Reactivation of latent herpes simplex virus infection by ultraviolet light: A human model

John J. Perna, D.D.S.,* Margaret L. Mannix, R.N.,* James F. Rooney, M.D.,* Abner Louis Notkins, M.D.,* and Stephen E. Straus, M.D.** *Bethesda, MD*

Infection with herpes simplex virus often results in a latent infection of local sensory ganglia and a disease characterized by periodic viral reactivation and mucocutaneous lesions. The factors that trigger reactivation in humans are still poorly defined. In our study, five patients with documented histories of recurrent herpes simplex virus infection on the buttocks or sacrum were exposed to three times their minimal erythema dose of ultraviolet light. Site-specific cutaneous herpes simplex virus infection occurred at 4.4 ± 0.4 days after exposure to ultraviolet light in 8 of 13 attempts at reactivation. We conclude that ultraviolet light can reactivate herpes simplex virus under experimentally defined conditions. This model in humans should prove useful in evaluating the pathophysiology and prevention of viral reactivation.
(J AM ACAD DERMATOL 1987;17:473-8.)

On infection of an epithelial site, herpes simplex virus is taken up by local nerve terminals and spreads by axoplasmic flow to nerve cell bodies in the ganglia. The virus then enters a latent state, during which time infectious virus can no longer be recovered from the ganglia.[1,2] The state of the viral genome during latency is not known. Some investigators have suggested that it exists in an episomal form,[3] whereas others argue it may be integrated into cellular deoxyribonucleic acid.[4] Periodically the latent virus reactivates, travels down the axon, and produces the typical recurrent epithelial lesion.[5-7] Although the mechanism by which the virus reactivates is not clear, a number of factors have been implicated. In experimental animals, cutaneous irritation of the dermatome, direct trauma to the ganglion, and immunosuppressive agents have been shown to cause reactivation.[5-8] In humans, fever therapy, microneurosurgical procedures on the trigeminal root, and immunosuppression have been proved to favor virus reactivation,[9-13] and diverse reports suggest that the common cold, emotional stress, menses, and ultraviolet light do so as well.[5-7] Given the diversity of stimuli associated with reactivation, it is likely that there are some common pathways by which they exert their ultimate effect. If a reproducible and convenient means of inducing viral reactivation could be found, it might be possible to elucidate the mechanisms of reactivation and devise methods of prevention.

Among the factors possibly associated with herpes simplex virus reactivation, ultraviolet light appears to be the most amenable to safe and reasonable clinical study. In 1975, Wheeler[14] reported a pilot study and suggested that ultraviolet light could stimulate perigenital reactivation of herpes simplex virus in humans. Similar observations of ultraviolet induction of labial herpes simplex virus infections were recently reported by Spruance.[15]

From the Laboratory of Oral Medicine, National Institute of Dental Research,* and the Laboratory of Clinical Investigation, National Institute of Allergy and Infectious Disease,** National Institutes of Health.

Accepted for publication Jan. 28, 1987.

Reprint requests to: Dr. Stephen E. Straus, Medical Virology Section, Building 10, Room 11N113, National Institutes of Health, Bethesda, MD 20892.

Our study was initiated to further explore and statistically evaluate ultraviolet light as a stimulus for reactivation of herpes simplex virus in the perigenital area. We found that treatment with ultraviolet light, primarily of the B wavelength (UVB), triggered recurrences in four of five patients with prior herpes simplex virus infections of perigenital sites.

METHODS

Study population

Otherwise healthy patients between 18 and 50 years of age, with culture-confirmed herpes simplex virus infection involving the buttocks or sacral area and with six or more reported recurrences in the past year, were eligible for entry into this study. Women were required to be premenopausal and to have negative results on a pregnancy test. At the initial visit, informed consent and medical history were obtained, the site of infection was examined, and blood was drawn for routine laboratory testing.

Ultraviolet source

The source of ultraviolet light was four Westinghouse FS40 fluorescent tubes. These tubes emit UVB wavelengths (290-320 nm), which cause erythema.[16,17] The tubes were fixed to the underside of an adjustable bedside stand, and the stand was centered over the buttocks or sacrum so that the tubes were 25.4 cm above the skin. The stand, lamps, and buttock area were fully enclosed in drapes.

Determination of the minimal erythema dose

With the patient in a prone position on a stretcher, an area on the buttock or sacrum was selected that was near to, but not overlapping with, sites previously involved with herpetic recurrences. A cardboard template with four 1×1-cm square holes was secured over this area with tape. All remaining exposed areas of skin were covered with multiple opaque drapes. The four 1-cm^2 unshielded areas of skin were sequentially exposed to increasing durations of ultraviolet light. The test areas were observed at 24 hours to note the degree of erythema. A grading system ranging from 0 to 4 was used[16]: 0 indicated no response, and 4 indicated violaceous erythema with vesiculation. The minimal erythema dose was defined as the duration of ultraviolet exposure sufficient to cause minimal erythema with four sharp borders and was assigned a grade of 1 (Fig. 1, *A*). If there was difficulty in determining which of two exposure times to use as the minimal erythema dose, an intermediate time was chosen.

Method of reactivation

When possible, the selection of the test site was based on the location of a previous culture-positive herpes simplex virus recurrence. In the absence of this documentation, selection was based on patient history and physical examination of the area. Buttock and sacral sites that had been frequently infected showed scarring and hyperpigmentation. A cardboard template containing a 3×3-cm square aperture was secured with tape over this site, the surrounding exposed area of skin was covered with multiple opaque drapes, and the ultraviolet light source was centered 25.4 cm over the unshielded area. The exposure time for attempted reactivation was three times the duration of the patient's previously determined minimal erythema dose. This resulted in marked erythema with four sharp borders by the next day (i.e., grade 2 or 3). Blistering did not occur and most burns were free of discomfort, but mild local pain was occasionally reported. At no time was grade 4 erythema observed.

Reactivation was attempted from one to four times in each patient, depending entirely on the patient's willingness to submit to testing. The interval between reactivation attempts varied from 38 to 116 days and was dictated by patient availability. Participants were closely followed to document spontaneous and ultraviolet-induced recurrences during the study period. All patients were examined within 24 hours of the onset of symptoms suggestive of a recurrence. All suspicious sites were cultured and photographed. Treatment with acyclovir, one 200-mg capsule five times daily for 5 days, was provided for any clinically or virologically confirmed herpetic recurrence, whether associated with ultraviolet treatment or occurring spontaneously on the buttocks or genitalia.

Definition of an ultraviolet-induced recurrence

Lesions occurring at or within 1 cm of ultraviolet-induced erythema were arbitrarily defined as "ultraviolet induced" if they appeared within 6 days after exposure. All other recurrences were labeled "spontaneous." All recurrences were diagnosed clinically by the appearance of grouped vesicles, pustules, or ulcers and were confirmed by recovery of virus from the lesions.

Virus isolation

Freshly aspirated or swabbed lesion material, obtained within 2 days after the appearance of lesions, were inoculated into human embryonic kidney cells and human diploid fibroblasts. The tubes were examined daily for 14 days for cytopathic changes characteristic of herpes simplex virus replication.[18]

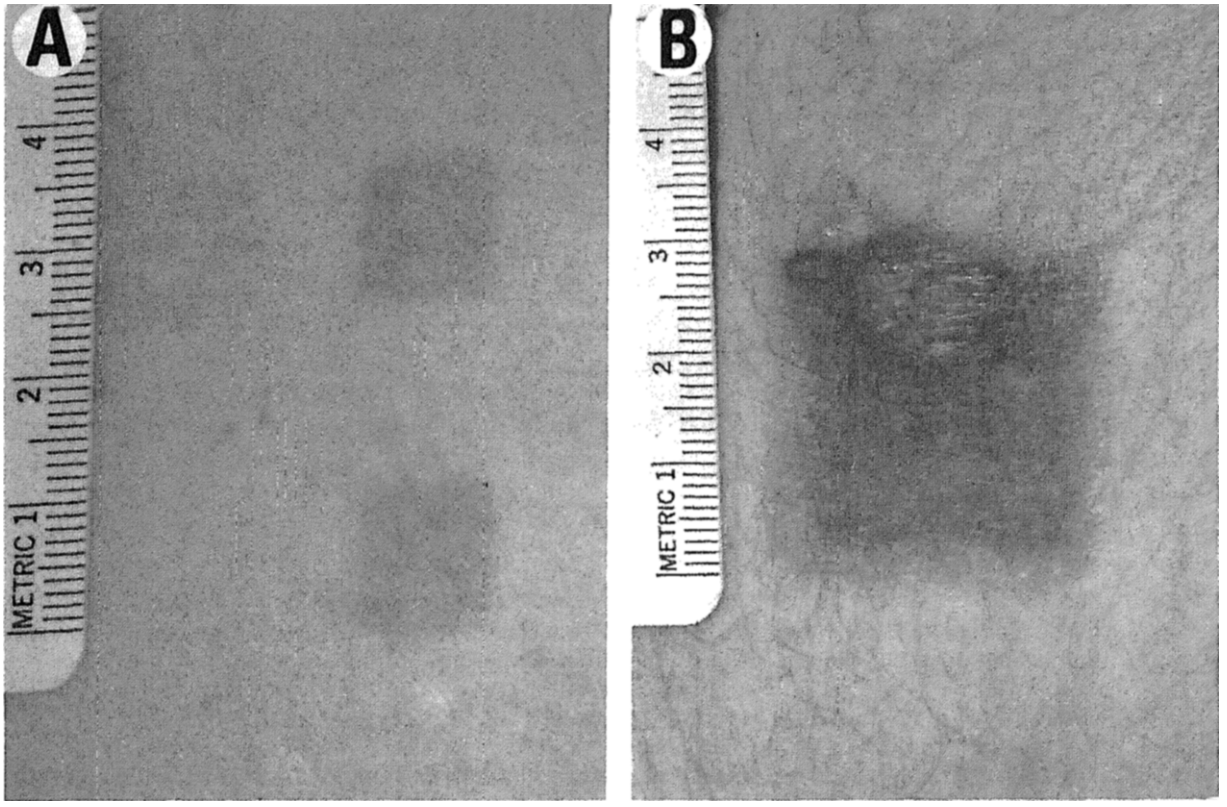

Fig. 1. Ultraviolet-induced cutaneous erythema and recurrent herpes simplex virus infection. *A*, Determination of the minimal erythema dose by incremental exposures of 1 × 1-cm areas of skin to ultraviolet light. Exposure to ultraviolet light: *lower left*, 1 minute with no visible erythema; *upper left*, 2 minutes with diffuse erythema; *lower right*, 3 minutes with erythematous area with four sharp borders; and *upper right*, 4 minutes with slightly more distinct erythematous area with four sharp borders. The minimal erythema dose for this patient was 3 minutes. *B*, Ultraviolet-induced reactivation of herpes simplex virus. Vesicular lesions are within the 3 × 3-cm area of ultraviolet-induced erythema. The photograph was taken 5 days after ultraviolet exposure of the patient's sacral area.

RESULTS

Five patients were enrolled in the study. Their age, sex, race, and history of recurrent herpes simplex virus infections are indicated in Table I. None had identified ultraviolet exposure as being associated with herpetic recurrences. Each patient was then exposed to ultraviolet light (e.g., Fig. 1, *A*) to determine the minimal erythema dose. For the four white patients it ranged from 3.5 to 5.0 minutes (average, 4.2), and for the one black patient it was 21.0 minutes.

The temporal relationship between ultraviolet exposure and the appearance of lesions is illustrated in Fig. 2. After 13 exposures, lesions developed within 1 week in 10 instances, and these reactivations occurred between day 3 and day 7. No further reactivations occurred in any patient until day 17. Eight of the ten lesions developed before day 6 and were located within 1 cm of the site of ultraviolet exposure. These eight reactivations were defined as "ultraviolet induced." Seven of these eight infections developed within the borders of ultraviolet exposure, and one occurred 1 cm lateral to the burn site. Of the 10 lesions that developed within 1 week of ultraviolet exposure, two occurred in an anatomic site distant from the area of the burn. Both of these occurred in the perineal area of Patient 1 on day 7 after separate ultraviolet exposures.

Although 8 of the 13 reactivation attempts

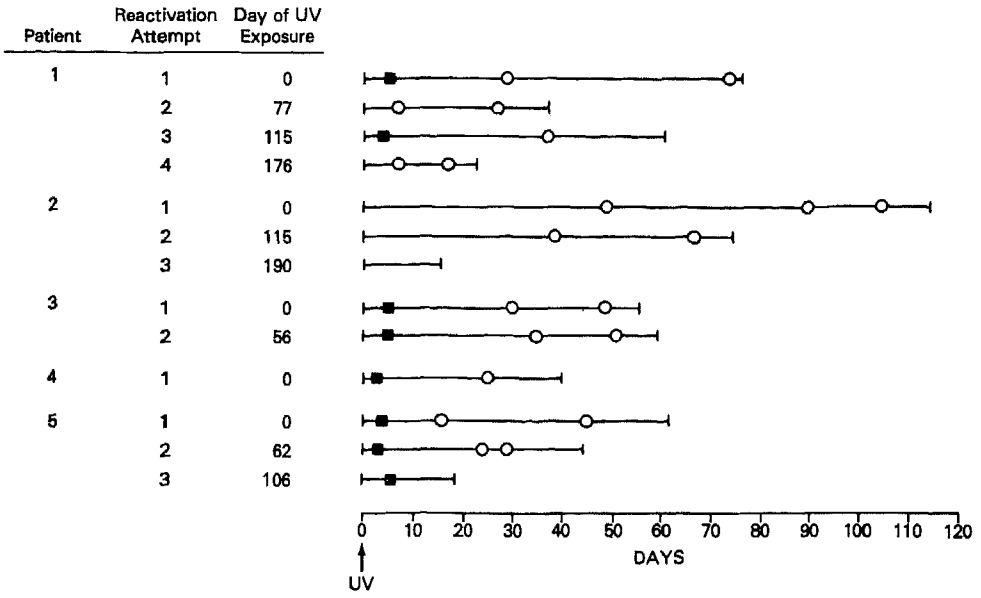

Fig. 2. Ultraviolet *(UV)* light *(arrow)* was administered on day 0 of each independent reactivation attempt. Column marked "Day of UV Exposure" indicates when patient was exposed to ultraviolet light during the course of the study. Solid blocks indicate lesions occurring within 6 days after exposure and within 1 cm of the erythematous area; these lesions were considered ultraviolet induced. Open circles indicate lesions occurring at 7 days or thereafter and outside the area exposed to ultraviolet light; these lesions were considered spontaneous.

Table I. Reactivation of herpes simplex virus by ultraviolet light

Patient No.	Age (yr)	Sex	Race	History of recurrent HSV (yr)	MED (min)	No. of reactivations/No. of attempts	Positive cultures/induced lesions
1	34	F	W	11	4.0	2/4	2/2
2	38	F	W	15	5.0	0/3	—
3	26	M	W	2	4.5	2/2	1/2
4	48	F	W	2	3.5	1/1	1/1
5	45	F	B	6	21.0	3/3	3/3

HSV: Herpes simplex virus; MED: minimal erythema dose.

(62%) were successful (Table I and Fig. 2), there was considerable variation among individuals. Reactivation was successful in every attempt in Patients 3, 4, and 5. In contrast, only two of four reactivation attempts were successful in Patient 1, and none were successful in Patient 2. Dark skin color did not preclude successful reactivation in either the black or the white patients. Confirmation that the lesions were due to herpes simplex virus came from recovering infectious herpes simplex virus from seven of the eight ultraviolet-induced lesions (Table I). The one episode that was culture-negative occurred in a patient who had already self-initiated oral acyclovir treatment.

While participating in this study, all five patients had spontaneous herpetic recurrences (Fig. 2) at one or more body sites. The mean (± SEM) length of time between exposure to ultraviolet light and the ensuing ultraviolet-induced recurrence was 4.4 ± 0.4 days. This period was significantly shorter than either the 27.0 ± 3.9 days between ultraviolet exposure and the first spontaneous re-

currence or the 23.4 ± 3.6 days between spontaneous recurrences for which there were no intervening ultraviolet-induced recurrences (each comparison, $p < 0.001$, with the use of a modified t test).

DISCUSSION

A problem that has delayed progress in the understanding and treatment of herpes simplex virus infection has been the lack of a manipulable human model. The administration of ultraviolet light to cutaneous sites where previous reactivation has occurred may provide such a model. Our study showed that ultraviolet light could reactivate herpes simplex virus in over 60% of all attempts. Induction of a recurrence was unsuccessful in only one of five patients. Similarly, in 1975, Wheeler[14] noted that three of his patients developed recurrences after exposure to ultraviolet light, and Blyth et al[19] reported an increase in reactivation after ultraviolet treatment of latently infected mice. In our study, reactivation after ultraviolet exposure occurred predominantly at or near the site of ultraviolet exposure, rather than at other perigenital sites of previous spontaneous recurrences. This supports the concept of site specificity in the reactivation of herpes simplex virus by epithelial irritants.[20] Our findings are also in accord with those of Spruance,[15] who recently reported ultraviolet induction of orolabial herpes.

The mechanism by which ultraviolet light reactivates latent herpes simplex virus is not understood. One possibility is that epithelial injury or inflammation releases mediators that travel up the nerve to the ganglion, where they directly or indirectly cause reactivation. A variety of mediators are released at an inflammatory site, including prostaglandins, which are thought to play a major role in ultraviolet-induced erythema.[21] Our human model of reactivation might therefore be useful for testing the efficacy of sunscreens and anti-inflammatory drugs, including prostaglandin inhibitors, in preventing ultraviolet-induced herpes simplex virus recurrences. The possibility that stimuli which induce erythema and inflammation, other than ultraviolet light, might cause recurrences at sites of previous herpetic infection merits investigation.

Two basic approaches are being evaluated in the management of herpes simplex virus infections. The first is vaccination to prevent the establishment of the latent infection.[22] The second is antiviral agents to treat the infection once it is established.[7,23] Our studies point to a third approach that might be applicable to some patients suffering from a latent infection with frequent recurrences: the identification of factors that cause reactivation. If specific factors can be identified, it might be possible to avoid them or to devise methods of intervention. This approach is more likely to be useful for individuals in whom ultraviolet exposure of affected areas is common, such as those with orofacial recurrences. Sun-blocking agents might prove efficacious, and anecdotal reports suggest that they are useful. Alternatively, there might be a "period of vulnerability" during which time the administration of a short course of an antiviral agent such as acyclovir might prevent the development of recurrences. Prophylactic treatment could be administered selectively during periods of anticipated high risk. If successful, this regimen would reduce the frequency of recurrences while avoiding the use of long-term antiviral treatment.

REFERENCES

1. Stevens JG, Cook ML. Latent herpes simplex virus in spinal ganglia of mice. Science 1971;173:843-5.
2. Walz MA, Price RW, Notkins AL. Latent ganglionic infection with herpes simplex virus types 1 and 2: viral reactivation in vivo after neurectomy. Science 1974; 184:1185-7.
3. Rock DL, Fraser NW. Detection of HSV-1 genome in central nervous system of latently infected mice. Nature 1983;302:523-5.
4. Puga A, Cantin EM, Wohlenberg C, Openshaw H, Notkins AL. Different sizes of restriction endonuclease fragments from the terminal repetitions of the herpes simplex virus type I genome latent in trigeminal ganglia of mice. J Gen Virol 1984;65:437-44.
5. Openshaw H, Sekizawa T, Wohlenberg C, Notkins AL. The role of immunity in latency and reactivation of herpes simplex viruses. In: Nahmias AJ, Dowdle WR, Schianzi RF, eds. Human herpes-viruses: an interdisciplinary perspective. 1st ed. New York: Elsevier/North Holland, 1981:289-96.
6. Klein RJ. The pathogenesis of acute, latent and recurrent herpes simplex virus infections. Arch Virol 1982;72: 143-68.
7. Straus SE, Rooney JF, Sever JL, et al. Herpes simplex virus infection: biology, treatment, and prevention. Ann Intern Med 1985;103:404-19.

8. Openshaw H, Asher LVS, Wohlenberg C, Sekizawa T, Notkins AL. Acute and latent infection of sensory ganglia with herpes simplex virus: immune control and viral reactivation. J Gen Virol 1979;44:205-15.
9. Keddie FM, Rees RB, Epstein NN. Herpes simplex following artificial fever therapy. JAMA 1941;117: 1327-30.
10. Pazin GJ, Armstrong JA, Man TL, Tarr GC, Jannetta PJ, Ho M. Prevention of reactivated herpes simplex infection by human leukocyte interferon after operation on the trigeminal root. N Engl J Med 1979;301:225-30.
11. Naraqi S, Jackson GG, Jonasson O, Yamashiroya HM. Prospective study of prevalence, incidence and source of herpes virus infections in patients with renal allografts. J Infect Dis 1977;136:531-40.
12. Meyers JD, Flournoy N, Thomas ED. Infection with herpes simplex virus and cell-mediated immunity after marrow transplant. J Infect Dis 1980;142:338-46.
13. Rand KH, Rasmussen LE, Pollard RB, Arvin A, Merigan TC. Cellular immunity and herpes virus infections in cardiac-transplant patients. N Engl J Med 1977;296: 1372-7.
14. Wheeler CE. Pathogenesis of recurrent herpes simplex infections. J Invest Dermatol 1975;65:341-6.
15. Spruance SL. Pathogenesis of herpes simplex labialis: experimental induction of lesions with UV light. J Clin Microbiol 1985;22:366-88.
16. Fitzpatrick TB, Eisen AZ, Wolff K, Freedberg IM, Austen KF. Dermatology in general medicine. 2nd ed. New York: McGraw-Hill, 1979:952-3.
17. Harber LC, Bickers DR, Epstein JH, Pathak MA, Urbach F. Report on ultraviolet light sources. Arch Dermatol 1974;109:833-9.
18. Blair JE, Lennette EH, Truant JP. Manual of clinical microbiology. Bethesda, MD: American Society for Microbiology, 1970.
19. Blyth WA, Hill TJ, Field HJ, Harbour DA. Reactivation of herpes simplex virus infection by ultraviolet light and possible involvement of prostaglandins. J Gen Virol 1976;33:547-50.
20. Sekizawa T, Openshaw H, Notkins AL. Site specificity of epithelial irritants in the reactivation of herpes simplex virus. J Infect Dis 1985;152:841-2.
21. Harbour DA, Hill TJ, Blyth WA. Recurrent herpes simplex in the mouse: inflammation in the skin and activation of virus in the ganglia following peripheral stimulation. J Gen Virol 1983;64:1491-8.
22. Cremer DJ, Mackett M, Wohlenberg C, Notkins AL, Moss B. Vaccinia virus recombinant expressing herpes simplex virus type 1 glycoprotein D prevents latent herpes in mice. Science 1985;228:737-40.
23. Hirsch MS, Schooley RT. Treatment of herpes virus infections. N Engl J Med 1983;309:963-70, 1034-9.

ABSTRACTS

Epidermal Langerhans cells—a target for HTLV-III/LAV infection

Tschachler E, Groh V, Popovic M, et al. J Invest Dermatol 1987;88:233-7

Skin biopsies of 7 of 40 human immunodeficiency virus (HIV)–infected persons demonstrated that Langerhans cells were the only epidermal cells to react with a monoclonal antibody specific for the HIV core protein p17. Also, in one of the biopsy specimens, viral particles characteristic of HIV were seen in Langerhans cells.

J. Graham Smith, Jr., M.D.

The effect of isotretinoin in six patients with cutaneous T-cell lymphoma

Neely SM, Mehlmauer M, Feinstein DI. Arch Intern Med 1987;147:529-31

Six patients with cutaneous T-cell lymphomas were treated with isotretinoin, 1-2 mg/kg/d. All experienced symptomatic relief within 2 to 8 weeks of starting drug therapy, although pretreatment and posttreatment biopsy specimens were unchanged. Isotretinoin, thus, provides good palliation of symptoms and signs associated with cutaneous T-cell lymphoma in patients unable or unwilling to comply with standard therapy.

J. Graham Smith, Jr., M.D.

Adrenocortical micronodular dysplasia, cardiac myxomas, lentigines, and spindle cell tumors—report of a kindred

Danoff A, Jormark S, Lorber D, Fleischer A. Arch Intern Med 1987;147:443-8

In a family encompassing three generations, six of eleven evaluated members had two or three elements of a triad comprising adrenocortical micronodular dysplasia, mucocutaneous lentigines, and cardiac myxomas.

J. Graham Smith, Jr., M.D.

Treatment of patients with acquired immunodeficiency syndrome and associated manifestations

Kaplan LD, Wofsy CB, Volberding PA. JAMA 1987;257:1366-74

Current recommended treatment for opportunistic infections associated with acquired immunodeficiency syndrome is discussed, with recommended therapy for the primary disorder as well.

J. Graham Smith, Jr., M.D.