Informed Opinion

A Possible Psychoneuroimmunologic Basis for Recurrent Genital Herpes Simplex

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Genital herpes simplex is a vexing problem for both patients and physicians. For patients afflicted with herpes simplex, the chronic and recurrent nature of the disease, coupled with the therapeutic intractability of the malady, fosters a sense of anguish and helplessness that leads some to despair of ever recovering. For physicians, the therapeutic dilemma of destroying the latent viral genome of herpes simplex within the privileged sanctuary of an infected host's sacral ganglia represents a task that is presently beyond their medical scope. The therapeutic alternatives available to physicians, limited as they are, and the peculiar biologic behavior of the herpesvirus within the protected confines of the neural tissue, sometimes create a defeatist attitude towards both the disease and medical intervention.

The sad dicta "learn to live with it" and "nothing can be done" have frequently been conveyed to patients by physicians experienced with genital herpes simplex. This "hanging of crepe" strategy[1] only serves to increase the pessimism and compound the depression of an afflicted person; this type of "truth telling" of conveying a grim outcome of disease can, like a voodoo doctor's hex, be self-fulfilling.[2] Belief in the certainty of a bad prognosis can create feelings of futility and despair that hinder recovery.

Data from an epidemiologic survey of 375 patients with genital herpes simplex[3] seem to support the apparent futility of therapeutic intervention in the recurrent form of the disease. Yet this apocalyptic judgment with its apparent support for therapeutic nihilism, logical and scientific as it may seem, is faulty and the conclusion is fundamentally flawed, for it fails to take into account the basic immunologic forces within patients. These forces are immediately directed against the virus and actually effect recovery (temporary though it may be) from individual episodes of genital herpes simplex. Likewise, there are moral imperatives, for, while herpes simplex may not at this time be curable in a biologic sense, physicians can nevertheless provide succor and support to patients. The negative hypothesis also fails to consider the "magical" component of a physician's ministrations—that is, the physician's reassuring and consoling nature, or the shamanistic ritual of the office visit. Likewise, the possible therapeutic influence of placebos[4] is underestimated by this faulty conclusion.

Regardless of the value of medical intervention, the fact remains that genital herpes simplex has a profound influence on patients' emotional well-being. It is generally acknowledged that patients' psychologic perception of illness and their ability to cope have a significant impact on both their body chemistry and their capacity to recover from illness.[5] This view of the duality of mind and body, couched in vague and nonquantifiable psychologic terms, has been generally received with skeptical but tolerant acceptance by the medical community. Only recently has a more scientific psychophysiologic basis for this conclusion been elucidated, and the neurochemical mediators that govern these processes defined.[6,7]

Evidence is emerging that emotional stress and anxiety surrounding disease are integrated through hypothalamic centers in the brain, which in turn trigger neurohumoral mediators that may react with receptor lymphoid cells to suppress the immunologic capacity of the host.[8] Before examining in some detail the molecular basis for this proposed psychoneuroimmunologic axis, it seems appropriate to consider some of the psychodynamic conflicts occurring in patients who have recurrent genital herpes simplex. It is also important to examine the media's perception of the dis-

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ease as it affects patients. Finally, it is necessary to understand the dilemma of a physician confronted with a patient with recurrent disease.

Psychologic Factors

For some patients the initial episode of genital herpes simplex is terrifying, given the almost universal, though incorrect, perception that the disease is incurable and that there is nothing to be done. Likewise, a limited understanding of the condition, or spurious information gleaned from friends or the news media, often exacerbate their fears. Aside from the pain, fever and toxemia that often accompany primary genital infection, many patients' first reactions are those of anger and resentment vented against the sexual partner who is thought to be responsible for the infection. In other situations, the reactions include bewilderment and confusion, as patients whose sexual consorts do not have the disease vainly attempt to understand the means whereby they became infected (autoinoculation, asymptomatic viral shedding or reactivation of previously latent disease). Regardless of the circumstances, patients are confronted with a situation that is alien to their prior medical experience: They are infected with a disease that strikes at their most basic biologic drive; there is no apparent way to rid themselves of the virus, and they perceive themselves to be physically and emotionally stigmatized.

Patients who have the recurrent form of genital herpes simplex often feel depressed and vulnerable as a consequence of the infection; they convey feelings of sexual isolation and lowered self-esteem. They often become pessimistic over the repeated failures of various therapies to alter the course of their disease. Genital herpes simplex infection often comes to dominate a major part of their daily thoughts and the impact of the infection on their sex life is often devastating. Relationships with actual or potential sexual consorts become colored by worry over the communicability of the infection. Real or imagined concerns about the disease result in withdrawal of some patients from interpersonal relationships, while others choose celibacy as a permanent and established mode of behavior. Some persons have conveyed the irrational belief that the infection is a penalty for real or imagined transgressions in life.

This recitation of patients' attitudes towards their malady may be viewed by some as melodramatic, if not exaggerated. Yet the psychic toll exacted by genital herpes simplex on sufferers is unique, given the protracted course of the disease and its maddening recurrences. The dimensions of emotional suffering and personal tragedy resulting from genital herpes simplex have not been previously documented. Among the comments made by patients during our own epidemiologic survey, the following quotes are representative:

The continuing outbreaks of herpes simplex make me suicidally depressed. I am hideously unhappy and constantly depressed.

Highly sobering . . . very destructive. The "kiss of death" upon any hopes of sexual fulfillment and its broader implications.

It's a crippling and depressing disease. It makes me angry that I am afflicted, and despite my best efforts it continues to plague me.

It is dreadful and has destroyed my sex life. My husband's, too. It is fortunate that we really had a full sex life previously and therefore are content to be friends. We are completely faithful, but it is really a shame.

Herpes made my life so miserable that I wanted to commit suicide. I don't believe I will ever be healed and normal again.

I am embarrassed at having it and find it difficult to inform a new sexual partner at the beginning of a relationship for fear of what he might think.

The Communications Media

Genital herpes simplex infection has attracted national attention in the lay press, radio and television. The common perception of the public—fostered by members of the communications media—regarding the incurability of the disease and its intractability to conventional medical management have created a profound degree of anguish and despair among those afflicted patients who derive their primary information about the disease from nonmedical sources.

While reporting on the national epidemic of genital herpes simplex, the news media and slick cover magazines have often unnecessarily sensationalized the problem. Lurid headlines have appeared trumpeting the Dantean nature of the affliction: "Herpes Simplex: The New Sexual Leprosy" *(Time,* July 28, 1980, p 76), "A New Incurable Venereal Disease Called Herpes Is Sweeping the Country" *(People,* October 1, 1979, pp 49-54) or "Lovesick: The Terrible Curse of Herpes" (*Rolling Stone,* March 4, 1982, pp 23-24). The articles go on to document some of the known medical facts about genital herpes simplex, but offer readers little hope of recovery, or even respite from the disease. Reporters seem more intent on clever style and journalistic embellishment than on a calm exposition of a sensitive subject. As but one example, stated in the *Time* article, was that ". . . the 'virus of love' infected entire college dormitories and rode the wave of rising divorces and crumbling monogamy." The author went on to say that when patients seek medical help, they will be given ". . . incorrect information and false hopes for cure." As if to infer that a patient is something of a pariah, the article ended with a flip anecdote that after a patient had been informed by his physician that he had herpes, the physician refused to shake hands with him as he left the office.

Genital herpes simplex has also received national attention on many talk shows on both radio and television. Television coverage of the issue by *60 Minutes* (CBS-TV, "400,000 New Cases Each Year," March 4, 1981) dwelt on the personal tragedies of a number of persons infected with the disease. A highly select group of patients belonging to a self-help chapter of the American Social Health Association was interviewed. Little emphasis was placed on the fact that the group consisted exclusively of persons with chronic infection who banded together in an association formed for educational and supportive purposes; thus the group was not representative of the general population of patients.

The *60 Minutes* segment covered the concerns of some members over communicating the infection, their fears of infection during pregnancy and their anxieties about cancer being induced by herpes simplex. Listening to the tragic stories led some viewers with whom I counseled to believe their own clinical courses would be chronic, that they would never be able to have a family and that they were doomed to acquire cervical cancer. Anecdotal reports and testimonial comments thus became the perceived verities by which the public came to understand that herpes simplex was a tragic and hopeless problem. Only a small portion of the television program was devoted to physicians and health professionals whose scientific statements could scarcely undo the negativism and hopelessness conveyed by the program. While the narrator intimated that there were new therapeutic agents on the horizon, no effort was made to highlight the fact that—pregnancy and cervical cancer aside—genital herpes simplex was essentially a trivial temporary infection in which most patients eventually experience long periods without recurrences.

Physicians and Genital Herpes Simplex

Physicians understandably retain a strong belief in the ability of drugs to effect recovery from illness. Whereas they have the intellectual awareness that the apparent response to therapy is sometimes the consequence of the natural course of the disease, they nevertheless commonly attribute their own intervention as the primary means whereby their patients recover. This confidence in the sometimes miraculous properties of modern drugs has a firm foundation in truth. Each year new and increasingly sophisticated pharmaceutic agents are introduced to broaden physicians' armamentaria.

For physicians confronted by patients with chronic recurrent genital herpes simplex, however, the therapeutic cupboard is often bare, given a patient's failure to have responded to previous treatment. Reports in scientific journals are often the primary source wherein physicians first learn of newly available forms of treatment. As new drugs reach the early stages of clinical testing, or as studies appear that suggest that older drugs have shown therapeutic benefit against genital herpes simplex, there is often an enthusiastic rush to administer these agents. Hope rises in both patient and physician alike that the new treatment will bring surcease from the maddening recurrences.

A beguiling list of purported remedies and cures for genital herpes simplex infection has appeared in scientific publications touting the benefits of ether, heterocyclic dyes and light, idoxuridine, vidarabine (adenine arabinoside) and other such topically applied agents. In addition, medical journals have carried articles at various intervals on the initial success of heterologous vaccines such as smallpox, influenza, poliovirus and bacillus Calmette Guérin or homologous vaccines such as Lupidon G (Hermal-Chemie Kurt Herrmann, Hamburg, West Germany) and herpes simplex antigen as hoped-for "magic bullets." Subsequent reports of double-blind trials have shown the many topical and systemic remedies to be without merit as compared with placebos. In some instances the potential hazard of treatment, such as the possible risks of smallpox immunization, may have outweighed any intrinsic placebo benefit.

Because of the apparent failure of modern medicine to find a simple cure for genital herpes simplex, patients' perception of the desperate nature of their affliction has intensified. The view that physicians cannot "cure" their disease has spurred some patients to turn to nonmedical sources for care and information. Disenchanted with the medical profession, some patients have sought help from various organizations and cults promising relief from the relentless problem. A good deal of superstitious dogma and naive assertions, carefully dressed up as authenticated fact, have been laid before the public both from medical and nonmedical sources. Anecdotal reports, testimonial letters and uncontrolled clinical research on agents such as L-lysine, vitamin C, zinc tablets and even yogurt have been accepted by some as scientific fact. Failure to respond to each and every newly suggested treatment reinforces a patient's belief that all treatments are worthless.

The therapeutic pendulum thus swings widely from do-nothing approaches to a try-anything attitude. Sadly, both patient and physician develop a mind-set that nothing works and there is little to be accomplished by traditional medical standards. "Learn to live with it" becomes the implicit message.

The Psychoneuroimmunologic Basis for Herpetic Recurrence

Whereas herpes simplex infection of the lip is no less an infectious disease and affects a far larger number of persons in the United States, the development of recurrent lip lesions does not carry the same impact on a patient's psyche as that of the genital variety of the disease.

Our epidemiologic survey indicated that an unusually large number of patients (86%) claimed that emotional stress activated their genital herpes simplex infection. Aside from its incitant nature, it may be speculated that the chronic emotional stress engendered by this recurrent infection may also impede recovery from infection.[5] One should be careful to note that while emotional stress may trigger attacks, it does not follow that specific behavioral traits lead to or actually cause disease. It is a punitive myth to interpret the development of chronic, recurrent genital herpes simplex, or any disease, in purely psychologic terms.[9] It should also be emphasized that genital herpes simplex is often considered to be activated by factors other than emotional stress. Drug-induced immune suppression, coital friction, overexertion, sleeplessness, menstrual provocation and masturbation have all been implicated and generally do not have psychologic equivalents. But the anxiety and depression that beset many patients with chronic recurrent genital herpes

simplex may have important and pervasive influences on the recurrences.

Evidence linking recurrent genital herpes simplex to biochemical alterations induced by the hypothalamic perception of emotional stress is both complex and tenuous. A full understanding of these influences will not be available until there is a better grasp of the exact neurochemical mechanisms in the sensory ganglia that hold the viral genome of herpes simplex in check.[10] Correlations between aggressive psychopathic states and high titers of antibodies to type 1 herpes simplex virus have been reported,[11] albeit there are contrary views.[12] Likewise a relationship has been established between virus-neutralizing antibodies and mental illness,[13] including psychotic depression.[14,15] Findings of studies have suggested that latent herpes simplex of the brain might inhibit biogenic amines and thus be responsible for psychiatric disease such as depression,[14] though the view of herpes simplex virus as the proximate cause of affective disorders seems far-fetched. Nevertheless, low-grade herpes simplex encephalitis has been implicated as the cause of periodic organic psychosis in at least one reported case.[16]

While the intraneuronal mechanisms governing the maintenance of herpetic latency are poorly understood, there are intriguing clues that the mechanisms influencing activation of genital herpes simplex from latency may, in part, be related to adrenergic stimuli. In one study,[17] herpetic keratitis was reactivated in rabbits by administration of epinephrine. Additional support for an adrenergic trigger mechanism was found in a study of rabbits latently infected with herpes simplex virus. Neither cortisone nor pyromin, a drug that raised rabbits' temperature, activated latent disease. Of ten animals given epinephrine, however, six had reactivation of herpes encephalitis.[18] Whereas the release of epinephrine and cortisone are well-known accompaniments of acute physical stress in humans,[19] there is substantial evidence that mental and emotional stress result in profound alterations of the adrenal medullary response, levels of norepinephrine in the brain and a host of other endocrine responses.[20] Study of the interplay between hormonal alterations induced by emotional stress in humans and actual physical impairment in health wrought by these biochemical influences has constituted the life work of Hans Selye.[21]

Close links between emotional stress and herpes simplex infection have been noted for some time,[22-26] though there are some contrary views.[27] Herpetic recurrences can be triggered by suggestion during hypnosis,[28] and psychotherapy has been shown to be effective in terminating recurrent episodes of herpes simplex.[22] Studies of the favorable response of patients who have recurrent herpes simplex to the administration of placebos[29,30] further support the strong links between the disease and a patient's emotions. The precise mechanism whereby placebo administration benefits patients with herpes simplex is not understood, but a lessening of anxiety and a positive expectation of recovery brought about by a physician's intervention may be of major significance.

A recent book[6] has dwelt in great detail on the subject of a "psychoneuroimmunologic axis" as an integrated unit that has significant influence in governing immunity of a person to infection, and even to cancer. It is believed that the hypothalamic perception of stress may set into motion humoral mechanisms influencing pituitary function or other biochemical mediators that have ultimate and profound effects on immune regulation. In support of such a hypothesis, studies in rats have shown that electrolytic lesions in the anterior hypothalamus produced changes in the cellularity of lymphoid tissue and decreased responsiveness of lymphoid cells to concanavalin A.[31] The effect on immune suppression was seen four days after the lesion was produced, but the immune response returned to normal within 14 days. The changes were not mediated through the release of corticosteroids.

The surface membranes of circulating lymphocytes contain hormonal receptors that may respond to neurohumoral mediators.[32] Thus it may be hypothesized that the central nervous system influences immunologic functions by fluctuations in the release of neurohormones that alter the lymphocyte plasma membrane, thereby rendering the immunologically competent cell less responsive in its surveillance role. Chronic stimulation of the hypothalamus induced by continued emotional stress might theoretically result in prolonged immunosuppression through the release of these neurosecretions. In support of such an explanation, Roszman and Brooks showed that patients harboring brain neoplasms, some of which were adjacent to the hypothalamus, were profoundly immunosuppressed, as determined by a variety of in vitro and in vivo immunologic measures.[33] Other anatomic explanations, largely unexplored, have shown the existence of sympathetic pathways between neural centers and immunocompetent tissue.[34]

In addition to the neuroregulatory influences of the hypothalamus on immune function, a number of laboratory investigations have advanced the thesis of stress-induced modulation of the immune system[35] and behaviorally conditioned immunosuppression.[36] Such studies have documented alterations of B-cell and T-cell function as a direct consequence of stress-related events. Extensive research focusing on behaviorial characteristics supports the fact that about 70% of physical illness occurs when patients feel helpless or hopeless.[37] In another study,[38,39] stress-induced immune suppression was observed as alterations of B-cell and T-cell function in 26 bereaved spouses. Furthermore, responses to phytohemagglutinin and concanavalin A were significantly diminished in the bereaved group, though the actual numbers of B and T cells were normal, as were plasma cortisol levels. The findings of measurable alterations in immune function resulting from the stress of bereavement lend credible support for the fundamental concept of stress-induced changes

in the immune response. Adrenocorticosteroid-induced suppression of lymphoid function is another well-known phenomenon[40,41] and may itself lead to a degree of immune suppression.

The links associating the emotional state of patients who have genital herpes simplex infection with regulatory influences on host immunity or reactivation of disease from latency are indeed tenuous, but there is evidence that patients with recurrent herpes simplex do have subtle deficiencies in immunologic responsiveness.[42] There are intriguing, though peripheral, clues that pharmacologic agents such as chlorpromazine hydrochloride[43] and lithium[44] may decrease the frequency and severity of recurrent genital herpes simplex infection through their influence on a patient's emotional conflicts, though the effects of these agents on the virus, much like those of other administered drugs, may be placebo in nature.

A Physician's Role in Patient Management

Given the failure to date of traditional medicine to find a cure for genital herpes simplex, what can a physician do in advising and assisting patients? The unalterable fact remains that in attempting to fathom the complex immunologic mechanisms that lead to recovery from infection, it is truly the patient who is the ultimate healer. In encouraging this recovery, one of the most potent tools available to a physician is the confidence placed in the physician by the patient, as well as the physician's knowledge, solace and support. Physicians have traditionally worn the mantle of "healer," and it is this very perception that often leads to a successful therapeutic outcome. Thus in doctor-patient relationships, physicians should bring all their healing skills to bear with weight equal to that of their scientific abilities. This process requires a willingness by a physician to talk things out and to help a patient confront the practical issue of coping with the problem. A sincere and realistic attitude must be cultivated in the patient that in time the recurrences will diminish and the condition improve. The improvement will be a result of a combination of good medical management on the part of the physician and that of the patient's own native immunologic resources; likewise, intellectual and psychologic insights, stress reduction and an abiding faith in the restorative elements of mind and spirit will effect this result.

Patients should be encouraged to become actively engaged in their own health care, to regain a sense of control over their body, maintain a positive attitude and cultivate an inner sense of peace and reflection. The techniques used in achieving this goal include holistic practices such as meditation, yoga, stress-reduction exercises, conditioned relaxation and even the use of guided imagery in which patients perceive their ganglia as being "cleansed" of the virus. It is important to emphasize that these techniques are not antithetical or antagonistic to traditional medical practices, and patient acceptance of such advice from quite sophisticated persons is remarkably high. For patients with major psychic overlay who are less receptive to this approach, traditional management with psychotropic drugs such as antidepressants should be considered.

Physicians should work towards educating and enlightening their patients as to the natural history of recurrent genital herpes simplex and thus lessening the enormous burden of ignorance borne by some patients. Patients should be instructed to avoid intercourse when they are actively infective, but to follow their regular sexual patterns when they are not. They should be aware that there is some risk, as yet undefined, that they may be asymptomatically shedding the virus.[45] Women should be informed of the importance of frequent Papanicolaou smears because of the association of cervical infection from herpesvirus with cancer, and they should be instructed to seek proper medical advice if they become pregnant.[46] By reducing anxieties about the disease and exposing the many myths about herpes simplex, the negative influences of helplessness and depression can be reduced. A survey by the American Social Health Association of 4,000 members suggested that among the many physician-directed therapies used in management, the single item providing the most lasting benefit was "conscious stress reduction."[47]

Physicians should not emphasize therapeutic nihilism to patients nor convey too gloomy a picture regarding genital herpes simplex infection. There is clear evidence that newly developed antiviral agents such as vidarabine[48] and acyclovir[49] may be effective in the management of herpes simplex in newborns and in immunologically compromised persons, as well as in herpes simplex encephalitis. While not preventing recurrences, these new antiviral agents do represent important advances in patient care. Likewise there is hope that newly developed techniques of injecting neurolytic agents into the skin may spell an end to the maddening local recurrences of infection.[50]

Placebo therapy has been advised in selected cases of herpes simplex,[29,30] but it would be improper to recommend institutionalizing this therapy for all patients. The traditional negative connotation of the word "placebo" should not prevent physicians from recognizing its possible benefits. Whereas some have suggested that the administration of a placebo is deceptive, dishonest and unethical, it is generally acknowledged that physicians who are self-confident, attentive to their patients' emotional needs and who have faith in the treatment they endorse are likely to induce positive health changes merely as a consequence of their behavior.[51] This attitudinal approach to patient care embraced by most physicians can be readily construed to carry the same therapeutic weight as that induced by the administration of a placebo.

Physicians' relationships with their patients and their particular attitude towards illness have a profound influence on the outcome of disease.[52,53] Patients who have genital herpes simplex recurrens do generally im-

prove or achieve long-lasting remissions and, while the time interval to improvement is unknown, it is reasonable to conclude from data gathered in an epidemiologic survey[3] that at least half of the patients have protracted periods of clinical remission within five years of disease onset.

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