Raising the Consciousness for Identifying and Controlling Viral STDs: Fears and Frustrations

Thomas Parran Award Lecture

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PREPARATION TO receive such an honor as the Thomas Parran Award is an interesting process. Initially, there is excitement and nervousness; eventually these feelings are replaced by the fear of deciding what to say. Such an event requires a real speech, not a slide presentation. Moreover it is an award based on "lifetime achievement" and named after a person of history. One's self- perception is not to feel that you have much history - let alone be told you've been around a field long enough to be called historical. However, the "lifetime achievement" designation does serve a purpose...to look back and reflect on what you have been doing for the last 20 years. Self-reflection is not an activity that our society of researchers rewards very often. After all, we are given public monies to push the envelope of knowledge forward, to seek out new problems, new issues, new technologies. We are rewarded for the new, not the old. Each box of slides is to depict something different. Each invitation to lecture demands something innovative. "Take few prisoners, walk forward. Okay, you can list leeward or starboard a little, but don't bore us with the old stuff."

I promise not to bore you tonight—certainly King Holmes, in his introduction, has warmed up the crowd! But the call from Julie Schachter informing me of the committee's decision regarding the Parran award has brought with it all sorts of reflections. First was a perhaps prescient connection, one that my mother-in-law made when she first heard of the Parran Award years ago. Thomas Parran's brother was the obstetrician in Washington, DC, who delivered my wife Amy. Now, this could be taken several ways. My interpretation is that this portended Amy's role as "The shadow on my land" — portending her role in the furtherance of my career, initially, as the person who would sit at the dining room table (we never had a house with a study until much later) and work with me in constructing the line listings on the patients enrolled in my early studies of Reye's syndrome and genital herpes.[1-6] Amy's handwriting, unlike mine, was legible. This allowed some semblance of consistency in results as one poured through each recitation of the listings. This "keeping the data honest" was a function later taken over by computers and most importantly by Drs. Jackie Benedetti and Judith Zeh who are the doctoral level statisticians to our viral disease research projects in Seattle and whose vigilance and intelligence have been a cornerstone of our work.

The reflections from the call also brought a flood of memories on which I will digress because they include so many people involved in this society. Yes . . . it took a whole village to raise this investigator.

How Did It Start

How did I even get to this place? Well, it started with a friendship for over 25 years now with Walt and Peggy Stamm. Walt and I met as Epidemic Intelligence Service (EIS) officers at the Centers for Disease Control and Prevention (CDC) where we investigated an outbreak of hepatitis in a hemodialysis unit in Valhalla, NY. My first *New England Journal of Medicine* paper described this work.[7] It was Walt who told me to look at the infectious dis-

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ease program in Seattle, and it was Marvin Turck who recruited me to Seattle when I attended my first Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) meeting in Chicago in 1974.[8] This led to my first momentous meeting with King Holmes, my postdoctoral mentor at the University of Washington.

It was for me a moment indelibly inscribed in my memory bank. King's reputation as a hard-driving raconteur preceded him. I myself was nervous and excited as all new fellows are in embarking on their future lifelong career. I did not really question the wisdom or choice of my elders in assigning me to King; I was assured that "mother university" would take care of me during these 2 to 3 years of training. I popped my head into his office on July 1, 1975 — said "Hello, I'm Larry Corey." I was pleased he at least recognized the name and he said "Let's have lunch." His office had a spectacular view of Mt. Rainier. Later I learned that it was of enormous utility to King because it gave his advisees something to look at as they sat next to him while he trashed every other sentence that they wrote, every paper they wrote. For many years, he diligently rewrote all my carefully crafted sentences; sentences that he called "old world dribble." Of course my fellows believe that I do the same thing that King did to me, but without the view!!!

Anyway, there was small talk as we rode down the elevator. We entered the typical hospital lunch line. As I pushed the plastic tray through the line, King asked his first question, "What were my interests." I answered, "Viral diseases." He looked back at me quizzically. (I imagined he was thinking, "Where did Marvin Turck get this guy?") I plowed forward with "There aren't many internal medicine virologists so I thought that would be a good career niche."

King looked at me, paused, and said—laconically, I might add—"Sex is my career niche."

I paled...the memory is still indelible. *Kosher home, grandfather's a rabbi in the old country...studious...basically a nerd, moved to a city without corned beef, barely a bagel in sight, and then going to work on sexually transmitted diseases (STDs). My mother was telling people I was going to be a cardiologist. What am I doing here!!*

But what I was doing was learning the tools of one of the world's best trades, academic infectious diseases, from one of the world's best craftsmen and teachers. As a mentor, King was unparalleled. He led by example, had unending energy and patience. He opened doors, watched me walk and then run through them. He was first teacher, then colleague, and now a most dear friend.

The training atmosphere in Seattle was unparalleled. My fellowship colleagues were Gary Schoolnik, Walt Stamm, Joel Meyers, Bob Jones, Bill Bowie, Luci Tomkins, and Henry Rosen. The faculty included Bill Kirby, Bob Petersdorf, Paul Beeson, John Sherris, Seymour Klebanoff, Harry Beaty, George Ray, and Russ Alexander. All were there to teach and help. I learned (1) that to cooperate meant quicker progress; (2) not to be afraid to solve problems quickly, you'll have more ideas than energy; and (3) when asked to participate in a program, say yes. "I'm happy to help you do this project," and "Yes, I think we can do this study."

There was enthusiasm and a feeling that the opportunities were large. Establish a cohort, study a disease, and success would follow. Collaborate - learn to write and follow-up on your patients. In an understated manner King said at that first lunch, "There's this viral disease called genital herpes that no one knows much about, let's study it." Harry Adams had started to study genital herpes the year before I arrived.[9] King introduced me to a physician's assistant named Michael Remington who taught me about clinical STDs and introduced me to the clinic and disease that has occupied much of my career. We started together in 1975 and have been together since. Mike has seen more genital herpes simplex virus (HSV) than anyone on this planet, and I learned then and now to listen to him. Parenthetically we have named our new disease management clinic devoted to herpes "the Remington Clinic."

These "early years"— as I will term them, were also marked with other major mentors; one in particular is not very well known to this audience. His name is Paul Strandjord, and he was chair of the Department of Laboratory Medicine at the University of Washington and my direct "boss" for over 16 years until he retired in 1995. It was Paul who taught me how to administratively be a leader and who conceptualized the administrative structure of the medical virology division within the University of Washington School of Medicine. We developed a "vertically integrated" division —that is, a division within clinical pathology that not only ran a vigorous diagnostics division but also encompassed a far-reaching clinical and laboratory investigative program. This integration between research clinics and laboratories would speed transfer of laboratory discoveries to the clinic. Investigative cohorts would assess new laboratory assays quicker than traditional methods. These ideas were prophetic, and this structure has been perhaps the single most important ingredient in the Seattle viral disease success story.

However, other ingredients were also important. Chief among them were colleagues and friends — both within the STD and herpes virus field. Some came to Seattle for their career sojourns. Tom Quinn, Peter Piot, Jorma Paavonen, Bob Brunham, Eric Sandstrom, Ned Hook, and Ann Rompalo helped expand the problems and perspective on HSV infections. Hunter Handsfield returned from San Diego to run the King County STD Clinic and became a critical colleague and dear friend. Zane Brown, who trained at Utah, came to the Department of Obstetrics and Gynecology as a faculty member and initiated a truly productive 20-year collaboration.

Collaborators within the field of genital and neonatal herpes included Steve Straus at the National Institutes of

Health, Richard Whitley at Alabama, Andre Nahmias of Emory University, Ann Arvin and Charles Prober at Stanford, Yvonne Bryson at University of California, Los Angeles, Steve Sacks in Vancouver, Larry Stanberry in Cincinnati, and Adrian Mindel in London and now Sydney. While we competed, we also cooperated. There was camaraderie to the field.

During the early 1980s the STD field was a boom: Case rates were skyrocketing and new syndromes were being defined.[10–12] My field of genital herpes led the way. It was the prototypical viral STD — hepatitis B was treated by gastroenterologists who did not want to admit their infection was an STD. Cytomegalovirus — well— it was for immunocompromised persons and newborns. Human immunodeficiency virus (HIV) was not yet in the scene, and human papilloma virus (HPV) and cervical cancer were a nascent field. However, genital herpes was a clearly defined chronic STD. Media and patient concerns were heightened.[13-15]

I threw myself into the thick of this boiling pot. Perhaps it was not hard. Incidence rates were booming, and we could see two to three persons daily with true primary infection.[16,17] These patients, especially women, were sick with fever, chills, headache, dysuria, huge genital and/or pharyngeal lesions, barely examinable whether male or female. Once monthly a case of herpes simplex virus type 2 (HSV-2)–associated aseptic meningitis was admitted to the University of Washington hospitals.[16] Primary genital herpes had replaced disseminated gonococcal infection as the hospitalized STD. The two fellows in the Seattle program who handled inpatients were Dave Martin — investigating Reiters Syndrome — and myself, seeing patients with aseptic meningitis caused by HSV, HSV encephalitis, and then neonatal herpes. My first faculty office was located at the Children's Hospital & Medical Center, and we saw a steady stream of cases of neonatal HSV, nearly one a month.[18–20] Recently Zane Brown, my obstetrical colleague, published a paper this past year on why we saw so many neonatal HSV cases. It is because neonatal transmission occurs nearly exclusively among those women who acquire first episodes of HSV in the late third trimester.[21] As such, it follows closely incident cases of HSV. Educational and medical strategies to attack neonatal herpes were not in place in the early 1980s. In fact, 15 years later they are still not in place — an issue to which we shall return.

There were no therapies or cures. My first plenary talk at ICAAC reviewing genital herpes had me showing a blank slide for effective therapies of genital herpes.[22] Albert Sabin espoused ether therapy, as if one could dissolve the virus away.[23] I conducted a study of this compound and produced a crying rate of 30% with application of this medication to genital lesions. It produced another *New England Journal of Medicine* paper, but it did little to my reputation in Seattle as a "healer."[24] Not everything that burns when it goes on works. I apologized to my patients profusely.

Shortly after this study, perhaps out of guilt, I started working on an idea for a patient advocacy or an educational effort for genital herpes. Two staffers with the American Social Health Association, Carla Hines and Sam Knox, helped execute the idea and we established the HELP organization now called the Herpes Resource Center.[13,25] A. Martin Lerner of Wayne State University also helped in this endeavor. We initiated a quarterly newsletter called the HELPER, which is now in its second decade of publication and has a circulation of over 20,000.[26] Charlie Ebel, who is in the audience today, was the medical writer for the HELPER and had the gift of being able to take arcane scientific topics such as subclinical shedding and make it into understandable lay prose. The HELPER has been the prototype for the detailed medical newsletters on HIV and breast cancer that their advocacy groups now publish.

The Acyclovir Years

The real breakthrough in my career came in the early 1980s. Three things occurred: luck, great colleagues, and great postdoctoral fellows. I think almost everyone close to me has heard my admonition, "It is better to be lucky than good," or has seen the small quilting on the wall of my office that says "If at first you succeed, try hard not to look astonished." Well, I was lucky — for the antiviral drug acyclovir was dropped into my lap.[27] The stars were in the right order; we had spent the previous 3 years learning how to study a potential therapy for genital herpes, how to chart lesions, culture the virus from lesions, and record and analyze the information necessary to demonstrate a potentially effective therapy.[4,6,9,15,16,24] Acyclovir brought working relationships with Trudy Elion, David Barry, Dannie King, and Gray Davis from the Burroughs Wellcome Corporation. Planning and coordinating the studies of acyclovir for genital herpes was a true collaboration, and we led acyclovir (actually, I think the drug led us) to approval as the first fast-tracked drug in infectious disease.[28–34] Who would have predicted that this nucleoside analog would be perhaps the safest anti-infective drug we currently have to treat an infectious disease?[35] One of the seminal studies in this journey was one using intravenous (IV) therapy for severe genital herpes, a study Ken Fife and I conducted at the University of Washington Clinical Research Center.[29] The trial was a double-blinded trial in which patients with severe primary genital herpes were admitted for 5 days of IV therapy or saline placebo. It became very clear to us that something very momentous was happening to half of the patients. Yes, when you have a dramatic therapy, the double blind does not always hold.[29]

This study charted the course for the rest of the acyclovir development program. Once we knew what the compound could do, it became easier to do more far-reaching studies. Oral therapy for primary infection[31,34,36] and daily therapy for suppression quickly moved forward.[33,37] The concept of

using an antiviral on a daily basis in healthy people was mind boggling to most physicians and scientists. There were warnings of dire consequences from several colleagues. More than once, I was pulled aside at meetings and lectured about the danger of our daily suppression studies of oral acyclovir, especially concerns about future malignancies or sterility. [38,39] What moved these studies forward quickly but methodically was enthusiastic and clever postdoctoral fellows: Ken Fife, John Douglas, Greg Mertz, Rhoda Ashley, and John Sullivan-Bolyai. Each brought their intellect and hard work to these early studies of the therapy of genital and neonatal herpes. I think that we cut a wide swath in the field of genital herpes therapy in a very short time period. Within 4 years it was largely over — oral therapy emerged as an effective form of therapy for first infection, recurrent infections, and suppression. Studies of IV therapy for treatment of encephalitis and the neonate were being led by Rich Whitley and Ann Arvin.[40,41] Licensure and press conferences took place; the studies made it on to the CDC STD guidelines.[42] There ensued a pause or perhaps even a malaise. During my morning run I'd bemoan "what do I do next?"—the excitement seemed to have ended...

But the malaise was short-lived because HIV arrived. In 1985, Bob Coombs came to Seattle as a postdoctoral fellow to work on HPV. The immunodeficiency syndrome of gay men was being tracked by Ann Collier and Hunter Handsfield in Seattle, and it became clear that we needed to initiate a virological program in HIV. Shortly after HIV was identified, Bob went to Martin Hirsch's laboratory at Massachusetts General Hospital to learn how to culture HIV. From 1986 until my sabbatical in 1993 with Ed Mocarski at Stanford, HIV was a constant preoccupation.[43–47] It is still one as we in our group struggle on the difficult issues of how to develop an effective HIV-1 vaccine.[48–53]

With Ann Collier, I established the University of Washington ACTU, one of the original 14. My colleagues graced me with chairing the executive committee of the largest clinical trials program in history. It grew from 14 to over 53 academic medical centers.

The years between 1988 and 1991 were tumultuous ones for me personally. As chair of the AIDS Clinical Trials Unit Executive Committee, there was constant travel to the other Washington and exposure to the difficult issues between researchers and HIV activists. Perhaps my early years dealing with the frustration of ineffective therapy with genital herpes helped in this area. The issues of an activist's role in designing clinical trials and scientific agendas are complicated and clearly worthy of reflection. It is an area of interest that one day I have vowed to write about, but not tonight.

Research Findings and Public Health Programs

Tonight, I want to talk about the extension of research messages into the clinical care and public health sector.

For, while we as researchers have our insular meetings and our own standards of accolades, the purpose of dollars from public monies to support medical research is to translate these research findings into an improved, public good. I will personalize this and, as you might expect from the title of this talk, "Raising the Consciousness for Identifying Viral STDs: Fears and Frustrations," the issue of translating clinical research in genital herpes to public health control for genital herpes has been, for me, a convoluted and sometimes frustrating process.

The theme I will be espousing tonight is that translation of research findings into routine medical practice, and more importantly public health practice, is not straightforward and that we as medical researchers need to spend more time and effort in this arena. Let's look at our own work over the last 20 years and what it has done for the public health.

If I can toot our horn a bit, we have spent the public monies given to us fairly effectively. We have accomplished the following goals:

1. Developed the currently used serological and clinical classification for genital herpes.[15–17]
2. Defined the natural history of genital herpes, documenting its frequency, site of reactivation, and a disconcertingly high reactivation rate.[54–57]
3. Demonstrated the role prior HSV-1 had on ameliorating first episode infection and increasing the frequency of the subclinical acquisition of HSV-2.[15,16,28,57,58]
4. Showed the differences in the natural history of genital HSV-1 and HSV-2 in the adult and the lower morbidity of HSV-1 in the neonate.[59,60]
5. Demonstrated the first effective therapy for primary HSV-2 and conducted the first studies of long-term suppressive therapy for clinical recurrences.[28,31,33]
6. Rhoda Ashley perfected the western blot serology that has become the gold standard for defining seroconversion to HSV-1 and HSV-2 and for defining past HSV-2 from HSV-1 infection[30,61]; Rhoda has led the fight to reduce the use of inaccurate commercially based enzyme immunoassay (EIA) serologies and has pioneered the development of accurate commercially based, type-specific serological assays.[62–64]
7. With Laura Koutsky, showed that most persons do not present with "classic" genital herpes but present with what has been labeled atypical lesions; these atypical lesions are a misnomer for in actuality these "atypical lesions" are the most common manifestations of genital herpes.[65]
8. Defined the natural history of subclinical shedding.[66–69] These studies showed that HSV reactivation is 5 to 10 times more frequent than previously appreciated. When measured by PCR-based methods, HSV-2 can be detected on genital mucosa on average 20% of days.[68,69] Thus, for teaching and epidemiological pur-

poses, this makes genital herpes more akin to a persistent rather than intermittent infection. Thus, it appears that the exposure rate of neonates and sexual partners of HSV-2 seropositive persons are high; making the exposure per transmission ratio also high (i.e., a lower efficiency of transmissions than previously appreciated).[69] Our recent data suggest that the sexual transmission efficiency of HSV is about the same as HIV, about 5 per 10,000 coital events, or .02% of sexual contacts.[70] Although the transmission rate per exposure may be low, the high reactivation rate has implications for the role subclinical HSV shedding plays as a cofactor in HIV disease transmission and acquisition, an issue I discussed in the plenary session yesterday.

9. In a study with Andria Langenberg that has been largely ignored by people in the public health sphere, we showed that most HSV acquisitions are really symptomatic and that the vast majority of HSV-2 seropositive persons have unrecognized symptomatic infection. We demonstrated that with a 15 minute counseling session with a health educator; most persons can be taught to identify clinical recurrences.[71] I will return to this issue later.
10. In recent studies led by Anna Wald, we have in the last 3 years provided firm footing to the concept that it is HSV-2 seropositivity that is the major driver for infectiousness and transmission; our PCR-based studies show that nearly all HSV-2 seropositives, whether symptomatic or with unrecognized infections, shed subclinically.[72,73] We and others have shown that subclinical shedding accounts for nearly all the HSV-2 transmissions perinatally or sexually.[74–80]
11. Showed the benefits of daily acyclovir for reducing subclinical shedding, suggesting that antiviral therapy can in selected situations be a tool for reducing transmission.[81,82] A multicenter study to test this concept is about ready to start. Such a study is necessary to quantitate the value of this approach, but it is difficult to conceive that the 95% reduction that oral anti-HSV compounds produce in reducing subclinical shedding will not translate into some clinical benefit.
12. With Steve Straus and collaborators at Chiron Corporation, showed that immunotherapy can affect a chronic viral disease in humans.[83,84]
13. Our 15-year quest for an effective vaccine against genital herpes has been to date unsuccessful.[70,85–90] However, David Koelle and Chris Posavad of our group have recognized that the critical immune responses to HSV are cytotoxic T cells, that the quantity of the HSV-specific CD8+ T cells influence the severity of disease in immunocompromised patients, and that infiltration of such cells in genital lesions is associated with viral clearance from lesions.[89–92] These data lay the groundwork for greatly improved immunotherapeutic approaches to herpesvirus infections. The laboratory is currently attempting to identify the viral antigens to which these CD8+ T cells are directed.[93]

Yet for all these research accomplishments, the objective data show that we have done little for the public health. Last week's publication in the *New England Journal of Medicine* by the CDC on the 31% increase in HSV-2 seroprevalence in the United States has aptly shown that little of this work has been translated into even a nascent public health policy.[94]

A Paradigm Shift

I would like to spend time examining this issue and perhaps suggest that we in the American STD Association and ISSTDR must lead a paradigm shift about viral STDs, and I will contend that if we make this paradigm shift we will reenergize our public health programs and our own field. The shibboleth "it's too expensive and too hard to initiate programs for viral STDs with current strapped resources" is a self-defeating prophecy and one that will forever mire us into what I will call the linoleum-like landscaping for STD control. Frankly, I like carpeting, and my wife prefers marble, but my theme tonight is that we must argue both more broadly and persuasively for programs designed to reduce the spread of viral STDs. For, if we look at ways to initiate new programs for viral STD control, rather than espousing excuses as to why we cannot do something, we personally, and more importantly, the health of our constituency, will be improved. In fact, I passionately feel that if we do not move forward we will as a research field and as a medical society die.

I am not espousing a novel concept here. Thomas Parran, in his book, *A Shadow on the Land,* stated the following:

> The bright side of a career service in public health is that an able man has a considerable opportunity to give his whole mind to the learning and doing of his task. The dark side may be expressed by the much quoted saying that the strongest impulse of the human race is "just to sit." Under lax leadership, every group with civil service or other job protection tends to develop a certain number of fat-heads and chair-warmers. The same thing is true of business and industry. The answer for it is energetic leadership under which men who are good to start with cannot degenerate into drones.[95]

Although some of the terms used here are "dated," the idea is not. Parenthetically, one quickly learns from reading classical works how bright our early brethren were and what differentiates them from us are our technological tools in problem solving, not our intellect, as demonstrated in the next quote from Dr. Parran:

> So far as the well-being of the human race is concerned, I look upon the great question of syphilis today as ... no

longer a question of treatment, mercy or no mercy, that time has passed and now it is a question of prevention or the protection of the well for the sick. It is no longer a question for the therapist, but one for the public health.[96]

The similarities between *Treponema pallidum* control in the 1930s pre-penicillin and HSV, HIV, and other viral STD control are remarkable. The basic concept is simple: The object of public health prevention is to reduce transmission or acquisition of an STD, and while the tools to do so may be imperfect, to not even attempt to muster a control program with available tools is just wrong public policy.

As shown in Table 1, the clinical and epidemiological similarities between the acquisition of viral and bacterial STDs are similar. Both viral and bacterial STDs are usually acquired from an asymptomatic carrier. In both, the source contact can often be identified — increasingly so in viral STDs, which are chronic and hence a major feature for social networks of persons with sequential monogamous sexual relationships.[97] Clinical diagnoses are poor in both bacterial and viral STDs, and laboratory-based assays are required for an etiologic diagnosis. These laboratory assays precipitate case contact investigation. One difference is that most therapy for bacterial STDs are curative and viral STDs are not. In other words, viral STDs are analogous to bacterial STDs in the Thomas Parran era. Lastly, as shown so frequently by papers presented at this meeting, both viral and bacterial STDs increase the risk of HIV transmission and acquisition.[98–105]

Table 2 depicts the current model at STD clinics for control of bacterial STDs. Public STD clinics are geared to treating the symptomatic patient. They also have screening programs for identifying the asymptomatic carrier by either culture or serology, whatever is more effective. Lastly, they engage in source contact investigation. Yet despite the similarities between the acquisition, transmission, and diagnosis of viral and bacterial STDs in Table 1, I know of no current program within public health departments that uses the concepts of Table 2 for the control of genital HSV infections. My dearest hope is that the Fleming paper and the CDC's recent commitment to initiate a program to monitor

TABLE 1. Similarities Between Bacterial and Viral STDs

Index Cases	Bacterial Pathogens	Viral Pathogens
Usually acquired from an asymptomatic carrier	✓	✓
Source contact can often be identified	✓	✓
Serological test can accurately identify source contact	✓* (*T. Pallidum*)	✓
Laboratory assay required to define infection	✓	✓
Treatment of infection shortens duration of symptoms and complications	✓	✓
Increases the risk of contracting HIV-1 infection	✓	✓

TABLE 2. Current Model for Control of Bacterial STDs

- Establish service clinic for treatment of symptomatic persons.
- Establish screening program for asymptomatic carriers in high-risk populations.
- Use serological screening to identify carriers.
- Source contact identification using specialized investigators or self-repeating systems.

antiviral resistance to HSV-2 signal a new appreciation for these issues.[94]

You could ask what is required to develop an HSV control program. There are, in my opinion, two parts to this question: (1) Are the tools available to do it? and (2) Is there the will or desire to do it?

Let's discuss part 1: Are the tools available to initiate a screening program for HSV-1 infection in STD clinics? Here the answer is clearly yes. Type-specific serological assays have been available in reference laboratories for a decade.[106] Moreover, commercialization of these products has occurred in the last 12 months. [64] Although laboratory assays such as viral cultures or antigen detection and accurate HSV serologies are going to cost more than a Thayer-Martin plate, they are similar in cost to a chlamydia ligase chain reaction (LCR). With high volume testing, the cost of a chlamydia LCR is about $13; this is similar to the estimated cost of an HSV specific serology by EIA.[107,108]

How about part 2 of the query "Is there the will or desire to tackle this problem?" In my opinion, herein is the issue. Let's digress a bit and discuss the issues surrounding and identifying persons with unrecognized or subclinical HSV. In other words, let's look at the medical and public health reasons to diagnose unrecognized genital herpes and change our current paradigm of "Ignorance is bliss." After all, why not let sleeping dogs lie?

The reasons for diagnosing HSV are clear and shown in Table 3: (1) Most HSV-2 seropositives are truly symptomatic (80%) and with serological identification and a short counseling session can be shown to have clinical disease.[89,109] (2) Moreover, emerging data indicate that once told they have genital herpes, patients increase their condom use and the frequency of having sex during periods of

TABLE 3. Clinical Reasons for Diagnosing Genital Herpes

Most HSV-2 seropositives are truly symptomatic.
- 20% know they have the disease.
- 60% have unrecognized infections.
- 20% are asymptomatic.

1/3–1/2 of those with unrecognized infections are misdiagnosing their recurrences as other maladies.
- Costly.
- Not good clinical practice.

75% of persons with either unrecognized infection or asymptomatic infection shed virus subclinically by viral isolation. By PCR-based assays this is likely to be even higher.

lesions decreases. In a recent HSV-2 vaccine trial the transmission rate per contact event was reduced by half as counseling messages about transmission were given.[70] (3) Additionally, as shown in our study by Langenberg et al., many of the women with unrecognized genital herpes with HSV episodes get misdiagnosed[88] as having yeast or other vaginal or bacterial infections and are given inappropriate therapy. Our study on this issue was conducted before over-the-counter vaginal prescriptions were available. I suspect the figure in Table 3 is, in reality, even higher.

If we believe identification and counseling offer some public health benefit, it seems to me the vast weight of the evidence suggests that initiating control programs for genital HSV prevention via identification and counseling are both approachable, necessary, and cost-beneficial.

Feasibility of a Serological Screening Program

As discussed earlier, what makes a control program for HSV-2 possible is the development and commercialization of type-specific serological assays, assays that allow for routine screening for HSV-2 in high-prevalence situations. The two areas I would first propose as demonstration projects for such a serological screening program are (1) STD clinics and (2) Ob/Gyn practices in which serological screening for HSV would be performed in the third trimester (Table 4). This latter approach is directed at preventing neonatal HSV (albeit it will identify carriers and susceptibles). Here the intervention would be to identify women who are susceptible to acquiring HSV in the last trimester of pregnancy. Thus, the intervention would be to identify women who lack HSV-2 antibodies who are sexual partners of persons who are HSV-2 seropositive (or HSV-1 seropositive in the HSV seronegative women). The goal of screening and counseling is to prevent acquisition of HSV in the late trimester.[21,110-112] As this occurs in only about 15% of couples, this is in our opinion a very definable objective. [21,110-112]

For the STD field, I feel that a serological screening program to identify HSV-2 seropositives in STD clinics is what we must undertake. At this state of our knowledge, I cannot and should not state what is the "best or most correct" approach. Should all STD attendees be screened? Should only select high-risk ones be screened in an attempt to keep HSV and HIV from co-circulating in the same populations? Studies on such issues need to be conducted. But action needs to be taken now. On an epidemiological basis the HSV-2 epidemic has preceded the HIV epidemic in nearly all population groups.[94-100,113,114] It is a dangerous situation to increase the efficiency of transmission of HIV by several-fold and acquisition by twofold. This is great for the HIV-1 virus but bad public health policy for the populace.[113-115]

Table 5 depicts the reasons why a serological screening program for HSV-2 is likely to useful. First the "hit rate" will be higher than most other screening programs we initiate; in most STD clinics, 35% to 50% of attendees who undergo testing will need to be "counseled." To me this makes it an obvious success. However, to Thomas Parran "chair-warmers" it brings out such nervous palpitations as to the amount of work it will take to identify so many people with a chronic transmittable viral disease that the discussion gets mired not in public health good, but with the high cost of such a program and the difficulty in initiating counseling messages. The simple fact of the matter is that there are substantive data to show that counseling messages to persons with viral STDs does produce some reduction in risk behavior.[115-118] Certainly this reduction is less than complete, but it is substantive.

Let's look at the potential scenarios of such an effort from such a screening program in Seattle (Table 6), where the studies show the prevalence in the STD clinic as 40% in women and 30% in men. As shown in Table 6, a serological screening program would, in a 2-year time period (we see 5,000 new women and 5000 men yearly), identify 3,400 and 2,650 HSV-2 seropositives. As a comparative figure, the clinics now diagnose about 250 women and 150 men yearly (800 in 2 years) with genital herpes (80% HSV-2). Thus, one would increase the STD diagnosis for herpes from 800 every 2 years to 6,000 every 2 years, a 7.5-fold increase.

Yes, such a program would take work, but it would also be good clinical practice because, as discussed earlier, 25% of these HSV-2 seropositive women with unrecognized HSV-2 think they have other maladies, usually urinary tract infections, vaginal yeast, and bacterial infections, and are getting ineffective and costly therapies for their conditions. Moreover, once these people are identified and told about HSV-2, half of the women and a similar figure in men will recognize they are really symptomatic.[71] As 75% of such persons shed HSV-2 by viral isolation, they are potential transmitters. The higher rates of shedding demonstrated by polymerase chain reaction studies among these people are likely to drive this figure up even more.[68-73] So, at a minimum by serological screening we have identified a new

TABLE 4. Population for Initiation of a HSV Control Program

Initiate serological screening programs for the "chronic carrier" of HSV-2 using type-specific serology
STD clinics
3rd trimester pregnant women in regions with high-incidence rates of genital herpes or high rates of neonatal herpes

TABLE 5. Why Might a Serological Screening and Counseling Program for HSV-2 Be Useful for Public Health Reasons?

- "Hit rate" will be higher than any other STD (25%–50%).
- Subclinical shedding is the major mode of HSV-2 transmissions.
- Education and counseling appear to reduce the transmission of HSV-2 among sexual partners.

TABLE 6. Summary of a Postulated Serological Screening Program for an STD Clinic—10,000 New Male and 10,000 New Female Patients

		Women	Men
a.	Estimated seroprevalence of HSV-2	40%	30%
b.	No. of HSV-2 carriers that would be identified	4,000	3,000
c.	No. of newly identified cases of HSV-2 (85% of b)	3,400	2,550
d.	No. who have unrecognized clinically symptomatic infection once counseled (50% of c)	1,700	1,275
e.	No. receiving wrongful therapy (30% of d)	510	(?)
f.	No. who are subclinical shedders only (25% of c)	850	640
g.	Total no. of new cases of HSV-2 identified who are potential transmitters (d + f)	2,550	1,915
h.	No. of newly identified HSV-2 seropositive people whom we cannot tell whether they have clinical disease or at risk of transmitting disease (c-g)	850 (1,700)*	635 (1,275)
i.	No. of people told they do not have HSV-2	6,000	7,000

*Total no. newly identified who have no clinical illness and may or may not be shedders.

clinically significant STD in 20% of all women and 15% of all new male attendees with an assay that is similar in cost to a chlamydial LCR.

To me the cost-benefit in such an approach is so obvious that I would turn the question around — *why aren't STD and venereology clinics clamoring to do this?*

Clearly this approach will require resources. It would take time and money to spread the news about this viral STD to large numbers of men and women. But how this is done can also be innovative. I would like to remind the audience that the studies we published on identifying HSV-2 carriers were conducted with university students who used pictures and graphics that our professional staff developed for the expressed purpose of identifying genital herpes.[71,73] We in Seattle have models for such educational materials, and I am certain other organizations experienced in these areas can do even better. But one thing is clear, STD and venereology clinics need to develop better patient educational materials to perform the following: Describe genital herpes — what are its complications? How it is transmitted; how it can be treated; how transmission can be decreased. Moreover, these materials must be available in differing media forms such as CD-ROM, video, or audiotapes.

I see great opportunity in the field for health education in STD clinics. The paradigm of the one-on-one clinician visit to counsel persons on acquisition and transmission is inefficient, expensive, and frankly not feasible for the effort. Just because this approach is not feasible does not mean we abrogate our responsibility to do health education. What we need to do is develop new models; to deliver patient education materials such as videos, interactive CD-ROMs, and group education sessions are all ways to deliver information and to develop new types of employees for the STD field. We must acknowledge that reading pamphlets is not what most of our clientele best understand or find palatable. In my opinion, "electronic media" is the way to help deliver the message; the electronic medicine can deliver a health message efficiently and cheaply. The purpose of my talk tonight is not to delve into the details of such an HSV control program but to make a single point. It seems to me that it does us all good to start to tackle the issues of how to cope with chronic viral STDs.

Again Dr. Parran was prophetic when he said, "The first job in syphilis control is to teach."[119]

Next, I think we can also help public health control by paying attention to HSV more at the "point of service" (Table 7). This means more attention to diagnosis and more attention to the potential of using suppressive therapy to reduce transmission. Table 7 illustrates a few situations in which I feel we need to use suppression more frequently. Subclinical shedding is high in the initial 6 months postacquisition.[67,120] For many persons, it would appear prudent to initiate therapy at diagnosis until education efforts are embraced.

Too often we approach the viral STD with the attitude, "It's too expensive to treat, counsel, and deal with this. We in the public STD clinic are here for a quick pop-in and pop-out, we're public not private health care. Therefore, it must be cheap and quick." This philosophy is somewhat puzzling to me, as we do not see this in many other public health sections. Would we get far with immunization and tuberculosis control if long-term follow-up was not a part of the program? Acyclovir is now generic - it is affordable. I am not advocating spraying the clinic or spiking the water with

TABLE 7. Suggestions for Improved Clinical Management of Genital Herpes

Aggressively diagnose, educate, and treat newly acquired cases.
Use suppressive acyclovir more frequently for persons who refuse to use condoms and have multiple sexual partners.
Consider use of suppressive acyclovir during early post–acquisition period among persons who feel they will not be abstinent.

antivirals — quite the contrary. But I am advocating that identifying persons with an STD and treating it is not a wrong public health policy.

Our current aversion to use serological screening to identify persons with symptomatic HSV-2 because it is expensive and might cause "psychological morbidity" to those who are HSV-2 seropositive but do not know they have the disease is terribly misguided and self-serving. People do not like to transmit infections to others. Yes, it is difficult as a health professional to tell someone they have something they do not want to have. It is made even worse when we as the health care providers cannot cure this person of the malady and function in the role of "healer." But isn't it more difficult to be accused of transmitting an infection that in 1% of persons leaves them hospitalized, that in 20% to 40% will cause a woman to have a subsequent cesarean section, and invariably leads to chronic morbidity?[16] After all, haven't we learned enough from social networks that even if only 50% of genital HSV acquisitions are symptomatic, identifying the undiagnosed carrier will reduce symptomatic first- episode disease and medical morbidity in a large number of people.

Again Thomas Parran was right on two accords. His action plan for *T. pallidum* is pertinent today: identifying the cause, identifying the contacts, treating the patient with the disease, and educating the patient as to the mechanism of transmission (Table 8). It is the public health agency that must be required to participate in these tasks. Moreover, his ideas that it is government that must lead the way to public health control are also, in my opinion, correct. "In general, it may be said that in no place in the world has syphilis declined without active government interaction. A nationally coordinated attack upon it seems as necessary as upon an invading army."[121]

Closing

To date, an HSV vaccine has alluded us. However, I feel we should be optimistic that an effective vaccine will eventually emerge, perhaps even with one of the products in clinical trials now. In the interim, we must develop a plan for reducing the skyrocketing rates of HSV-2 that are occurring worldwide. One of the functions of our society must be to initiate such demonstration programs. Current resources, while not perfect, are not trivial and are likely to have some success. With the seroprevalence of HSV-2 at such high rates it will take time to see an effect. Perhaps the best we can expect would be a slowing of the rate of infection over the next few years.

TABLE 8. Thomas Parran's Platform for Action for Control of *T. pallidum* (Pre-Penicillin)

- Identify cases.
- Identify contacts.
- Enough money to make treatment possible. It is not in the public interest to retard therapy, especially by cost.
- Public health agencies must be "re-aligned" to participate in the above tasks.
- Citizens must be informed as to the means and methods of individual and public protection.

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