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The Myth and Realities of Genital Herpes

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Genital Herpes simplex is a sexually transmitted disease which has reached epidemic proportions in the United States. The following paper reviews the pathophysiology of this disease as well as its medical managements. Various aspects of the psychosocial impact of genital Herpes will be discussed as well as holistic approaches to the disease. Finally, an epidemiologic survey will be reported addressing the critical issue concerning the duration of clinical infection and degree of infectious communicability.

Genital Herpes simplex infection is a major cause of sexually transmitted disease in the United States accounting for more than 500,000 new cases annually. As public awareness of this problem has increased, an ever burgeoning element of myths and misinformation surrounding genital Herpes has arisen to obscure a more scientific view of the disease. This review is intended to examine the realities of what has tragically and incorrectly been referred to as, "The Incurable Venereal Disease."

Genital Herpes is *not* the ultimate tragedy in life. The real tragedy is the unnecessary sense of futility and anguish that often become a pervasive part of the individual's life. Real or imagined concerns over Herpes result in some patients withdrawing from interpersonal relations. This separation from the physical and spiritual nourishment that comes from love, deprives them of a source most helpful in their own recovery.

Patients with genital Herpes often feel vulnerable, isolated, and helpless in the face of seeming therapeutic intractibility of their malady. They may develop fears of never being able to sexually function in a normal fashion. They may even come to believe that this infection has been visited upon them as a penalty for real or imagined transgressions in life. This pervasive sense of frustration and depression that comes to typify the character and personality of the afflicted individual has biochemical equivalences in the host's body.

It is my belief that the emotional concern and anxiety surrounding the patient's preoccupation with recurrent infection may be one of the main trigger mechanisms responsible for activating latent ganglionic infection. It has been known for some time that emotional stress can alter an individual's susceptibility to disease, but only recently have scientists gained insight into the complex mechanisms governing these matters. It is generally known that psychic stress is perceived within hypothalamic centers of the brain, thereby

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evoking neurochemical mediators from the pituitary gland which, in turn, stimulate hormonal alterations within the body by influencing endocrine gland function such as thyroid, ovary-testis and adrenal glands. The profound changes in the finely tuned mechanism of the host's own internal chemistry, as evidenced by increased cortisone production from the adrenal cortex, have been demonstrated to influence those elements in the blood (T-cell lymphocytes) that govern both cancer surveillance and destruction of infective organisms. The consequence of a sustained fall in T-cell lymphocytes that are required to fight viruses may result in an increased susceptibility to infection, or may cause activation of latent infection from an involved sensory ganglia.

The Nobel Prize Laureate Jonas Salk has referred to a "psycho-neuro-immunologic axis" in describing the somatic or body equivalences of emotional stress. This particular designation, psycho-neuro-immunologic axis, has implicit inferences which tie together the emotional content of illness, with the patient's attitude and anticipation of recovery. The composite of this perception of illness and hope of recovery may induce changes within the patient's body chemistry and immunologic competence that may have significant bearing on the host's adaptation or maladaptation to illness. Because infection with Herpes involves one of the most fundamental of human instincts, the individual's sexuality, the spector of chronic and unremitting disease of the genitals strikes at the core of this basic drive. Thus, a disorder, Herpes simplex, which requires an intact immunologic response as a means for recovery, may induce an emotional state of mind in the sufferer (i.e., anxiety about sexuality, infectivity, etc.) that triggers disease from latently infected ganglia; it is possible that adrenalin (epinephrine) from the adrenal medulla might be the neurochemical mediator of this function. Likewise, anxiety may result in suppression of those cellular agents (T-cell lymphocytes) that mediate recovery from infection; again, cortisone from the adrenal cortex may be the hormonal mediator, and T-cell depression has been known to persist for upwards to six months after periods of bereavement. This complex neurochemical-immunologic circuitry that I have described is an attractive theoretical model built on collaboratory evidence in both animals and humans, and has scientific foundation in Hans Selye's work on stress.

Patients with genital Herpes often hear conflicting stories from both lay and professional sources. Many so-called "verities" regarding this infection have little foundation in scientific fact. Apocalyptic pronouncements from self-proclaimed experts often estrange individuals from seeking out help from physicians. These crass, usually non-medical pundits who write for the lay press, cultivate a defeatist attitude towards therapy, and thereby engender further frustration in the minds of the sufferers who most need reassurance and solace.

At the other end of the therapeutic spectrum are groups espousing remedies for Herpes which are not only without merit, but are inherently dangerous. A good deal of superstitious dogma and Olympian assertions, carefully dressed up as authenticated therapeutic facts, have been laid before the public. Medicine, itself, has not been immune from these misrepresentations. Sadly, some physicians have enthusiastically endorsed bankrupt remedies for either specious reasons or else for their inability to offer viable alternatives to patients. Anecdotal reports, testimonial letters, and uncontrolled clinical research studies on genital Herpes have been accepted by some well-intentioned physicians in the guise of scientific fact. In earlier years orthodox medical journals carried articles on topical treatment with ether, heterocyclic dyes, idoxuridine, Ara-A, and other such surface remedies as an effective means of management of genital Herpes, until subsequent double-blinded reports found these remedies were almost entirely without value when compared to placebos. Medical journals contained articles in which the authors touted the systematic administration of agents such as lupidon G, influenza, polio and smallpox vaccines or idoxuridine, isoprenosine, Ara-C, etc., as magic bullets for Herpes, while, once again, subsequent studies demonstrated these treatments as ineffective, dangerous, or both. One need not sit too harshly in judgment on these first clinical reports, for this is the "stuff" of scientific research.

Failure to respond to each and every newly suggested treatment is perceived by the patient as a grim verdict. Each failure reinforces the patient's belief in the futility of *all* treatments. The therapeutic pendulum thus swings widely from a "do-nothing" approach, to a "try-anything" attitude. Sadly, both patients and physicians develop a mind-set that there is really nothing to be done. "Learn to live with it" becomes the implicit message as patients sink further into anguish and despair.

Physicians themselves have been influenced by their negative therapeutic experiences with Herpes and sometimes in self-defense have approached patients with a "Hanging of Crepe Strategy." This strategy or technique is usually employed in more serious and specific situations such as terminal cancer or severe cardiac disease, in circumstances where survival or death hang delicately in the balance. The approach to the family with the "Hanging of Crepe Strategy" entails projecting the bleakest, most pessimistic prediction of the patient's outcome. This is done presumably in an effort to lessen the family's suffering if the patient dies of the illness. The physician employs the strategy by informing the family that the acutely ill patient will almost certainly die of the illness. Only unexpected turns of events relating to the physician's intervention *might,* but only might, restore the scales to a balance, and preserve the patient's life.

"The Hanging of Crepe" is an absolute no-lose strategy for the doctor. If the patient dies, death is ascribed to the inexorable progression of natural

events, and the physician's image is not tarnished. The doctor is perceived as a dedicated healer struggling against overwhelming odds to save the patient. Yet if the physician succeeds in the struggle to save the patient, he or she not only wins the family's gratitude, but the physician's reputation and esteem rise since the doctor is viewed as a valiant, almost god-like individual who persevered in the face of overwhelming odds. The employment of this strategy precludes attributing events to spontaneous recovery by the patient unrelated to the physician's actions, but argues rather that the doctor saved the dying patient. Thus, regardless of the outcome of the illness, the physician will be perceived as personally blameless as to the therapeutic outcome of one's ministrations. While feeling obvious human concern for the patient, the physician has limited professional responsibility for any therapeutic failure.

The principle defect in the "Hanging of Crepe Strategy" is the surrender of intellectual honesty and integrity. This is not to say that physicians willfully deceive patients with terminal illness—no less so than painting a bleak picture for patients in the case of genital Herpes simplex. Nor does it infer that doctors knowingly use orchestrated stereotyped plans to inform each and every patient of medicine's inability to effectively treat Herpes simplex. Rather, it seems that the "Hanging of Crepe" strategy is an unconscious, almost reflexive action that is occasionally employed to reduce the physician's anxiety regarding the perceived therapeutic limitations. At the same time this strategy creates a psychologic climate in which patients are given to intellectually understand that their infection is indeed quite serious.

The concurrence by both the patient and the physician on the futility of finding a cure for Herpes, the intractibility of the malady, sometimes to the physician's best efforts, is perhaps one of the most serious psychological barriers to recovery because of the influence of therapeutic defeat that is indelibly etched on the patient's mind. What is defective in this doctor-patient mutual despair is a preoccupation with the word "cure" and a de-emphasis of the fact that Herpes can be treated. Do oncologists tell their patients with malignancies that "There is no cure," or "Learn to live with it"? Rather, do they not approach their patients with the view that new treatments are afoot, that existing means of management can be employed to hold down the progress of the disease, and that in many instances the cancer will be cured or even spontaneously disappear.

The attitude of therapeutic nihilism in Herpes simplex and resignation to disease flies in the face of good medical practice and fails to acknowledge the known regenerative and restorative forces that are at the core of human uniqueness. The current awakening of interest in the subject of "wellness," and movements in the field of holistic medicine are tangible evidences that physicians, no less than the patients they serve, are looking to adjunctive, if not alternative, means of treating ailments.

If infection with Herpes simplex is indeed triggered by endogenous factors

such as emotional stress, depression, and hopelessness, as well as overexertion, sleeplessness, and physical stress, it then follows that physicians must focus their talents on these manageable imperatives. The physician's role in orchestrating patient's recovery from genital Herpes involves, in part, an ability to create a healing milieu in which a feeling tone of enthusiasm and confidence is conveyed to patients. A sincere and realistic attitude must be engendered in patients that they will, in time, truly recover from infection. The recovery will be the consequence of good medical management, psychologic insight, stress reduction, and an abiding faith in the restorative elements of their mind and spirit.

This therapeutic approach embraces recognition that physical, emotional, and spiritual factors are entwined in the fabric of the patient's illness. The physician must engage patients in a realistic goal of altering those factors that impede recovery. Holistic medicine, no less than orthodox medicine, has at its root the recognition that patients themselves must be active participants in their own recovery. Compliance with, and adherence to, the programs outlined to patients must be repeatedly emphasized. Physicians and patients must be bonded in a shared goal of recovery from infection. It is not beyond the scientific training and professional scope of the author to infer that mysterious, powerful, and profound spiritual forces exist which facilitate recovery.

An important responsibility of physicians is to assist patients to fully comprehend the nature of their affliction. In so doing the spector of futility and anguish that characterizes many patients' perception of this malady can be lightened. The following material has been prepared as a means of demonstrating the pliability of the patient-doctor-disease triad—it may also serve the more practical function of providing a source of cognitive and emotional insight to those individuals concerned with this particular disease, in whatever capacity.

In summary, it is important to emphasize that there is an ongoing commitment by many physicians around the country to investigate basic biochemical and immunologic aspects of Herpes simplex virus and new treatments for the infection are constantly being sought by major pharmaceutical industries. As new drugs reach the stage of clinical evaluation, they are selectively introduced to testing, but the interval between animal-laboratory research and human experimentation is often long. Nevertheless, there are at present in-place treatments which involve both conventional and holistic medical approaches that can be employed to foreshorten attacks and modify the frequency and severity of genital Herpes. The material which follows will hopefully provide better insight into the pathophysiology of genital Herpes simplex infections. In addition, we will examine some of the social and psychological factors that bear on the disease; finally, we will mention some simple and basic means whereby patients may treat themselves.

Specific Issues in Genital Herpes Simplex

Can One Cure Attacks of Genital Herpes?

Rather than address myself directly to this query, I believe that the question should better be posed, "Can one treat infection?" The reply is an unqualified "yes," although it is not possible at this time to biologically cure Herpes simplex infection.

This statement should in no manner be construed as disquieting to the reader, nor should it provide reason to surrender to the oft-times Dantean pronouncements of the lay press. One could, as well, inquire of a physician, "Can you cure diabetes?" or "Can you cure high blood pressure?" It is obvious that these medical conditions can be successfully managed with effective drugs, adherence to diet, exercise, and stress reduction. The lay press emphasis on the word "cure" in reporting on the subject of Herpes infection has only served to discourage patients and create a defeatist attitude on the part of the patient. There is no room for therapeutic nihilism in the management of patients with Herpes simplex infection.

While physicians cannot at this time promise a biologic cure for genital Herpes, they can with some confidence suggest current techniques to destroy the virus in the skin and modify the course of the disease. What is eminently clear is the fact that with vigorous local treatments of this infection, attention to matters of stress reduction, native immunologic factors of host defense, plus the use of various systemic or topical agents which may influence the course of infection, patients can realistically anticipate either eventual recovery, or a decrease in the frequency and severity of attacks of Herpes simplex.

The Nature of the Herpes Simplex Infection

Herpes simplex infection is a skin disease caused by a virus that is unique to humans. The infected patient is the only natural reservoir of disease. Herpes simplex is the cause of one of the most widespread infections in the world. Approximately 75 percent of the population develop Herpes simplex of the lips at some time during their lives, and 10 percent of individuals between 18 and 35 years of age have Herpes labialis more than three times yearly. Only 1 to 2 percent of the population develop chronic lip Herpes.

Genital Herpes simplex is antigenically, biochemically, and morphologically distinct from the Herpes that causes lip infection. There are approximately 500,000 new cases of genital Herpes each year, placing this infection third in incidence behind gonorrhea and nonspecific urethritis as the most prevalent venereal disease. It appears that there has been an absolute increase in the number of patients infected with genital Herpes during the past decade. The explanation for this phenomenon is not known, but there is

speculation that a mutation of the type I Herpes virus has occurred.

Three distinct features which are characteristic of Herpes simplex infection consist of: (1) *latency,* which denotes that the virus "sleeps" in a non-structural form in the sensory nerve ganglion between attacks; (2) *chronicity,* which implies that the disease tends to persist for long periods in the infected host; (3) *recurrences,* in which various factors such as emotional stress, over-exertion and genital friction tend to activate the latent infection and produce clinical relapses.

The virus causing genital Herpes infection consists of submicroscopic bits of DNA contained within a tough fibrous capsule. There is an inner core of double stranded DNA which is coiled in the form of a doughnut. This genetic material is surrounded by a protein capsid, which is, in turn, covered by a tegument and, finally, wrapped by an envelope which helps the virus resist physical agents that might destroy its infectivity. The virus forms an icosahedron containing 162 capsomeres which resembles a hexagonal prism with hollow cylindrical ducts.

When the virus enters a living cell, it casts off its protein coat, and viral DNA complexes migrate to the nucleus of the infected cell. Viral DNA is transcribed in the nucleus and thereafter moves to the cytoplasm where it induces synthesis of structural viral proteins to make a new coat. The enveloped virus may migrate directly to adjacent cells to induce new infection without ever passing into the extracellular compartment, at which site the virus could be attacked by the host's own lymphocytes. It is this distinctive feature by the Herpes virus of passing directly from cell to cell, protected in its intercellular environment, that accounts, in part, for the difficulty of the host's immunologic agents to attack and to destroy this intercellular parasite.

Between 80,000 and 120,000 copies of viral DNA are produced in each cell during the viral cycle that may be as short as 12 hours. This observation emphasizes the need to begin treatment as soon as inflammation is perceived so as to inhibit the rapid viral replication. Infection by the Herpes virus is finally halted by a combination of specific and nonspecific host defense mechanisms consisting of macrophages, T-cell lymphocytes, immunoglobulins, lymphokines, interferon, and other protective elements. The host defense elements lead to cellular rupture of the involved cell and extracellular destruction of the virus.

Transmission

There are essentially two types of Herpes simplex: Type I which produces infection above the waist, i.e., Herpes of the lips; and Type II which produces infection below the waist, i.e., genital Herpes. Between 10 and 30 percent of genital Herpes are due to Type I variety.

Herpes of the lips may be acquired by kissing someone who is infected or

from an individual who harbors the virus in the salivary secretions. It may be acquired as a consequence of an upper respiratory infection with Herpes type I, by oral droplet spread from an infected host, i.e., by a sneeze, or from glasses, towels or other fomites contaminated by the virus.

Genital Herpes may be acquired by: (1) intercourse with an infected partner who has active genital lesions; (2) by sexual caresses from individuals having Herpes of the fingers, i.e., Herpetic whitlows; (3) sexual intercourse with a female partner who has no obvious external genital lesions, but may harbor the virus in infected cervical lesions; (4) coitus with a woman who is an asymptomatic cervical secretor of the virus; (5) oral-genital modes of sexual relations between partners who have fever blisters of the mouth, or who may asymptomatically secrete the virus in the saliva; (7) autoinnoculation to the genitals from infected secretions of the mouth; and (8) endogenous re-infection, wherein latent ganglionic infection is reactivated, and (9) blood born spread of the infection to the skin of the genitals.

Recurrence

The very first infectious episode of genital Herpes tends to be a violent clinical event which may include genital blisters, pain, swelling, and systemic toxicity. In approximately 60 percent of primary infections the virus moves in a retrograde fashion and invades the Pudendal nerve, which supplies sensation to the genital skin. Viral particles move by way of this neural pathway to the sacral ganglion which is the nerve plexus for the patient's pelvis. Once in this ganglionic staging area the virus enters a period referred to as latency. In this state of clinical quiescence, the virus is non-infectious. It exists as a non-structural, non-encapsulated bit of genetic material integrated into the DNA of the host's own nerve substance and is essentially indistinguishable from normal nerve. If one examines the ganglion during latency by means of an electron microscope, the virus cannot be identified. If, however, the ganglion is exterpated and placed in culture media conducive to the growth of the virus, encapsulated forms of the virus will be seen within ten to twenty days. Surgical procedures that involve transection of nerves distal to the infected ganglion will interrupt direct axonal flow and prevent recurrences of infection. Evidence in support of these statements are reviewed by Bierman (1976a).

The virus is maintained in a latent state until various factors such as emotional stress, over-exertion, or fever trigger productive and replicative infection. The virus awakens from its "sleep" and infective particles then travel *down* the nerve trunk and ultimately gain access to the skin through fine nerve endings. The virus reappears at the same anatomic site corresponding to the involved nerve rami of the Pudendal nerve. Once in the skin, the parasitized cells are taken over by Herpes for replicative purposes thereby

inducing cell death. A new cycle of recurrences has begun.

Given the fact that local therapy may be able to destroy the virus in the skin, one must reflect on the fact that topical agents can never gain access to the distant sacral ganglion wherein the viral genome exists between attacks. In a like manner, systemically administered drugs such as Levamisole (Bierman, 1978) or BCG vaccine (Bierman, 1976b) which enhance host resistance, are unable to attack the virus in its immunologically privileged sanctuary in the host's ganglion. Even metabolic poisons such as Virazole (Bierman, Kirkpatrick, & Fernandez, 1981) and Ara-A (Kaplam, 1977; Whitley, Soong, & Hirsch, 1981) cannot destroy the latent virus because they cannot selectively destroy DNA in the ganglion without poisoning native DNA in the nerve. The genetic material of the virus is indistinguishable from the host's DNA. Nor do these drugs even physically gain access into the neural tissue of the sacral ganglion.

Persistence of Infection

It is most unusual for patients with Herpes simplex to fail to recover from an attack within a seven to ten day period, except for the primary infective episode which may take upwards of a month to heal. Often there are reasons for the skin to fail to heal: (1) the patient may really *not* have Herpes simplex, but rather another skin disease which involves the genitals such as psoriasis, eczema, or yeast infections; (2) treatment with some agents may induce "iatrogenic disease," i.e., topical treatment itself may irritate the skin and inhibit normal healing; (3) patients are occasionally so overly concerned about their infection coupled with their fear of infecting a loved one, that every minor skin irritation resulting from chaffing by rough clothes, masturbation, or coital friction is magnified quite out of proportion to its actual significance; (4) normal skin appendages such as sebaceous follicles, minor skin cysts, or simple bacterial folliculitis are incorrectly perceived by the patients as herpetic manifestations; (5) the Herpes infection may have been destroyed by topically applied agents, but the skin erosions often take a considerable time to heal because of the cytotoxic influences of the virus on epidermal cells; (6) bacteria or yeasts may colonize the open erosions after the virus has disappeared and produce secondary infection; (7) there is evidence that not every "episode" of Herpes is infectious. In a report on Herpes labialis it was discovered that while Herpes virus could be cultured from most blistering episodes, there were occasions in which abortive skin lesions appeared and healed in a brief period of time. In these latter instances, the viral cultures were most often negative. It is believed that quite early in the virus replicative stage, immune mechanisms effectively destroy the virus but not before cytotoxic damage has been induced in the epidermal cells.

The presence of Herpes in the skin can be easily and inexpensively deter-

mined by scraping the skin and looking for typical intranuclear inclusion viral elements by special stains. In actual practice this is not always practical or reliable. Blood tests to measure antibody titers against Herpes Type I or Type II are not reliable indicators of past or present infection. The ultimate proof as to the presence or absence of viral infection with Herpes simplex can be determined by culturing the skin.

Coitus and Infectivity

Sexual intercourse may be resumed when the crusts of the lesion have fallen off and the skin is no longer open or eroded. On the average, this interval will be between seven and ten days following the initial appearance of blisters. Studies reveal that Herpes simplex is most infectious during the period of skin redness and blistering (Spruance, Overall, & Kern, 1977). The titer of the virus diminishes during the ulcer-crust stage and is undetectable during the healed stage.

There is no evidence that the virus is present in the skin between attacks, and thus cannot be transmitted to one's sexual partner. The theory that semen is a source of infection has been effectively disproven (Denture, Drylie, & Kaufman, 1978). As discussed in previous sections, the virus exists only in the host's neural tissue in the latent periods between attacks.

There are, however, some disquieting studies that suggest upwards of 20 percent of women who are without outward signs of genital Herpes may harbor and secrete Herpes virus in cervical fluids (Rattray, Corey, Reeves, & Holmes, 1978; Willmont & Mair, 1978). It has been known for some time that approximately 3 percent of individuals who have no active lip infections may secrete Herpes Type I in their salivary secretions (Spruance, et al., 1977). Oral-genital sexual play is probably the means whereby asymptomatic individuals who secrete Herpes Type I in the saliva spread genital infection to their partner. In a like manner, the presence of Herpes Type II in cervical secretions may serve as a potential source of infection to men having coitus with asymptomatic women.

Despite this observation, there is no firm data to prove that the incidence of actual sexual transmission of Herpes Type II is significantly high in asymptomatic women who are cervical secretors. I personally believe that the incidence is low because: (1) the actual viral titers have not been regularly measured in cervical secretors; (2) the concordance of active cervical secretion may not match the actual moment of coital activity; (3) native immunologic defenses may protect partners from infection (i.e., unpublished studies reveal that only 33 percent of married individuals acquire infection from their already-infected spouse); (4) good post-coital hygiene may minimize infection.

Nevertheless, it is advised that women employ nonoxyl-9 vaginal creams preparatory to coitus if they have Herpes. Conceptrol$^{(R)}$, Koromex$^{(R)}$, and

Delfan(R), have "in-vitro" antiherpetic effects (Donsky, 1979) albeit clinical studies are not totally supportive (Vontver, 1976). Listerine mouth wash should be employed prior to oral-genital sexual play, for thymol appears to have herpicidal activity (Knight, 1976). Finally, if there are concerns about infectivity by the man, a condom should be worn rather than risk the chance of infecting a partner. Conant (Note 1) has shown that Herpes simplex cannot penetrate through the micropores in a condom; the use of a condom will also protect against infection from asymptomatic cervical secretors.

Pregnancy and Herpes Simplex

During pregnancy probably nothing of a serious nature will happen to the woman or the fetus, given the fact that they are under careful obstetrical management. In those instances when women acquire primary attacks with Herpes Type II during the first trimester of pregnancy, there are rare documented cases in the literature of intrauterine infection and abortion. In most instances, however, first trimester infection with genital Herpes, even though painful to the mother, will not pose a threat to the fetus. A woman's ability to conceive and bear children is *not* compromised merely by a history of having had genital Herpes simplex.

The most serious problem posed to the pregnant woman is the acquisition of initial infection with Herpes Type II during the last trimester of pregnancy. The presence of active, infective herpes cervicitis or vulvovaginitis at the time of vaginal delivery may result in infection of the newborn in 40 to 60 percent of cases. Because of the newborn's immunologic immaturity, Herpes infection may lead to severe internal disease, neurologic manifestations, and death in half of infected infants born by the vaginal route. It is critical to add at this point that this circumstance does not usually occur in women delivered by Caesarean section. In actual practice the concordance of infectious vaginal delivery is uncommon and only 100 to 200 cases of Herpes of the newborn are reported each year, and often from mothers of lower socioeconomic status who are unable to seek out proper obstetrical care. The risks of neonatal infection at term are greater for primary rather than recurrent genital Herpes because of partial native immunity. Pregnant women should be advised to avoid intercourse late in pregnancy if they or their husbands have active lesions. For those who will not abstain, a condom is essential. The risk of orogenital transmission of Herpes should also be recalled.

An obstetrician can perform routine Pap smears or viral cultures of the cervix during the final weeks of pregnancy. If one has not experienced attacks during the last trimester, vaginal delivery may be considered. If one is infected near to the time of delivery, a Caesarean section is advised. The infant is generally safe as long as the amnion is intact, and even for hours after rupture (Kilbrick, 1980).

Herpes and Cancer of the Cervix

There does appear to be a substantial body of scientific evidence incriminating Herpes virus as an etiopathogenic agent in cancer of the cervix (Adelusi, 1978; Nahmias & Roizman, 1974). Much of the evidence to suggest a proximate relation between the virus and the development of cervical carcinoma is based on retrospective epidemiologic evidence of serum antibodies against Herpes Type II in groups with or without cervical malignancy. Cervical carcinoma has been induced in mice through innoculation with Type II Herpes viruses. There is a considerable amount of other inferential data from studies of immunofluorescence, presence of soluble Herpes antigens in extracts of exfoliative cells. These studies indicate that infection with the virus precedes neoplastic changes in the cervix.

However, this view of the proximate relation between Herpes and cervical cancer has some serious challenges (Rotkin, 1976). There is a question whether this association is epiphenomenal (both cancer and Herpes occurring simultaneously without relation to one another) or whether the relation is a causal one. It is believed that only the presence of infectious virus in cases of Herpes cervicitis or the presence of the latent virus in the cervical tissue can be considered in the mechanism of neoplastic induction. Most women with recurrent genital Herpes do not have concurrent Herpes cervicitis. In one study only 4 percent of women with genital Herpes of the recurrent variety had concordant Herpes cervicitis, although other studies have noted higher concordances.

Studies suggesting an etiopathogenic relation which are based on highly select clinical groups must be looked at with some caution. Socio-economic factors must be weighed in validating these studies for many reasons: (1) low income socio-economic populations may not seek out early gynecologic attention; (2) these groups may fail to have frequent Pap smears. These studies thus may not relate to middle income women who regularly have gynecologic examinations.

Those factors that seem to have a proximate relation to cancer of the cervix include: (1) early age of coitus; (2) promiscuity; (3) low socio-economic status; (4) uncircumcized male partner; (5) genetic influences; (6) personal hygiene; and (7) smoking habits.

Thus, while there is considerable evidence suggesting Herpes simplex Type II may play a role in induction of cervical neoplasia, no causal and absolute relations have been established. Nevertheless, women who have recurrent attacks of genital Herpes should have routine Pap smears every six months. If there is evidence of atypical features on the smear, early treatment by current gynecologic means should prove definitive.

A Vaccine Cure For Herpes?

I regret that much of what the lay and medical press has published on new methods of treating Herpes has, upon subsequent examination, proved to be without merit. The initial enthusiasm over photodynamic inactivation of Herpes (Meyers, Oxman, & Clark, 1975), or the use of topical ether (Corey, Reeves, & Chiang, 1978) or Ara-A (Spruance, Crumpacker, & Haines, 1979) or administration of smallpox vaccines for immunoprophylaxis against Herpes (Kern and Shiff, 1959) has given way to reports which not only failed to show therapeutic benefits, but in many instances were found to be dangerous (Berger and Papa, 1977).

These uncontrolled therapeutic thrusts have neglected to take into consideration the fact that many patients respond favorably to placebos, or to their physician's enthusiasm. In one study 50 percent of patients with Herpes labialis reacted favorably to repeated administration of sterile water (Kern, 1979). An important medical aphorism is "Primum Non Nocere" (First No Harm). Doctors should have some reservation over utilizing chemotherapeutic or biologic agents that have potential serious side effects.

The fact exists that physicians have a poor understanding as to the natural course of untreated Herpes. Doctors have a tendency to ascribe patient response to their treatment as being indicative of the pharmacologic properties of the drug, whereas, in point of fact, recovery may have been the consequence of native immunologic mechanisms. It is for this reason, that only those clinical studies where drug administration has been double blinded can be accepted as scientifically valid. Even double blinded studies are subject to error without proper pairing of comparable patients.

The most serious criticism that can be leveled against published accounts of "cures" has been the almost total absence of controls and double-blinds in the experimental design. Follow-up studies have not been performed to determine whether Herpes recurred once treatment has been discontinued. The methodology of quantifying responses has been crude, i.e., "improved," "better," or "worse" are almost meaningless determinants. Most studies do not bother to use statistical analysis of their data. There is no inference in these criticisms that doctors have falsified data—my remarks are intended to chide doctors to utilize more careful means of documentation, consider placebo effects, and minimize bias.

Linus Pauling's own personal prestige and endorsement has been a powerful influence for groups promoting vitamin C in the treatment of various diseases. As double blind studies followed, vitamin C faired no better than placebos in the treatment of advanced cancer (Creagan, Moertel, & O'Fallon, 1979) and in addition was shown to have potential serious side effects (DiPalma, 1977). Advocates for a particular "cure" for Herpes must provide better scientific evidence than their own personal endorsement and

anecdotal reportage in the guise of factual documentation.

In an attempt to prevent recurrent attacks of infections, physicians have turned to vaccines as a possible means of influencing Herpes simplex infection. Despite the conquest of smallpox, polio, measles, and other viral infections employing killed or attenuated vaccines, the unique biological properties of Herpes simplex make an immunologic approach an unobtainable goal. Homologous vaccines (vaccines made from extracts of Herpes virus) have been studied and investigated in animal and human research programs for over 40 years. No carefully constructed scientific study has yet proven the Herpes vaccines to be effective in preventing infectious relapses. Lupidon G has been the most widely publicized homologous vaccine. Despite claims from Nasseman's lab in Germany that Lupidon G prevented infectious recurrences, the overwhelming evidence is that the vaccine is not only without therapeutic benefit, but is potentially dangerous (Bierman, 1976a).

The Food and Drug Administration had prohibited the introduction of homologous vaccines into the United States because of concerns that the vaccine may predispose individuals to the development of cancer. Animal studies have shown that injections of homologous Herpes vaccines predispose to metastatic forms of cancer (Duff, Doller, & Rapp, 1973). It is well known that Herpes viruses are oncogenic in animals (Levine, 1976). Latent ganglionic infection occurs in immunized mice even in the presence of high titers of neutralizing antibodies (Price, 1975). There is a substantial body of scientific evidence in animal studies that this approach to immunologic manipulation is dangerous and totally without benefit (Scriba, 1978).

There have been some attempts to produce Herpes antigens that are derived from the virus capsule and free of vital DNA. These antigens have not been of sufficient potency to induce significant immunologic responses and have effectively been abandoned (Wise, 1977).

For those individuals who persist in their belief that a vaccine will ultimately be discovered, let me pose the following question: How can medical science develop a vaccine against Herpes when the individual is unable to immunize him or herself by virtue of repeated attacks of the infection? There is evidence to suggest that antibodies produced by Herpes Type II may inhibit recovery from infection by means of immunologic enhancement (Bierman, 1976a). Vaccine immunoprophylaxis of genital Herpes by homologous vaccines is sadly unreliable and at this time an unachievable goal.

Other approaches to the management of recurrent disease have entailed the administration of the heterologous vaccines. Heterologous vaccines are defined as biologic agents that are antigenically unrelated to the Herpes virus. Attempts to immunize patients with recurrent Herpes simplex by repeated smallpox vaccinations had a popular following for almost 30 years, until double blinded studies convincingly proved that active smallpox vac-

cine was no more effective than a placebo (Kern & Shiff, 1959). In addition, there are considerable risks of adverse effects from immunization including generalized smallpox, gangrenous changes in the skin, blindness, allergic encephalitis, and even death.

In recent years anecdotal reports by Tager (1974) and later by Lincoln and Nordstrum have appeared extolling the virtue of repeated oral Polio vaccine as a means of preventing Herpes infections. There has been interest following a favorable report regarding the benefits of repeated innoculations of Influenza vaccine employed as a means of stimulating host defense against Herpes viruses (Miller, 1979). Miller's studies, as well as reports of the previously cited authors, are uncontrolled and there are, at present, no adequate follow-up reports. There exists no common antigenic determinants that are shared by these viruses and Herpes simplex and any immunologic consequences of active immunization will call forth humoral and cellular responses directed only at the invading virus. In addition, there are no animal studies that reveal heterologous vaccines in the prevention of Herpes, nor is there scientific evidence that they modify the course of the virus in humans.

Treatment Considerations and Conclusions

Military tacticians teach, "Know thine enemy." This caveat is no less applicable to patients with genital Herpes simplex. Some individuals become so overwhelmed by misinformation from friends, faulty reporting by the lay press, or by misinterpretation of statements by physicians that they surrender to despair. They come to perceive the distorted view that the condition is incurable, and draw the incorrect conclusion that there is nothing to be done except to bear the torment of recurrent infection.

To begin, one must learn everything one can about the condition. Among the several sources of reliable information, one can find many articles on Herpes in biomedical libraries, of course, but the best source is *Sexually Transmitted Diseases,* a quarterly sent free by request from the United States Department of Health, Education, and Welfare, Public Health Services, Venereal Disease Control Division, Atlanta, Georgia 30333. One can also keep current with progress in research on Herpes simplex by subscribing to H.E.L.P., a quarterly published by the American Social Health Association, 260 Sheridan Avenue, Palo Alto, California 94306.

While I have emphasized the need to establish an accurate diagnosis as well as the importance of seeking out proper medical advice when first afflicted by the infection, there are several practical techniques that can be employed by patients for their own management of recurrences. Herpes simplex Type II seems to be thermolabile and can readily be destroyed "in vitro" by temperatures of 40° C. Local hot compresses to the site of Herpes simplex for ten minutes four times daily may abort attacks if begun soon

after onset of skin discomfort. In a like manner the application of ice cold compresses for a thirty minute period four times daily has been demonstrated to be of help. The compresses may be followed by the application of Listerine(R) which is applied with a Q-Tip(R) to the area (Knight, 1976; Raab & Lorincz, 1981). Betadine(R) cream may also inhibit the virus (Friedrick & Masukawa, 1975). It should be stressed that the infective site should be kept as dry as possible to avoid maceration, and topical drying agents such as merthiolate may be preferable to Betadine cream.

In general one should look to various techniques of stress reduction as adjuncts to treatment. Conditioned relaxation training from audio tapes, meditation, Yoga, biofeedback, and other techniques are most beneficial in reducing the adrenergic influences responsible for reactivation of disease. It is important to emphasize that there is no incompatability between physicians utilizing both orthodox and holistic approaches to patient management. Holistic medicine is not alternative medicine but rather a helpful adjunct to care, adding another dimension to the physician's armamentarium.

Patients should be advised to avoid over-exertion, sleeplessness, and tight fitting clothes. Coital friction and vigorous masturbation sometimes trigger activity and lubricating creams such as KY(R) jelly can be employed to diminish friction and irritation. If women have concurrent yeast infections or symptoms of nonspecific vaginitis, or if the man has associated prostatitis, medical care should be sought, for intercurrent urologic problems can trigger attacks. Some individuals have found L-lysine helpful (Griffith, Norins, & Kagan, 1978) albeit other sources are not as sanguine (Milman, Scheibel, & Jessen, 1980).

Until the present time, physicians had only anecdotal reference concerning their patients' recovery. I undertook an epidemiologic survey of genital Herpes simplex of 825 patients seen up to May 1980, and received replies from 425. The patient's average age was 27, with a range of 14 to 70 years. Of the respondents 53.8 percent were men and 46.2 percent were women. Single individuals constituted 36.1 percent of the survey, married 25.0 percent, and divorced 22.3 percent. At the time of response to the questionnaire, the mean number of years which patients had been infected was 4.5 years. When asked whether they had recovered from infection, 52.7 percent replied "Yes," while 47.3 percent answered "No." This statement is a highly encouraging statistic regarding recovery from Herpes, which has never been reported with any degree of scientific accuracy. The 50 percent mean recovery rate of *all* patients in the survey was seven years. A second curve was constructed, excluding the group unresponsive to therapy. When patients who had recovered were asked, "How long did the infection last?", 18.7 percent replied "one year," 18.7 percent replied "two years," and 13.3 percent replied "three years." Three years was the mean recovery time, while by five years 73.3 percent of the respondents had recovered. It is an interesting observation that only 10.8

percent of patients had only a single episode of genital Herpes whereas a more accurate and acceptable figure, and one usually reported in the literature, is 40 percent. Thus, the recovery curve was obviously influenced by the removal of the group unresponsive to therapy which may tend to suggest a more chronic course for Herpes overall. When asked to compare the number and severity of attacks of genital Herpes to the previous year, the responses were 58.8 and 60.8 percent for "less frequent" and "less severe" respectively. Patients concluded that topical therapy did not modify the number of attacks, but agreed in the majority of instances that local measures were able to relieve the symptoms and shorten the length of individual attacks. The same statement generally held true for systemic therapy.

"Emotional stress" was the single most important triggering mechanism (86.4 percent), while "intercourse" (66.0 percent), "lack of sleep" (51.5 percent), and "overexertion" (37.7 percent) followed. It is somewhat reassuring to learn that only 25.3 percent of respondents had transmitted Herpes to their sexual partner, while 57.7 percent had not, and 17.2 percent were uncertain.

Finally, it was significant that 19.9 percent of women had abnormal Pap smears, while 4.8 percent had a history of cancer of the cervix. For men, 13.3 percent had a history of prostatitis, while none of the respondents had cancer of the prostate.

The patient population was overwhelmingly white (95.9 percent) and skewed to the high socio-economic groups. Only 8.6 percent of respondents made less than $10,000 yearly. While there is additional material yet to be derived from this survey, the above data should be taken as encouraging proof that patients should be optimistic regarding their own ultimate recovery.

The promising areas of research in Herpes treatment seem to be in the production of selective metabolic poisons that interfere with viral replication without, at the same time, poisoning the host. At the present time drugs such as Ribavirin (Bierman, et al., 1981), Ara-A, and more recently, Acyclovir are undergoing investigation. I have studied two of these drugs which, though seemingly able to foreshorten attacks of infection, seem unable to prevent recurrences. The limiting feature of these agents is that they fail to destroy the latent ganglionic infection, and only seem to work during the productive stage of viral replication or during a viremic stage when the virus is carried in the bloodstream. I am presently employing the topical agent 2 deoxy D glucose which holds some promise of preventing initial retrograde ganglionic infection, and does seem to foreshorten individual attacks of Herpes for some patients (see Blough & Giuntoli, 1979). However, not all the evidence is consistent concerning the efficacy of this treatment (Corey, 1980).

While I generally emphasize the benefits of holistic medical approaches to patient management, there are intriguing reports regarding the use of mind

altering (psychomimetic) drugs in the management of recurrent Herpes. Chlorpromazine (Chang, 1975) and lithium (Lieb, 1979) show some promise, while mood elevating drugs such as amitriptyline have been helpful in many patients unresponsive to conservative therapy. Besides its known influences in modulating manic-depressive episodes, lithium has the unusual property of inducing reversible leukocytosis and has been shown to be a promising agent to reduce infection in patients receiving chemotherapy (Lyman, Williams, & Preston, 1981). If the psychoneuro-immunologic axis is as important as I have stressed in the activation of Herpes, research into neurochemical mediators of mood may prove to have therapeutic applications.

Other approaches that are being considered include modulation of pituitary influences in women who experience midcycle or premenstrual flare of Herpes. Progesterone has been shown to depress immune competence and increase susceptibility to Herpes (Baker, Phillips, & Roesser, 1980) no less than being responsible for inducing autoimmune reactions in women (Bierman, 1973). Some women seem to have fewer attacks of Herpes simplex while on oral contraceptives, while drugs such as danazol which can inhibit progesterone production are being considered.

Some patients with Herpes simplex may have subtle defects in the ability of their immune system to effectively destroy the virus. In the area of immune competence, there are tests currently available to measure both humoral antibody production and cell mediated immunity. These tests can usually be performed in a doctor's office, although it is important to mention that most individuals display intact immune defenses as measured by these parameters (Berman, 1975). I have investigated immune stimulants such as BCG and Levamisole in the past but am presently using typhoid vaccine as a means of "immune antibiosis" because of the known effect of this agent to induce leukocytosis and pyrexia, as well as the fact that gram negative endotoxins evoke release of pre-formed interferon from body stores. Interferon as an actual agent for treatment of genital Herpes is still years off as a practical consideration, and even then the drug does not destroy latent ganglionic infection (infectious relapses still occur).

Other areas of clinical research that are being investigated by my lab include topical immunotherapy with dinitrochlorobenzene. This agent which evokes a violent allergic reaction when applied to the skin has been shown to effectively destroy the virus of warts. The drug has been employed primarily on patients with lumbosacral Herpes. Our early studies on 25 patients suggest that the infection is often inhibited at the site of topical application, albeit new areas tend to develop in surrounding non-treated sites. Other areas of current investigation involve selective destruction of sensory nerves in the skin as a means of interrupting the apparent servomechanism that exists between the skin and the sensory neurons.

In conclusion, while the issues and answers presented in this paper are not meant to convey a final or sole answer to the dilemma of the Herpes simplex virus, the material is presented in the vein of an on-going effort to illuminate a complex, multidimensional problem. The anecdotal reports cited above concerning my direction in therapy of patients have yet to be subjected to double blind controls; they are mentioned to convey evidence of recent progress. The fact still remains that one must, of course, carefully document effectiveness before making claims of cure.

Nevertheless, there is every reason to retain a degree of optimism and hope when reflecting on the management of patients with genital Herpes simplex. One of the most important functions of a physician is to provide accurate scientific documentation to reflect the present state of our knowledge. In so doing, patients will have less emotional burden to bear, less frustration, more tolerance of their physicians, and a real hope for recovery.

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