video camera at the toll booth and the charge slip we have for lunch, we cannot afford to forget this most basic lesson.

As the Internet reaches to touch every business and every household and we face the frightening prospect that private information -- even medical records -- could be made instantly available to the world, we must develop new protections for privacy in the face of new technological reality. (Applause.)

Fourth, we must always remember that science is not God. (Applause.) Our deepest truths remain outside the realm of science. We must temper our euphoria over the recent breakthrough in animal cloning with sobering attention to our most cherished concepts of humanity and faith.

My own view is that each human life is unique, born of a miracle that reaches beyond laboratory science. I believe we should respect this profound gift. I believe we should resist the temptation to replicate ourselves. But this is a decision no President should make alone. No President is qualified to understand all of the implications.

That is why I have asked our distinguished National Bioethics Advisory Commission, headed by President Harold Shapiro of Princeton, to conduct a thorough review of the legal and ethical issues raised by this new cloning discovery. They will give me their first recommendations within the next few weeks, and I can hardly wait.

These, then, are four guideposts, rooted in our traditional principles of ethics and morals, that must guide us if we are to master the powerful forces of change in the new century. One, science that produces a better life for all and not the few. Two, science that honors our tradition of equal treatment under the law. Three, science that respects the privacy and autonomy of the individual. Four, science that never confuses faith in technology with faith in God.

If we hold fast to these principles, we can make this time of change a moment of dazzling opportunity for all Americans.

Finally, let me say again: Science can serve the values and interests of all Americans, but only if all Americans are given a chance to participate in science. We cannot move forward without the voices and talents of everyone in this stadium, and especially those of you who are going on to pursue a career in science and technology.

African Americans have always been at the forefront of American science. This is nothing new. Nothing -- not slavery, not discrimination, not poverty -- nothing has ever been able to hold back their scientific urge or creative genius. (Applause.)

Benjamin Banneker was a self-taught mathematician,

surveyor, astronomer, who published an annual almanac and helped to design the city of Washington. George Washington Carver was born a slave, but went on to become one of our nation's greatest agricultural scientists. Ernest Everett Just of Charleston, South Carolina, is recognized as one of our greatest biologists. Charles Drew lived through the darkest days of segregation to become a pioneer in blood preservation. And today you honor an African American doctor at Johns Hopkins **University** who is truly one of the outstanding physicians of our time. (Applause.)

All these people show us that we don't have a person to waste and our diversity is our greatest strength in the world of today and tomorrow. Now, members of the class of 1997, it is your time. It is up to you to honor their legacy, to live their dreams, to be the investigators, the doctors, and the scholars who will make and apply the discoveries of tomorrow, who will keep our science rooted in our values, who will fashion America's greatest days.

You can do it. Dream large. Work hard. And listen to your soul. Thank you and God bless you all. (Applause.)

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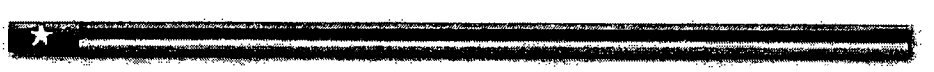

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