AIDS and Public Policy: What's Happening?

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May 3, 1995

Medical Grand Rounds, Mayo Clinic

Introduction

I am pleased to have been invited to talk with you today about the status of the AIDS epidemic. There has been a deadly hush surrounding AIDS of late -- and I choose those words carefully. There have been occasional bursts of press coverage detailing small bits of research progress or revisiting sharply focused policy issues, but those excitements tend to subside quickly, permitting the distractible American public to forget that anything of importance is even happening. Nevertheless, the epidemic of AIDS rampages on, ~~and the~~ fueled by sexual behavior + drug use, by discrimination, and denial but in my opinion the most potent vector facilitating further spread of the human immunodeficiency virus is **silence**.

I sometimes meet with disbelief when I try to tell people how serious the epidemic situation has become -- but the facts speak for themselves. By the end of this calendar year, more young Americans will have been diagnosed with **AIDS** than were killed in all of our armed conflicts since the Civil War -- and worse is coming, for hundreds of thousands more are in **earlier** stages of HIV infection, on their inexorable way to chronic, ultimately fatal disease. In that, we are suffering a disasterous loss of youth + talent that no nation can or should sustain passively.

And of course the country is seeded now with that deadly virus: it will never be gone. It is like the day after the dropping of the Hiroshima

bomb: one would surely prefer to live in a world without nuclear weapons, but suddenly that was no longer a choice. Likewise with HIV: we had been cavalier about sexually transmitted diseases once syphilis came under control. Even the advent of antibiotic resistance in gonococci seemed more like a nuisance than a cause for concern, and newer antimicrobial agents were simply moved up to the front line.

But now we must learn to live on a changed planet, coexisting with a novel microbial agent that is limited in its modes of spread but lethal in its consequences, for which neither curative treatment nor a general-use vaccine is likely to be available any time soon. We know a great deal about how to **avoid** the virus of AIDS, and a good deal about how to **prevent** it; but thus far we have taken poor advantage of that kind of knowledge, for we are not good yet at dealing with prevention in general, and especially not with behavioral change as a facet of health care.

Because of my background and training I have been caught up in the tragedy of AIDS since the very beginning -- in fact, one might even say since **before** the very beginning. The first cases of AIDS were reported in 1981, of course, but already in 1975 the leadership of the National Institute of Allergy and Infectious Diseases had become alarmed at the scale of the burgeoning national epidemic of sexually transmitted disease, which prompted them to declare it a major health problem for the country and a research priority for the NIH. To intensify interest in that area of infectious disease research, they called for program project proposals to stimulate studies by multidisciplinary teams of STD researchers. And to provide for a relatively even review (to assess the resultant applications),

they assembled a small "swat" team of microbiologists. Since I was doing research on herpesviruses and serving on an NIH virology study section at the time, I was one of the virologists they chose, and we participated in a series of site visits of the proposed venues of research. I didn't know it then, but it was a harbinger of my next two peripatetic decades, for we traveled around the country and got a first hand look at what was going on.

Between 1975 and 1980, those visits took us to several major American cities where academic medical centers coexisted with populations in which STDs were concentrated. ~~Indeed~~, most proposals included at least some clinical/epidemiological studies of groups of people characterized by extraordinary numbers of sexual partners -- indeed those numbers seemed to be escalating even as we did our reviews. We microbiologists were not a particularly worldly bunch, and I think we assumed that our amazement mostly revealed our naiveté, so we didn't say much out loud. Nevertheless, phenomena such as the sudden upsurge in prevalence of Entamoeba histolytica and the clear acceleration of hepatitis B spread prompted concern, and we often commented quietly (to each other) that conditions were ominously favorable for even worse STD and infectious trouble to arise out of what seemed to be major changes in sexual mores that had taken place in the decade or so preceding.

Afterwards, when I looked back, I realized that we had visited many of the major cities where what later came to be called the human immunodeficiency virus, or HIV, was spreading silently, and so in fact we **were** watching the beginning of the deadly pandemic of AIDS; for the initial acceleration of the U. S. epidemic is now thought to have taken place

in the early and mid-1970s. I don't mean to claim that we were prescient enough to foresee the advent of a new, hitherto unknown pathogen, but we did recognize that circumstances favored the microbes.

That point is of some interest, parenthetically, as new and vigorous discussions take place about so-called "emerging infections". Out of those deliberations is coming the consensus that there are many more potential pathogens out there; that there will probably never be a time when one can accurately anticipate **which** new pathogen will be able to gain a foothold -- but there **are** ways to recognize the context in which such events are made more likely. Urbanization, ecological and social upheaval and international travel are dynamics that are here to stay, and they offer fresh new horizons for unknown microbes.

We've come a long way from the confident days when I, as a medical student, perceived infectious diseases as a nearly-conquered field of study, or when the Surgeon General in 1969 declared them vanquished. Americans, and especially biomedical scientists and infectious disease physicians, were full of hubris heading into the 1970s -- and **hubris** is a particularly dangerous social malady. I think **that**, at least, has been cured by AIDS, for most people now do realize that HIV won't be the last such intruder, and that we need to learn **its** lessons quickly and well if we are to be ready for the next one.

But back to my central theme: the AIDS epidemic from the outset represented multidisciplinary trouble. In the fourteen years since ~~the~~ first recognition that a new, lethal STD was at hand, we have been challenged

far beyond the arena of complicated virology, immunology and molecular genetics of HIV itself. In addition, we have had to grapple with an astonishingly broad spectrum of issues and needs -- ranging from basic research priorities and clinical care of chronically ill young adults and their children, to matters of medical care access and financing strategies, to public education and prevention, and to an awareness of our relative backwardness in dealing effectively with the behavioral components of health-risky practices.

The very nature of the AIDS epidemic, with its intimate linkage to sex and to illicit drug use, and its disproportionate escalation in communities of color, has made it a sharp and destructive probe of our society, tearing apart the safety net for poor and vulnerable populations, and often plunging previously affluent young adults into those depths as well, as they become inexorably more ill with HIV disease. AIDS has swelled the ranks of the homeless, overfilled correctional facilities with immune-deficient prisoners whose access to health care is tenuous and whose susceptibility offers new horizons for old diseases like tuberculosis. It has devastated whole families, leaving increasing thousands of AIDS orphans in its swath, like isolated trees left standing in a burned-out forest. It has begged questions of sexual orientation, of female vulnerability in sexual relations, of race and ethnicity, of rural as well as urban mores, and of access to care that echo alarmingly in the shadows of our land. Those complex dynamics have made it as challenging a threat to public health as has existed in this century, and the policy issues posed have been almost infinitely varied. I will tell you right away, though, that there is one policy matter that we must **not** consider to be at issue: we **must** respond

to HIV and AIDS, and we **must** care for those caught in the path of this new and vicious virus.

Happily, the accelerating pace of biomedical scientific advance in the several decades **before** AIDS surfaced put us in a position at least to understand the nature of our new enemy and, to a remarkable extent, to delineate its pathogenic mechanisms. I strongly believe that rational and ethical public policy is best assured when it is based on sound science, and at least we have had **that** foundation on which to build, thanks to the wisdom of earlier investment in so-called basic research. From this experience we should be well armed against those detractors who sometimes bemoan basic science as irrelevant. We can say clearly, now, in the wake of the advent of HIV and AIDS, that -- far from being "irrelevant" -- **basic** science is research that is directed to questions for which we **do not yet appreciate the relevance.**

Today I would like to take a few moments to review the course of the epidemic and knowledge of it that has accrued since the first cases of AIDS were reported in the summer of 1981. Then I will summarize quickly where matters stand ~~today~~ with respect to the epidemic toll and to trends and changes in epidemiologic patterns. In the interest of time I will have to focus my attention on the United States; but I should at least mention that the global situation grows more dismal every year. Many millions of people around the world are now infected, far more are likely by the turn of the century, and Asia -- which seemed at first to have been spared -- is now the scene of the most rapidly growing epidemic of all, for

Much as I would like to tell you about the worldwide involvement in this,

it is estimated that 100,000,000 people will be infected with HIV by the year 2000, of whom at least 40% will be Asian.

After a brief description of the U. S. epidemic, I will try to address a series of issues, some scientific and some policy-based, having to do with HIV and AIDS. And at the end I will hope to have left enough time for questions about points of particular interest to you.

So, to begin.

A brief history of the AIDS epidemic

It is hard to believe that it **was** just fourteen years ago that the first few cases of AIDS were described in two clusters, one on the west coast of the United States and one on the east. As you know, they had been recognized because of the unusual occurrence of Pneumocystis carinii pneumonia or Kaposi's sarcoma, respectively, occurring in young men who had been previously healthy but who at the time of presentation were profoundly immune-suppressed because of a selective depletion of a specific subset of T lymphocytes. In due course the syndrome, with its distinctive immune collapse, that opened the way for a dizzying variety of infections and tumors, was given name and an acronym: acquired immune deficiency syndrome or AIDS.

All of those first cases, as it happened, occurred in gay men whose lifestyle had involved many, many sexual partners. It was an accident of history that AIDS began that way in our country, since in many parts of the

world it was conspicuously heterosexual from the outset; but tragically, for a while, concern about the new, deadly syndrome was muted, nationally, by pervasive homophobia. Matters weren't helped by the next recognition -- that is, that intravenous drug users were also becoming ill in much the same ways, and with the same tell-tale deficiency of T-helper cells (or CD4+ lymphocytes, as they were more properly labeled). The nation was in the midst of declaring a war on drugs -- and the fact that the new illness was declaring a war of its own on drug **users** seemed to many to be appropriate and almost reasonable (certainly not as unsettling as it should have been).

But soon there were men with hemophilia whose need for infusions of factor VIII concentrate had exposed them to blood products from literally thousands of donors; and then, the direct recipients of blood transfusions. And significantly, from **very** early on, the **heterosexual partners** of people afflicted by one of those other means were themselves becoming ill. That should have been a wake-up call, for it was at least clear from the outset that AIDS was a sexually transmitted disease, and there had never been a sexually transmitted infectious disease restricted to one sex. That is where our societal response went terribly wrong -- even as the whole world became enmeshed, with the dominant mode of spread worldwide being heterosexual intercourse, the United States remained ostensibly complacent, with people assuring themselves (as they still do) that it was "just those gays and addicts". Indeed, more than one leading scientist went so far as to assert, publicly, that "sometimes when you have a fire, you just have to let it burn itself out". Such utterances seemed to justify the silence of policy makers and politicians who wanted no part of

advocating for care and compassion in such a dangerously impolitic context.

Anyway, by 1983, the final component of the epidemiologic pattern became clear -- pediatricians recognized in some of their small patients a different but suggestive set of manifestations of immune deficiency unlike any they had seen before: while somewhat different from the adult syndrome, as it turned out, AIDS was afflicting infants and children as well. So before the causative virus was ever isolated, it had already been established that sexual intercourse, injection of substantial quantities of blood or blood products (either through transfusion, infusion or sharing of injection apparatus in the context of illicit injecting drug use), or birth to an afflicted mother were established as **the** modes of presumed transmission. By that time it was also widely assumed -- as noted earlier -- that an infectious, blood-borne agent was involved, and for a variety of reasons, investigators were hot on the trail of retroviruses.

Until 1978 there had never been a known human retrovirus. A great deal of work had been done with retroviruses of other species, and it seemed eminently reasonable that there should be human retroviruses as well, but efforts to isolate them had failed, despite a few "false sightings". Then in 1978 and '79, in Dr. Robert Gallo's lab at the National Cancer Institute, agents called HTLV-I and HTLV-II were isolated from people with rare varieties of leukemia, and they were established to be retroviruses with a predilection for T lymphocytes. As did many (but by no means all) other retroviruses, they immortalized infected cells, and their putative oncogenicity seemed intuitively reasonable. Today, their role in

malignant disease seems to be quite problematic, although HTLV-I has been linked to important neurological syndromes -- that, however, is a story for another day.

The success with HTLV-I and HTLV-II, including some of the techniques facilitating T cell cultivation on which their recognition had been dependent, led several investigators to suspect and then to pursue the possibility that the newly recognized T cell deficiency in humans associated with AIDS might also be due to a retrovirus: and, as the world has since learned in elaborate detail, three laboratories succeeded (in 1983 and 1984) in isolating and identifying what came to be called the human immunodeficiency virus, the causative agent of AIDS.

So by 1984 a number of crucial parameters were well established. There was a newly recognized human retrovirus; it seemed to cause dramatic reduction in CD4+ cell numbers in afflicted hosts, and the eventual consequences of that immune deficiency were the occurrence of both opportunistic infections and certain unusual but characteristic malignancies, notably Kaposi's sarcoma and non-Hodgkins lymphoma. The virus was certainly spread as a sexually transmitted pathogen, as well as by blood; and it **could** also be vertically transmitted from infected mother to child -- although it was evident that half or less of children born to an HIV-infected mother were themselves infected.

What was **not** known was how long all that took: no one even suspected that the median interval between onset of infection and expression of the distinctive diseases of AIDS would turn out to be more

than ten years! In fact, I recall vividly a time in 1986 when the CDC was accused of spreading undue alarm when it proposed to follow recipients of infected units of blood for as long as five years! But anyway, by 1985 laboratory successes had given rise to techniques for growing quantities of virus, sufficient to allow mass antigen production for testing of donated blood; and after May of that year, all blood donated in the U. S. was subjected to screening for antibodies to HIV -- with dramatic effect. Indeed, the fine tuning of blood tests for HIV -- and later for several hepatitis viruses -- has by now yielded the safest blood supply we have ever had. So that is good news -- almost the only good news I can point to today.

But one other piece of good news should be underscored: with the advent of the capability to identify infected individuals came the opportunity to test the epidemiologic assumption that those few modes of spread were the only ones that worked. Natural experiments were ready at hand and had been extensive: before a virus was suspected or precautions were advocated, literally thousands of family members had cared for hundreds of dying AIDS patients over weeks or months, wiping up secretions and sharing toothbrushes and utensils, tears and kisses -- and when the caregivers were tested, the absolute restriction on mode of spread was truly astonishing: not one instance of transmission had occurred in such settings in the absence of sexual intercourse!

And in the health care setting, where physicians and nurses had been truly brave in face of the unknown in early years, reassurance was equally profound. With the advent of the recommendation for universal

precautions in 1987, even hepatitis B transmission (one-hundred-fold more likely than HIV by the same routes) had been brought to a complete halt. Indeed, with the singular exception of one dental practice in Florida, where the dynamics of HIV transmission were obscure but clearly exceptional, no transmission from care giver to patient has ever been established; and the risk in the reverse direction is extraordinarily low -- even an accidental jab from a needle straight out of an AIDS patient has resulted in transmission at a rate of only three per thousand.

I will pass quickly over the biomedical and clinical insights accrued in subsequent years, even though they are truly impressive. Suffice to say, we know more about HIV than about any other pathogen of man, and the events during the ten years it takes to progress from initial infection to immunologic devastation of the host are increasingly well understood..

The insights have been disquieting, to say the least, although they are far from unfamiliar to students of so-called slow viruses -- indeed, prior studies of the lentivirus subgroup of retroviruses in other species have proved very useful in analyzing what is happening to humans as a result of infection with this newly pandemic agent. Immune responses are transiently effective at best, because the virus is capable of escape through rapid mutation within a given host. Indeed, there is no demonstrably protective immune response, despite early appearance of the high levels of antibody so useful in blood testing. And in the end it seems to be a battle of attrition between the virus, which replicates in vast quantities every day, and T cells, which are mortally afflicted in combat, replenishing their numbers slightly less well than does the virus. In almost all instances, it ends with

the virus winning. As noted earlier, the average interval from initial infection to AIDS is now known to be ~~nearly~~ between 10 — 11 years; and while many individuals remain asymptomatic and fully functional during those years, the likelihood that an HIV-infected person will remain healthy indefinitely is vanishingly small. A few people have seemed to win that battle of the T cells, and they are being studied exhaustively in an effort to discern what might constitute critical facets of an effective host response -- but thus far to no avail.

I should emphasize that, even though AIDS is novel in its effects in human populations, there is nothing other-worldly or mysterious about this newly identified virus. Indeed, its pathogenic features fit well into the patterns of disease caused by related lentiviruses of other species. What is new is not the virus, but rather its sudden world-wide dissemination. There is little evidence of infected humans before the 1970s, and none before 1959; but by molecular analysis it seems likely that the virus is older than that. I think most virologists subscribe to the hypothesis that it existed in isolated human enclaves somewhere in the world for decades or perhaps even a century or so before it escaped into the whirlwind of current social and ecological change.

But its success after that escape is truly stunning. In the United States we have had nearly half a million people diagnosed with AIDS in just under 14 years; more than 250,000 have died. At least another half-million are already infected, and it is estimated that between 40,000 and 80,000 new HIV infections occur each year in this country. The initial concentration of AIDS in major urban centers has been sustained; but in

terms of rapidity of growth of epidemic numbers, smaller communities and rural areas are now experiencing the fastest rate of increase. And keep in mind that most of those generalizations are about AIDS itself -- which gives a picture that is ten years out of date, since it takes a decade for most HIV infection to express itself in overt disease manifestations.

There are other trends: injecting drug use was always a particularly efficient and important means of transmitting the virus; but every year it plays a more deadly role. And the involvement of women is increasing steadily. Whereas only 7% of people with AIDS were women in early years, that has risen to a cumulative 13% as of 1994; and in 1994 itself, 18% of the 79,000 newly diagnosed cases of AIDS were in women. While some of them were infected through injecting drug use, fully half were infected through heterosexual intercourse; and the number of those in whom the partner had "no identifiable risk" had risen as well. And, very ominously, the estimated age at time of first infection with HIV has been dropping steadily. Even now, more than 20% of people with AIDS probably became infected as teenagers; but that will surely rise. Our dogged focus on "life styles" has blinded us to the fact that our kids are at serious risk -- for adolescence is the age of experimentation, and some of those experiments have now turned deadly.

And then there is the awful problem of racial divides, adding mistrust and problems of communication to the challenges at hand. Disproportionately now, the epidemic is ravaging communities of color. Last year for the first time, more than 50% of new AIDS diagnoses were in people of color; among infected women, 75% are either African

American or Latina, and the disproportion is even greater among children with AIDS. The extent of undue representation has been increasing each year, partly because of the growing prominence (as modes of HIV transmission) of injecting drug use and crack cocaine epidemics that have blighted their communities for years. This is not a new insight: the importance of injecting drug use as an efficient vehicle for the spread of HIV has been recognized from the outset -- and yet urgent recommendations for effective measures that could interrupt that mode of transmission remain unaddressed.

In short, the scale of the epidemic is quite massive. People have been inclined to say "Yes, but AIDS is only one disease -- there are many others to which we must attend, and AIDS has received enough attention." But let me give you a couple of other measures of its scope of destruction: by the end of this year, AIDS will become the leading cause of death for American men and women between the ages of 25-44, surpassing even homicide, suicide and accident! And it already is the leading cause of "years of potential life lost" in the country! At a rate of more than 40,000 new infections a year it is worse than even the hottest summer of polio epidemics in the '40s and '50s. The frightening paralysis of polio still gave a good chance of full or at least partial recovery; but while there are occasional "long term survivors" infected with HIV, the inexorability of progression to AIDS and death is nearly uniform. So it is, already, the most destructive epidemic our country has faced in this century, and in no way is it under control.

Biomedical science: progress and issues

I hope I have impressed you with the urgency of the problems presented by the AIDS epidemic. Let me turn now to a series of topics of current interest -- first in the realm of biomedical science. As you know, there have been a number of antiviral drugs developed in recent years to treat HIV itself: Zidovudine (or AZT as it is often called) was the first of these, achieving sufficiently dramatic therapeutic results in 1987 to result in early discontinuation of a placebo-controlled trial and subsequent rapid licensure. It remains a mainstay of anti-HIV therapy, but a number of changes have occurred in its assessment and use over subsequent years.

First, its inordinate toxicity early on was a major problem, much of which was ameliorated when it was subsequently learned that the dose needed to achieve good clinical response was only a fraction of the dosage initially recommended. That recognition played a role in the design and impetus for trials of so-called "early intervention" -- an effort to see if treatment during the asymptomatic stage of HIV infection could delay progression to fully expressed AIDS. It was in that context that controversy arose: most early studies done in the United States tended to support the use of AZT in early intervention contexts; but subsequent data arising from the European "Concorde" study contradicted many of those findings and suggested that the drug should be reserved for later use in symptomatic AIDS patients.

Another source of concern about AZT arose with the recognition that it lost its clinical efficacy in many AIDS patients after 18-24 months of treatment, correlated with and perhaps causally related to the development

of antiviral resistance of the patients' HIV isolates. The frequency and potential rate-limiting occurrence of viral resistance to AZT has played an important role in subsequent thinking. To sum up a very complex set of arguments: I believe there is fairly general agreement that AZT does not necessarily extend the overall life span of the HIV-infected patient, ~~and~~ as a result of which many clinicians have cooled to the practice of using it as an agent of "early intervention," preferring to save it for its therapeutic value for a time when serious manifestations of immune deficiency begin to dominate the clinical picture. In addition, the advent of other reverse transcriptase inhibitors such as ddI and ddC, to which resistance has also arisen, has prompted studies of combination-regimens in which AZT along with, or alternating with, one of the other agents has been used.

The drugs I have been discussing are all aimed at inhibiting the action of the reverse transcriptase enzyme encoded by the virus. There are intense efforts underway to ~~find~~ explore classes of drugs such as protease inhibitors that work through other mechanisms, and a number of these have been found. However, several of the most potent and promising have provoked almost immediately the appearance of antiviral resistance on the part of HIV, with startling rapidity, ~~such~~ which occurs such that their development has been abandoned abruptly, even before leaving the laboratory for clinical trials.

Throughout these studies runs a theme: the malleability of the human immunodeficiency virus genome presents -- and will continue to pose -- a serious challenge to drug developers. Even in a single individual, and in the absence of drug, the virus undergoes steady genetic change; and its rapid development of resistance to antivirals has prompted some investigators to suggest that a regimen of ~~several~~ three, or even four, drugs given

concomitantly to block several facets of viral replication at once may turn out to be necessary to achieve sustained inhibition of replication.

Before leaving the antiviral "scene" I should mention that drugs for other facets of AIDS have found important use -- particularly those directed against cytomegalovirus, which plays a devastating role in AIDS, producing blindness through damaging retinitis in as many as 30% of patients. The use of ganciclovir and foscarnet to treat such patients has forestalled that damage, but again, drug resistance has limited the usefulness of those agents. The same can be said to a lesser extent about acyclovir for herpes simplex....In sum, antiviral drug resistance is a specter looming in several contexts of HIV and AIDS care.

Probably the most important drug intervention in HIV disease has been the use of anti-Pneumocystis carinii drugs to prevent the pneumonia that was the dominant (and sometimes abrupt) cause of death of patients with AIDS in the early years. Many AIDS clinicians consider PCP to be a fully preventable disease; use of one of several prophylactic regimens is a key component of "early intervention", and in fact, in parts of the developing world, inexpensive sulfonamide prophylaxis against PCP is the **only affordable** component of the medical armamentarium against AIDS.

Somewhat less affordable but perhaps more important, early and consistent treatment for tuberculosis in previously-infected individuals can play a key role in patients' sustained well-being. Other therapies for opportunistic infectious agents such as cryptococcus and toxoplasma have been developed, as you know, and I won't take the time to continue with a

recitation of them -- I think the point to be made is that, at least in the United States and other parts of the developed world, the initial hopelessness of outlook for people newly diagnosed with HIV disease has given way steadily to thoughtful, effective strategies of intervention that can extend productive, useful lives. In the early years it was **notable** when a person lived more than a few months following the diagnosis of AIDS. Now it is very frequent that people with AIDS and with virtually no T cells can live two or three years, and some have led lives of good quality for much longer than that.

Those comments may seem to reflect modest hopes, but I don't mean to sound discouraging, only realistic. After all, in the years before insulin was discovered, juvenile-onset diabetes had a prognosis nearly as grim as does AIDS; and yet with the rational design of multifaceted regimens to replace insulin and sustain health, the life-expectancy of people with insulin-dependent diabetes has increased dramatically -- in many instances to near-normal longevity. If people ask specifically about the chances of finding a "cure for AIDS" I have to say I find it hard to imagine -- for at the outset of infection the viral genome is covalently woven into cellular DNA, including that of cells within the central nervous system. But for those already caught in the path of the virus, that doesn't make things hopeless, for the model of diabetes and of other chronic diseases is relevant, and research prospects for achieving viable regimens of care are rather bright.

Two other facets of biomedical research deserve some comment. First, I referred earlier, briefly, to the fact that understanding of the

pathogenesis of HIV disease has advanced considerably in recent months. You probably saw the reports from two laboratories of new insights into what is happening during the long, quiet asymptomatic years: far from being a time of quiescence, it appears that there is an ongoing "pitched battle" right from the outset, between viral replication and T-lymphocyte response, with host cells reacting against virus but themselves being killed in the process. The balance is sufficiently even that the net attrition of T cells mounts up only gradually... The clinical significance of such insight is clear: if one could, in the future, both identify infection and intervene with an effective antiviral agent or agents at a **very** early stage, it might be possible to abort ~~the infection~~ replication before the extraordinary genetic malleability of HIV had time to come into play, and before the tremendous drain on T cell reconstitution became disastrous and irreversible.

Second, work toward an HIV vaccine has prompted intermittent coverage -- only **there** the news is far less encouraging. Most of the efforts to date -- including nearly all the Phase I and II clinical trials -- have involved use of a subunit vaccine representing surface protein constituents of the human immunodeficiency virus, usually delivered via a recombinant vector or with an adjuvant to enhance immunogenicity. Some early problems, such as unacceptably poor antigenicity, have been overcome; but even so the present vaccine candidates have an expected efficacy of as little as thirty percent, which is what prompted NIH to suspend plans a year ago for large scale Phase III trials.

I find that to be a wise judgment for a variety of reasons -- one important one of which is that the American populations in which such

vaccine candidates could and would have to be tested are in themselves a research resource -- they are important groups of people in their own right; and their participation in one trial would almost surely prevent their enrolling in subsequent trials. I think it behooves us to be sure we are doing much more good than harm in such contexts.

As you may know, the World Health Organization has made the other decision -- that is, to proceed with large clinical trials of those or similar HIV vaccine candidates. That partly reflects a genuine difference of opinion, but of course it also pertains to populations at very different stages of the epidemic -- for in countries where seroprevalence of HIV among young adults is 20% or 30%, a rather different set of risks and benefits comes into the equation. [As a troubling aside, one of the four countries that had expressed interest in serving as a vaccine trial site -- along with Uganda, Thailand and Brazil -- was Rwanda! So the horrors we have witnessed in that devastated country, ~~are compounded even more~~ already ravaged by the AIDS epidemic, ~~and~~ are compounded even more, resulting in now ~~by~~ the collapse of one would-be vaccine trial site].

One final comment about vaccine research: many investigators had been hoping that in some way the **live** human immunodeficiency virus could be attenuated, so that it would provoke the full panoply of helpful immune responses (whatever those are) without causing disease -- in ~~exact~~ strong analogy to Sabin poliovirus vaccine, for instance. Happily, there exists ~~a~~ primate model in which such hopes could be tested; **unhappily**, the New England Primate Center recently reported that such a simian analog system yielded strongly cautionary results. They found that an attenuated simian

immunodeficiency virus, given to adult macaques, did indeed produce the kind of immunity and protection against challenge with virulent virus for which they had hoped. However, when four infant monkeys were given the same attenuated virus vaccine, they all developed immunologic deficits and two progressed to the simian equivalent of AIDS over several months. Thus, the genetic malleability of the retroviruses to which I have referred in other contexts appears to extend to **that** once-promising avenue of vaccine research. This is one tough group of viruses!!

Before leaving the topic of vaccines, I should make a final comment. Many people refer to a vaccine for AIDS with the same kind of perception that they have about a "cure" -- that once it comes, it'll be all over, and that **until** then no news is good. With that in mind, I once wrote a paper entitled "What would we do with a good AIDS vaccine if we had one?" in which I pointed out that, while a vaccine will be of crucial importance in populations with what I called "double-digit seroprevalence", in our country it will add little to the list of far more useful things we **already know to do** to prevent AIDS: timely and appropriate sex education as part of health education of our children; facilitation of condom usage by people who are sexually active; universal precautions carefully adhered to; and above all intervention in the desperately important epidemic of substance abuse that is fueling the epidemic of HIV and AIDS. (I'll get back to that in a moment).

In all likelihood even the best vaccine for HIV would be appropriate in the United States primarily for specific populations rather than for general use -- and even if one were to try to encourage its deployment, say,

among twelve- or thirteen-year-olds, can you imagine what the public "uptake" would be for an STD vaccine for their kids? So my answer to "What would we do with a good AIDS vaccine?", for Americans, is "Not much -- so we'd better get busy using what we know."

Policy issues

That brings me to brief consideration of some of the policy issues that fester in the climate of national irresolve about AIDS. I want to discuss several aspects of prevention that relate to testing and screening; then revisit the matter of substance abuse as it relates to the epidemic, and finally make a few comments about the cost of care.

It should be evident from what I have said thus far that our best hope for gaining control of this awful epidemic in the foreseeable future lies in the realm of prevention. We know quite a lot about what works and what doesn't, and in fact behavioral interventions in specific communities have had truly dramatic effect -- when they have been allowed to proceed. Changes in chronic (and particularly in pleasurable) behavior in the interest of health have been hard to come by in many venues, as the continued smoking by 30% of our population attests. At the outset of the epidemic, health educators considered a durable 5% change to be a very impressive effect in a given unhealthy behavior. And yet, in some gay communities that were experiencing as much as 18% seroconversion per year in 1980 and -81, that rate dropped to zero within the next three years, reflecting the efficacy of sustained, focussed health educational intervention.

That dramatic effect has predictably yielded to a less than perfect record of prevention in the past few years -- prompting some observers to say "See, it doesn't work!" And yet the new rates of infection are still more than five-fold lower than those awful early figures; and, quite significantly, many of those new infections are occurring in young men. I don't know why one should be surprised to find a generation gap here -- it occurs in virtually every other context. But it is of critical importance in AIDS, for one of the most ominous ~~and important~~ epidemic trends has been that steady drop in average age at time of first infection with HIV! -- in it is occurring in men + women, gay + straight --

Out of the experiences both in gay communities and in adolescent groups at high risk has come the insight that messages of prevention are probably best delivered by peers. Such peer education doesn't necessarily work, and it certainly doesn't happen automatically -- but with good support and guidance, youthful peer educators have helped significantly to convey useful messages of AIDS avoidance to their contemporaries.

In a somewhat analogous context, there have been some communities in which school-based health clinics have been established -- oftentimes serving as the only source of health information for youth whose families are severely dysfunctional. The National Commission on AIDS had the opportunity to visit one such clinic in New Orleans, and I was most impressed by what was going on. Kids clearly viewed the health educator and nurse as trustworthy and valuable sources of information, and they recounted their experiences of taking home advice and information to parents who had never had such access.

As a side comment: during that visit, some activists demonstrated against the establishment for refusing to allow condom distribution in the school. Clearly, in a ~~very~~ dominantly Catholic community that would have been a very difficult policy for the principal to adopt. We asked the kids what they thought about that, and their response was telling: they said that access to condoms themselves wasn't the problem -- it was access to information that was needed, and the school-based clinic, with the strong support of the principal, was supplying that!

Out of the AIDS years have come a number of insights about health education and prevention. First, information alone is of very short-term benefit in most contexts where risk is real -- particularly if it is partial, or sterilized by censorship, or fails to be delivered in the language of the intended listener, and preferably by a trusted source. Its value is considerably enhanced by ~~variety~~ insulin -- that is, the same message delivered in a variety of media and contexts is much more likely to "take." And its real usefulness -- particularly among youth -- can be seriously blunted unless there are adjunctive measures taken to change the dominant mores that put people at risk, and to teach them ways of avoidance that don't jeopardize their friendships and peer status. Those caveats make it far from simple, of course, but they are probably crucial to success -- and this IS a life-and-death matter.

In discussion of prevention, the matter of testing and screening invariably arise ~~for discussion~~, and that is appropriate -- for the serologic test for HIV antibodies is one of the most valuable resources we have. But whenever

the term "mandatory" comes into the discussion, much of that value is lost (or worse). It is crucial to keep in mind that, despite our best efforts, AIDS has invoked discrimination and hostility throughout the years of the epidemic, and matters are not much better now than they ever were. In such a climate, it can be a genuine act of courage for someone who perceives him- or herself to be at risk to seek testing -- and the knowledge of the test result is in itself of limited value.

The reasons to know one's serostatus are several: if the test is positive, anticipatory care can be instituted (such as assessment of CD4 status, prophylaxis against PCP if indicated, careful gynecologic evaluation and follow-up and the like), and people can protect their sexual partners by abstinence or by learning about safer sex. However All of that presupposes access to a medical care system, as well as careful counseling not only in the context of testing but **also subsequently**. It has been found that one-shot counseling has little value -- which isn't really surprising, for in the context of anxiety, very little health information can be conveyed.

So how have we used that crucially important tool?

I believe that ~~such use of~~ testing ~~and~~ counseling for individuals who are found to be seropositive has been done quite well in many venues; and there are increasing numbers of physicians who have incorporated HIV testing and discussions of sexuality into their practices accordingly. Many millions of Americans have indeed been tested. But I also think that a great deal of opportunity has been lost with people whose test is negative -- especially if they themselves had sought testing initially because of awareness of possibly risky behavior. If they are simply given ~~such information~~ their results briefly, they are far too inclined to interpret it as a kind of assurance that they

simply aren't the kind to become infected -- when indeed there is no such impervious kind of person; and risk behavior may continue.

Those comments explain one of the main reasons why I, for one, have opposed the "home test kit" approach that has been given the go-ahead recently by the FDA. I worry about the viability of plans being put forward to assure that seropositive results are delivered in a care setting (although the people who are working in that area are excellent). But I worry more about that potentially false reassurance of a seronegative result: data is accumulating to suggest that people are at their very most infectious for sexual partners in those few weeks before antibody appears, at the outset of infection -- and the temptation to keep up risky behavior while "checking in" occasionally with a home test kit may seriously enhance the danger of further spread.

One other situation in which testing has been debated rather hotly in recent months has been in the context of antenatal care. The impetus for renewed debate is fundamentally good news: a single, well-done study of pregnant women who were HIV-infected suggested that the risk of transmission to their infants in the perinatal period was lowered from 25% in the untreated group to 8% in infants whose mothers had received AZT during pregnancy, at delivery and who themselves were given AZT for a period of six weeks after birth. The study, labeled "076" by the NIH, has prompted suggestions that all HIV-infected women and their infants should be so treated; and in a number of states it has reactivated calls for the mandatory testing of pregnant women.

There are some real problems with that, in my view. While early findings suggest that AZT has not caused acute damage to treated infants, it is nonetheless a drug with considerable toxicity, and long-term effects would not be surprising. Under those circumstances, the fact that 3/4 of the infants born to HIV-infected mothers are not themselves infected with or without treatment raises serious questions.

Second, the matter of antiviral resistance -- which, as I have noted, is a persistent and growing problem -- is non-trivial here. The recommendation is being made **regardless** of the stage of infection of the pregnant woman; and it is likely that discontinuous treatment of the mother would be the rule, at least in contexts where most infected pregnancies are currently occurring. As a microbiologist, I worry a lot about that, for it has already been demonstrated that AZT-resistant HIV is transmissible, and we may be accelerating the invalidation of that important therapeutic agent, ~~limited as its efficacy may be.~~

And finally, whether due to lack of access to care or to social or personal circumstances in which HIV infection renders a woman vulnerable to discrimination or (sometimes) to battering, the benefits of instituting such a regimen may be overwhelmed by the harm that comes to her as a result. The well-being of infants is at issue, to be sure; but their ~~well-being~~ welfare is intimately bound up in the overall well-being of their mothers.

I find it hard to say such things, for as a pediatrician I care deeply about the ~~welfare~~ health of children and prevention of HIV infection is devoutly to be wished. However, it is NOT necessary to take the mandatory

approach to this, and there are models one can turn to that have worked well. The state of New Jersey, some years ago, was one of the first and worst to be caught up in the special facet of the AIDS epidemic that involved women and children -- and they went about matters in what I consider a sensible way. They ascertained that there were communities in which the likelihood of HIV in pregnancy was at or above 1%; and they took steps to be sure that treatment and follow-up would be available to all involved women. Having done so, they then adopted a policy of urging women to be tested as part of prenatal care -- and the uptake was nearly universal.

I cannot prove that things would have been worse with a mandatory approach -- but surely our experience with mandatory measures applied to ~~drug~~ testing of pregnant women suggests as much. In that case, women have often avoided any prenatal care whatsoever in order to escape detection -- and until the hostile aura surrounding HIV is dealt with, I fear the same might happen there.

Let me turn to drugs for a moment: I have noted at several points the urgency of need to deal more rationally with the American epidemic of substance abuse. If you haven't been directly involved, you may wonder what I mean -- for there has been much rhetoric devoted to our "war on drugs." It came as a great surprise to me, in 1986 when I was a member of the Institute of Medicine's task force that produced the report entitled Confronting AIDS, to learn that addicted people for the most part wanted desperately to be treated for their addiction ~~but that~~ such treatment was unavailable unless they were affluent or else could somehow keep their

motivation and resolve together over many weeks on waiting lists. When I last inquired a year or so ago, it was still the case that, in every large city in this country, a **poor** person would have to wait four ~~or more~~ weeks for the initiation of treatment. That's awful: we had declared a war on drugs with no accomodation for the prisoners of that war!

The Institute of Medicine group, and every major commission or expert group that has assessed the AIDS epidemic since, has made so-called "treatment on demand" for addicts its top recommendation, and has urged that laws restricting needle access (and which therefore promote sharing) be changed. We have made gradual headway in the latter context: needle exchange programs are now legal in 22 American cities, and there are now good data to show, first, that they do NOT increase drug use and, second, that they DO indeed reduce HIV spread. There were such data in other countries before, but now it has been established for ours as well.

It is difficult to overemphasize the importance of this! Whereas sexual transmission of HIV is mercifully inefficient, sharing of injection apparatus is not. It is the tinder that has sparked flashfire epidemics in cities around the world -- sometimes going from less than 1% of injecting drug users to over fifty or sixty percent infected within two years! We have a massive epidemic on our hands already -- the surest way to make it worse, unpredictably so, is to ignore the critical role played by substance abuse!

Finally, let me make a brief comment about cost of AIDS care. In early years of the epidemic, a number of cost studies were done assessing

annual or lifetime cost of care for people with AIDS, with estimates of averages that were astronomical. At the same time, studies were underway to look at ways to reduce those costs, particularly utilizing case management and exploring outpatient and home care alternatives. Suffice to say that the ~~latter~~ have proved increasingly useful and effective -- especially since the effectiveness of such measures as PCP prophylaxis has been recognized. As a result, the more recent estimates of lifetime cost-of-care for people with AIDS has dropped very significantly -- well into the range of other chronic, debilitating diseases or malignancies. I think that it is ~~an~~ important ~~perception~~ to correct, for in our planning for the future of health care in this country, there will be large numbers of people with HIV disease, and we cannot afford NOT to care for them.

A final comment: I think the medical profession must become much more deeply engaged in this epidemic. I have known far too many women who sought to be tested for HIV and were told by their physician "You don't need to -- you're not 'the type'". I have been alarmed by studies of physician practices in which half or less talked with their patients about sexuality and risk -- and in one such survey, virtually none talked to patients over the age of 50 about sex! I am amazed at reports that residents are trying to locate their residencies "away from AIDS," when the fastest growing (and least likely to be recognized) numbers of cases are in smaller cities and rural areas.

I think by now it should be patently clear that the HIV epidemic is much bigger than that -- that one can try to run, but one can't hide. It is past time that we recognized that we're all in this together; that an awful

shadow has fallen across our land and that only by ~~addressing~~ facing it directly, with care and compassion for those who have already found themselves in its path, will we finally bring this new pathogen under control. It will **not** be the last time we are so challenged, so we really do need to learn its lessons well. Thank you.