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The Natural History of Recurrent Facial-Oral Infection with Herpes Simplex Virus

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Fifty-seven episodes of facial-oral infections with herpes simplex virus (HSV) (cold sores) were studied in 41 ambulatory patients. Patients were examined within 24 hr of the onset of symptoms and for five consecutive days. Clinical parameters were assessed, lesion size was measured, and daily cultures for virus were performed. HSV was isolated in 61% of the episodes and was HSV type 1 in all cases. Serum neutralizing antibody to HSV was measured initially and 21 days after the onset of symptoms. All patients had antibody initially, but a fourfold or greater rise in titer was seen in only four patients. Lesion size and stage of healing were compared in patients with virus-positive episodes and those with virus-negative episodes. These two groups were found to be clinically distinct. Virus-positive lesions were larger, and the rate of healing was slower. This finding provides the first clinical correlation associated with the presence of HSV in cold sores.

The herpes simplex viruses (HSV) are ubiquitous agents that infect most people early in life. In population studies in Great Britain and the United States, neutralizing antibodies to HSV have been found in 40%–90% of adults [1, 2]. The primary infection probably occurs early in life, for by the age of 15 years, 90% of a study population had neutralizing antibody to HSV [2]. In a recent study of university students, however, only 30% had neutralizing antibody to HSV type 1 (HSV-1), a finding suggesting that the majority of children from middle-income families may reach adulthood without antibody [3]. It has been estimated that about one-third of the population of the United States experiences recurrent episodes of facial-oral infection with HSV, known as recurrent herpes labialis or "cold sores" [4]. The true incidence of recurrences is variable in different populations, but 15% of a group of young adults surveyed had recurrences of at least one lesion per year [5], and in another series of >1,000 young adults, 20% had recurrent episodes [6].

Facial cold sores appear to represent reactivation of latent HSV residing in the trigeminal ganglion, where it has become established following spread of the virus from the oral mucosa during primary herpes gingivostomatitis [3–10]. Although various circumstances such as trauma, emotional stress, fever, or exposure to sunlight are considered predisposing factors to the recurrence of herpes labialis, the mechanism responsible for viral reactivation is not known [11]. The presence of neutralizing antibody to HSV does not prevent recurrent episodes, and most patients with recurrent herpes labialis have high levels of neutralizing antibody at the time of recurrence [12].

HSV is present in lesions at the time of recurrence [13, 14], and HSV has been isolated from 88% of lesions in a study among young adults [6]. Serial changes in viral titers have been examined in two studies [14, 15], one of which

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[15] has been conducted concurrently with the present report. There is little other information on the quantity of HSV present, the duration of HSV in the lesions, or the correlation between the presence of HSV in the lesion and clinical manifestations. For an understanding of the disease and a critical evaluation of potential antiviral therapy, it is essential to describe the natural course of the illness and its virology. In this report we present the natural history of the clinical lesions and virologic features of recurrent herpes labialis.

Materials and Methods

Patients. Fifty-seven episodes of recurrent, facial, mucocutaneous infection with HSV (cold sores) were investigated in 41 ambulatory patients of either sex. All patients were seen within 24 hr after the first sign or symptom of the infection. The patients were otherwise in good health and refrained from taking any drug during the course of the study. A detailed history of recurrent cold sores was obtained from all patients on enrollment in the study. For five consecutive days the lesions were examined once daily as follows. The lesions were photographed, measured (length and width), and assigned to a stage (1–7) according to their general appearance: (*1*) no lesion, prodromal symptoms; (*2*) erythema or papules; (*3*) vesicles; (*4*) erosions; (*5*) crusts; (*6*) nearly healed; and (*7*) healed. All lesions were examined for the presence of virus, and any virus found was identified and titrated. Samples for viral cultures were obtained by scraping the lesions three times with a scalpel blade. For this purpose vesicles were opened and crusts were lifted. The scalpel blades and scrapings were kept in 2 ml of culture medium (see below) and stored at −70 C. Specimens of saliva were taken daily with a swab, which was stored under the same conditions. Blood was obtained from 18 patients on the first day of the study and three weeks later for determination of antibody to HSV.

Cells. Primary rabbit kidney cell cultures were prepared by mincing and trypsinizing rabbit kidney tissue by a multiple extraction method [16, 17]. The cells were grown in monolayers on 32-oz glass bottles in minimal essential medium (MEM) containing 10% fetal calf serum (FCS). At passage levels one to three, rabbit cells were removed from the glass by trypsinization, plated in 3-ml tissue culture dishes at a concentration of 3.3–4.0 × 10^4 cells/ml in the presence of MEM-10% FCS, and incubated in an incubator with an atmosphere of 5% CO_2. When the cells were 90% confluent, they were employed in the plaque assay of the viral isolates [18]. A diploid human fibroblast cell line derived from newborn foreskin (FS-350Q) was obtained from Dr. Michael Oxman of the Virus Research Unit at Children's Hospital Medical Center, Boston, Mass. These cells were grown on Dulbecco's modified Eagle's medium supplemented with 10% FCS and were employed in the microneutralization assays [19]. The Vero line of African green monkey cells was grown in monolayer cultures in 32-oz glass prescription bottles in medium 199 containing 10% FCS. Tissue culture dishes of Vero cells were prepared as described for the rabbit kidney cells and employed in the plaque reduction assays. All media were supplemented with 250 units of penicillin/ml and 250 μg of streptomycin/ml. FCS was inactivated at 56 C for 30 min.

Viruses. Clinical specimens from facial lesions or saliva were collected in 2 ml of medium 199 supplemented with 10% inactivated FCS, penicillin (100 units/ml), streptomycin (100 μg/ml), amphotericin B (2.5 mg/ml), and gentamicin (50 μg/ml). Specimens were stored at −70 C. Virus was isolated by plaque assays directly onto primary rabbit kidney cells. Rabbit cells were prepared as primary cultures and grown on MEM containing 10% FCS until cells were 90% confluent. Serial 10-fold dilutions of the specimens from facial lesions or saliva were prepared (from undiluted to a dilution of 10^{-5}), and 0.1-ml samples were inoculated onto plaque dishes and adsorbed for 1 hr at 37 C. Following adsorption, the inoculated cells were overlaid with MEM containing 2% FCS and 50% methylcellulose and were incubated for four more days in an incubator in 5% CO_2, according to the method of Rapp et al. [20].

The cells were fixed with a 1:3 mixture of acetic acid-methanol, and the plaques were counted. The titers were expressed as the log number of pfu/ml in the original sample. The saliva specimens were first inoculated into tubes of rab-

bit kidney cell culture, and those that showed HSV CPE were tested as previously described. The isolates of HSV were identified as HSV-1 or HSV type 2 (HSV-2) by a simplified microneutralization technique, according to the method of Stalder et al. [19]. The microneutralization tests were performed with FS-350Q cells. Reference antisera for use in the microneutralization test were HSV-1-specific antisera (VR3 strain, lot 12 from the Center for Disease Control [CDC], Atlanta, Ga.) and HSV-2-specific antisera (MS strain, lot 3 from the CDC).

Serologic studies. Titers of neutralizing antibody to HSV were determined by a 50% plaque reduction method. Vero cell monolayers grown to 90% confluency in medium 199 containing 10% FCS were inoculated with a constant dose of a standard pool of HSV-1 prepared in our laboratory by a high-dilution inoculation method. The standard pool of HSV was diluted so as to induce 50 plaques per plaque dish, and this standard test inoculum was used in the control and included in each assay. For each serum tested, duplicates of each dilution were prepared and mixed with the standard test dose of HSV. For control plates, phosphate-buffered saline (PBS) was incubated with the virus. The overlay, the incubation time, and the fixation of the cells were exactly as described above for the plaque assays. For each mixture of serum and virus, the number of plaques was counted, and the end point (expressed as serum dilution) required to reduce the number of plaques by 50% was calculated by the method of Reed and Muench [21]. The concentration of neutralizing antibody was determined in the initial serum and in the serum obtained 21 days after the initial visit.

Statistical methods. Distributions of lesion size, lesion stage, and viral titer for the HSV-positive and HSV-negative groups on each day of the study were examined for distribution type by histogram, skewness, kurtosis, and W-statistic [22], and the appropriate central measures were computed. The behavior of the three lesion measures with respect to time for both groups was examined by observing and comparing the shifts in histograms at each day and by plotting the appropriate means vs. time. In all cases plots of means vs. time showed a systematic time dependency that could be fitted to an appropriate curve. Differences in lesion stage and size between the two groups were examined by a variety of techniques, including covariance analysis, multiple sample comparison (in this case, Duncan's multiple range test [23]), and appropriate nonparametric tests.

Results

Clinical data. Fifty-seven episodes of facial infection with HSV were studied in 41 patients (13 men and 28 women); 36 episodes (63%) occurred in women, and 21 (37%) in men. Forty infections could be followed for five consecutive days, nine for four consecutive days, and eight for three consecutive days. The ages of the patients ranged from 15 to 70 years, but 58% of the infections were observed in patients 30–40 years old. The lesions were most often localized on the lips (46 cases). Both lips were equally affected, and no preferential area could be found on either lip. Other sites included the nose (seven cases), chin (one), and forehead (one). Patients stated that the cold sores tended to recur in the same location, but when the data on the location of recurrent episodes were examined, only 12 patients had more than one episode during the period of the study. These 12 patients had a total of 28 episodes. Only four patients had two episodes occurring in the same place, for a total of eight episodes in the same location. The remaining eight patients had 20 episodes, each in a different location. Therefore, only a minority (eight of 28, 29%) of episodes were actually observed to occur in the same location in this study.

All patients complained of recurrent cold sores, and the following facts emerge from analysis of these data. Most patients (26 of 41, 64%) had more than three recurrences per year, the most common frequency being one cold sore every three to four months. A large fraction (31 of 41, 76%) of the patients reported that cold sores were preceded by a prodrome where the lesion subsequently developed. The most frequent prodromal symptoms were itching (34%), tingling (27%), and pain (37%). A majority (31 of 41, 76%) indicated a temporal correlation between the cold sore episode and one or more external or internal predisposing factors. Upper respiratory tract infections (29%), fatigue (17%), emo-

tional stress (15%), physical trauma (12%), and exposure to the sun (10%) were the most common predisposing factors cited. Family infection was involved for 24 (58.5%) of the 41 subjects. The period from onset of the first herpes lesion was 6.5 years for women and 3.8 years for men. The lesions healed in six to 12 days, with a mean healing time of 9.3 days. On the last day of observation, 90% of the lesions were at stage 5, 6, or 7.

Virologic and serologic data. Culture results are shown in table 1. Fifty-four percent of the lesions contained titratable virus on the first day; 40% on the second day; and 18%, 5%, and 2% on the last three days. Evolution of the titer in individual episodes is shown in table 2. Titers were highest during the first two days of infection and fell off thereafter. The titer of HSV was measurable at least once in 61% of the cold sore episodes and always at some point within the first two days of the infection. The strains of HSV isolated were all type 1 as determined by microneutralization.

Specimens of saliva obtained during episodes of infection were cultured; of 245 specimens, only 18 (8%) were positive for HSV. All saliva specimens in which HSV was detectable were taken on days 0, 1, or 2 of an acute episode of infection.

Concentrations of neutralizing antibody to HSV-1 were determined in 18 paired sera taken at the time of the first visit for an episode of HSV infection and 21 days after onset. All patients had antibody at the time of onset of the cold sore, and only four patients (22%) had a fourfold rise in antibody titer. The mean reciprocal initial titer of antibody (±SD) in serum taken on enrollment in the study was 280 ± 183, and in serum taken on day 21 was 575 ± 610. The mean titer for the initial serum from patients with virus-positive episodes was 186 ± 112, and for those with virus-negative episodes, 364 ± 204. The mean titer for the sera taken on day 21 from patients with virus-positive episodes was 550 ± 203, and for those with virus-negative episodes, 643 ± 610. From these comparisons it can be seen that the mean antibody titer approximately doubled during the 21-day period for the total group as well as for those with virus-positive and virus-negative episodes. There were no significant differences in mean initial antibody titer, change in antibody titer, or antibody titer at day 21 be-

Table 1. Isolation of herpes simplex virus (HSV) type 1 from lesions of patients with recurrent HSV infections.

Day (no. of specimens tested)	No. (%) of specimens	
	With HSV	Without HSV
0 (57)	31 (54)	26 (46)
1 (57)	23 (40)	34 (60)
2 (56)	10 (18)	46 (82)
3 (44)	2 (5)	42 (95)
4 (45)	1 (2)	44 (98)

Table 2. Titers of herpes simplex virus, expressed as $\log_{10}$ pfu/ml, in individual episodes of infection.

Day				
0	1	2	3	4
2.02	...	...	...	...
2.65	1.7	...	...	...
2.66	3.11	2.77	...	...
3.41	6.19	4.04	...	...
3.70	3.99	...	...	...
3.90	...	...	...	...
4.13	3.50	...	...	...
4.48	3.83	2.36	...	...
4.53	5.53	3.33	1.6	4.11
5.00	...	...	...	...
5.42	4.00	...	...	...
5.48	6.78	4.06	5.95	...
5.54	3.47	...	...	...
5.60	...	...	...	...
5.67	...	...	...	...
5.72	...	...	...	...
5.73	...	...	...	...
5.85	...	...	...	...
5.86	...	...	...	...
6.18	3.37	...	...	...
6.26	5.15	...	...	...
6.47	4.08	...	...	...
6.50	...	...	...	...
6.60	5.63	...	...	...
6.69	5.04	3.10	...	...
6.73	...	...	...	...
7.30	4.6	...	...	...
7.30	7.34	...	...	...
7.30	6.20	...	...	...
7.60	...	...	...	...
7.60	3.22	2.65	...	...
...	7.43	5.7	...	...
...	3.04	2.7	...	...
...	6.1	...	...	...
...	3.5	1.1	...	...

NOTE. Dots indicate that the titer of herpes simplex virus was <10 pfu/ml.

Table 3. Summary of stage and lesion size in virus-positive and virus-negative episodes of facial-oral infection with herpes simplex virus (cold sores).

	Virus-positive*			Virus-negative†	
Day	Mean stage‡	Mean titer (log pfu/ml)	Geometric mean size§	Mean stage	Geometric mean size
0	2.83	5.48	34.8	2.68	15.3
1	3.97	4.65	33.9	3.77	11.1
2	4.71	3.18	25.8	4.81	9.15
3	5.0	...	19.2	5.12	6.71
4	5.22	...	13.7	5.94	4.94

*Thirty-five episodes of cold sores in which virus was isolated on one or more occasions.

†Twenty-two episodes of cold sores in which no virus was ever isolated.

‡Lesions were assigned to a stage on a scale of 1-7 (see Materials and Methods).

§Size of lesion was obtained by multiplying the length by the width of the lesion (mean size in mm^2). Since the log lesion sizes were normally distributed, the geometric mean size of lesions was determined.

tween the virus-positive and virus-negative groups (paired t-test, $P > 0.05$).

Statistical analysis. Patients were separated into those with virus-positive episodes and those with virus-negative episodes. All patients who had a lesion from which HSV could be cultured during any day of the episode were included in the virus-positive group, and patients who never had virus isolated were designated as the virus-negative group. The relevant daily means for lesion size and stage for the respective groups, as well as the mean daily titers of virus, are summarized in table 3. The daily virus titers were normally distributed, with the means decreasing systematically with respect to time over the first three days. The means for days 0, 1, and 2 could be fitted to a straight line, but the fit was not statistically significant. Because virus was isolated from only two lesions on day 3 and from only one lesion on day 4, the time course for this interval was indeterminate.

In both the virus-positive and the virus-negative groups, the logs of the daily lesion sizes were normally distributed. The log means of both groups decreased systematically with time (figure 1), in a manner which could be linear or exponential as judged from their goodness-of-fit measures. In either case the fit of the curve was statistically significant at the level of $P > 0.004$ or better. The respective time courses for the two groups differed markedly. The geometric mean sizes of lesions for the virus-positive group exceeded those for the virus-negative group by a factor of two or more over the entire range (table 3). Comparison of the respective geometric mean sizes over their entire clinical courses also showed significant differences (rank sum and sign rank tests, $P = 0.05$; and covariance analysis assuming linear behavior, $P < 0.01$). Moreover, the demonstration of day-by-day differences by multiple sample comparison of the raw distributions showed that the mean log sizes for day 1 were significantly different at the level of $P < 0.01$, and for days 2 and 3, at the level of $0.01 < P < 0.05$. There was no between-group significant difference at day 0 or day 4.

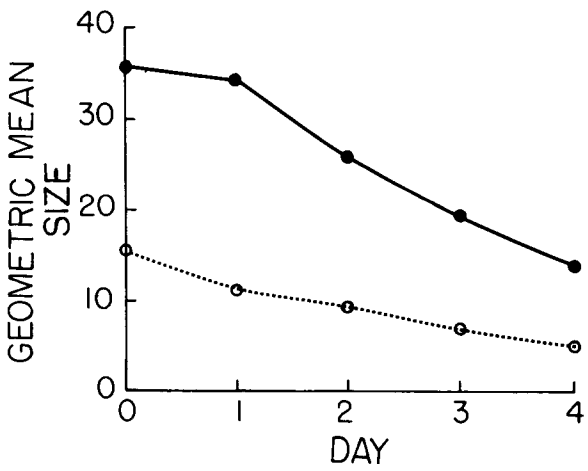

Figure 1. Geometric mean size of facial-oral lesions resulting from infection with herpes simplex virus, plotted as a function of day of episode. The log lesion sizes were found to be normally distributed and therefore the mean log lesion size was calculated. Lesion size was determined by multiplying length by width of the facial lesions in virus positive (●——●) and virus-negative (o - - - - o) episodes.

The daily mean stage scores were normally distributed in both the virus-positive and the virus-negative groups. The mean scores increased asymptotically with time toward the terminal stages (figure 2). Statistically significant differences between the two distributions could not be demonstrated by the same techniques utilized for log size comparisons, but a plus-minus test of slopes employing linear fit yielded a significant difference at the $P < 0.05$ level. The preferred curve fit ($P < 0.001$ as compared with $P < 0.01$ for the linear fit) for the time courses of both mean stages was a hyperbolic function of the form: stage $= (A + Bt)/(1 + Ct)$, where A is the intercept at day 0, and B and C are constants. Curve fitting yielded the following results: for the virus-positive group, stage $= (2.83 + 3.15t)/(1 + 0.486t)$ (equation 1); and for the virus-negative group, stage $= (2.68 + 1.74t)/(1 + 0.161t)$ (equation 2). The significance and interpretation of these equations will be taken up in the Discussion. The three clinical parameters—viral titer, lesion size, and lesion stage—exhibited correlations over the observed clinical course. The lack of statistical significance in the case of the titer correlations may be attributed to the lack of data for days 3 and 4.

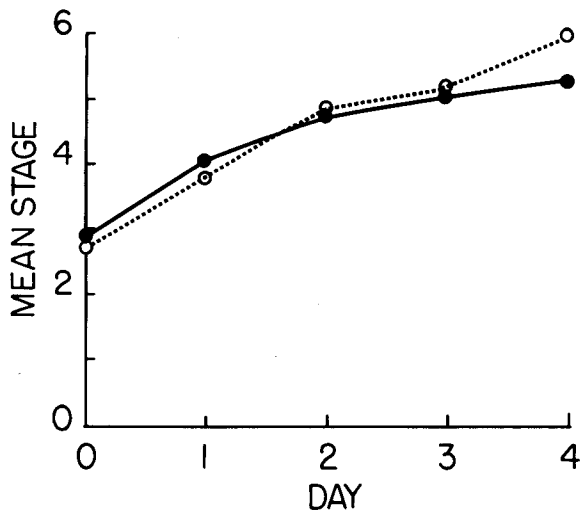

Figure 2. Mean stage of facial-oral lesions resulting from infection with herpes simplex virus on successive days of an episode. The mean stage of lesions in patients with virus-positive (●——●) or virus-negative (o - - - - o) episodes was determined for each day and plotted as a function of day of the episode. The stage of lesions was normally distributed, and the mean stage represents a normal mean.

Discussion

This study confirms and extends the findings of several others [12, 15, 24] in defining the natural course of oral mucocutaneous herpes lesions. At the end of the five-day observation period, 90% of the lesions were at stage 5, 6, or 7. Isolates of HSV were obtained almost exclusively within 48 hr of the start of symptoms, and after 72 hr the chances of isolating HSV were negligible. The titer of HSV was also maximal during the first two days and then rapidly decreased. In several other studies of herpes labialis, HSV has been isolated during the first three days of cold sores but rarely thereafter [13, 14]. These observations are supported by an animal model of cutaneous herpes infections in which the titer reached its maximum 72 hr after inoculation, at the time of the earliest manifestations of discernible disease [14]. These data suggest that any attempt to interfere with HSV replication at the lesion site by means of antiviral substances should be made as early as during the prodromal stage, if possible. The current study indicates that after two days of the clinical illness, antiviral treatment could not be expected to have an impact on the disease.

A significant finding of this study results from

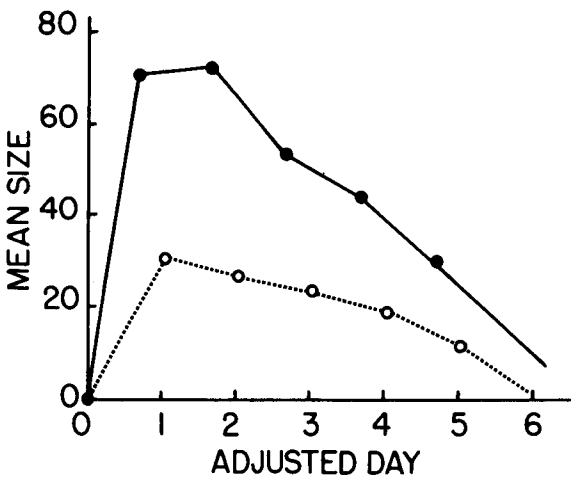

Figure 3. Mean size of facial-oral lesions resulting from infection with herpes simplex virus, plotted as a function of adjusted day of episodes. The starting point (day 0) is adjusted, with the lesion size defined as 0. Because the log of zero does not exist, mean size is plotted rather than mean log size of lesions in virus-positive (●——●) and virus-negative (o - - - - o) episodes for each adjusted day of the episode.

the comparison of lesions that yielded virus on culture with those that did not. The mean size of lesions in the virus-positive group was markedly larger than that in the virus-negative group (figure 1). The lesions appeared to be maximal or close to maximal in size at their onset and exhibited an exponential or linear decay over the period of observation. In the initial stages lesion size exhibited either a typical growth or an ascending exponential type of behavior, passed through a maximum, and then declined in a manner that went asymptotically to zero in a short time (figure 3). The mean size of the virus-positive lesions increased quite rapidly to twice the size of the virus-negative lesions and then decreased at a faster rate than that of the virus-negative lesions. The mean sizes of the two types of lesions peaked at approximately the same time relative to the estimated starting times. The areas under the respective curves, which are measures of the clinical course of lesion size, were markedly different from each other and may be a valuable parameter in evaluating the effect of antiviral agents.

The stage of lesions in virus-positive and virus-negative groups showed different progressions. Equations 1 and 2 (see Results) represent the clinical course of the mean lesion stage. The first derivative of these equations (equation 3 in table 4) defines a rate of progression through the clinical stages, which we shall call stage velocity (V). The average stage velocities over the clinical course of the respective episodes are compared together with the corresponding average stage reached at each observation day (table 4). These data show that the rate of progression of the virus-positive lesions to stage 3 was approximately one-third faster than that of the virus-negative lesions. Thereafter, the virus-negative lesions accelerated, progressing more rapidly through the vesicular-erosion-crust stages to the healing stages than the virus-positive lesions. This progression is reflected in the estimated average stage at each day, for which it is apparent that the virus-negative lesions began to forge ahead toward the healing stages at day 3, whereas the virus-positive lesions were not quite out of the crust stage by day 4. By extrapolating equations 1 and 2 beyond the observed range, it can be estimated that virus-negative lesions reached stage 7 at 7.1 days, whereas virus-positive lesions were still at stage 6 at 13 days.

Table 4. Comparison of stage velocity (V) for virus-positive and virus-negative episodes of facial-oral infection with herpes simplex virus (cold sores).

	Virus-positive		Virus-negative	
Day	Stage velocity*	Stage†	Stage velocity	Stage
0	1.778	3–	1.307	2.5+
1	0.806	4	0.969	4–
2	0.458	4.5+	0.747	5–
3	0.295	5	0.593	5+
4	0.205	5+	0.482	6

*$V = d(\text{stage})/dt = (B - AC)/(1 + Ct)^2$, equation 3. A, B, and C are defined in Results.

†Lesions were assigned to a stage on a scale of 1 – 7 (see Materials and Methods).

The clinical course of herpes labialis in those patients who had lesions from which virus could be isolated is characterized by larger lesion size during each day of the episode and a delay in reaching the healing stages of the lesions. An important corollary to these observations with implications for antiviral therapy is that since the presence of virus correlates with a more severe clinical course, an effective antiviral agent might be expected to provide two important clinical benefits in the treatment of recurrent facial-oral herpes, namely, smaller lesion size and a shorter time to healing. Alternative explanations for an apparent difference in lesion size and healing rate between the virus-positive and virus-negative groups must be considered. A systematic sampling error is unlikely because all viral samples were obtained and titrated in an identical fashion. The virus-negative patients did have a higher initial mean titer of antibody to HSV than did the virus-positive group, but this difference was not statistically significant. The higher mean antibody titer may have resulted in more rapid inactivation of virus, or the continual introduction of plasma containing neutralizing antibody into the lesions with scrapings on successive days may have masked the presence of virus. An explanation on the basis of higher antibody titers in the sera of patients with virus-negative episodes would be more reasonable if there were a striking difference in initial and day-21 titers of neutralizing antibodies, but such a difference was

not observed. The possibility that a virus other than HSV was causing the cold sore episode is also extremely unlikely, since no virus other than HSV has ever been found in cold sores, and since the clinical course of virus-negative lesions was exactly similar to that of the recurrent facial lesions from which HSV was isolated.

Virus was detectable in saliva specimens during the acute episode in 8% of the episodes and was high in titer from cultures taken early in the episode. In a concurrent, similar study, virus was present in 7% of salivary specimens [15]. Douglas and Couch [12] reported that virus could be isolated from saliva during an episode of recurrent mucocutaneous HSV infection in 24.1% of 29 patients. This value probably reflects a sampling error, since the current study contains more patients and episodes of recurrent facial-oral HSV infection than did that of Douglas and Couch [12]. However, Douglas and Couch did sample a larger volume of saliva in their attempts to isolate virus, a fact that may account for the discrepancy. The current data, for which a smaller volume of saliva was used in isolation attempts, indicate that the presence of virus in the saliva is infrequent.

All viral isolates obtained in this study were HSV-1, and each patient tested had antibody to HSV-1 at the time of onset of the cold sore. This result confirms the findings of other investigators and attests to the inability of neutralizing antibody to prevent recurrent herpes infection [1, 12, 16, 25, 26]. The magnitude of the antibody titer or an increase in this titer, as observed in four (22%) of 18 patients, is not helpful in documenting a recurrent episode of herpes labialis. The mean initial antibody titer in patients who had virus-negative episodes of recurrent cold sores was approximately double that in patients who had virus-positive episodes. This finding suggests that a higher antibody level at the onset of an episode of cold sores may indicate that a virus-negative episode, smaller lesion size, and a more rapid rate of healing is more likely to occur. The difference between antibody levels in the two groups was not statistically significant, however, and there was no appreciable difference in the rise in antibody level during the episode of virus-negative or virus-positive cold sores. The mean antibody titer doubled between the initial serum and the serum obtained at 21 days, but this effect was mainly due to a few patients who had a marked rise in neutralizing antibody level. In animals and humans, antibody coexists with virus, and infectious virus-antibody complexes that can fix complement have been demonstrated in herpetic lesions [13]. These complexes may mediate tissue injury, but their precise role in the pathogenesis of this illness remains to be elucidated.

The goal of this study has been to chronicle the natural clinical, virologic, and serologic course of recurrent facial-oral infections with HSV in order to identify parameters that sensitively reflect progression and regression of this rapidly evolving illness. This type of study is essential in determining the efficacy of antiviral therapy, a topic that is currently under study in this laboratory. Since the clinical picture of the virus-positive group is the more severe, we may associate severity in HSV cold sore episodes with (*1*) detectable HSV, (*2*) more rapid onset and progression to the vesicular stage, (*3*) slower progression to the crusting and healing stages, (*4*) longer duration, and (*5*) larger lesions, with larger areas under the time course curve. Because severity is associated with both larger lesions and longer average duration of lesions, the most appropriate (as well as convenient) measure of severity might be the area under the size-vs.-time curve because it reflects both parameters. In this study the virus-positive areas exceeded the virus-negative areas by a factor of approximately 2.5. It might be anticipated that one important benefit of effective antiviral therapy would be a reduction in lesion size and a more rapid healing time.

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