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Clinical and Virologic Course of Herpes Simplex Genitalis

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The clinical and virologic course of herpes simplex genitalis in women and men was examined in order to identify measurements useful in antiviral trials. Factors influencing the clinical course included initial disease versus recurrent disease, wet-skin versus dry-skin lesions, female versus male sex. Women with initial genital herpes had higher mean peak lesion virus titers than those with recurrent disease ($10^{4.5}$ pfu compared with $10^{2.5}$ pfu) and excreted virus longer (13 to 15 days compared with 6 to 8 days). Men with recurrent lesions had higher mean peak virus titers than women ($10^{4.0}$ pfu compared with $10^{2.5}$ pfu), but the duration of virus excretion was shorter (three to four days compared with six to eight days). There was pronounced variation in the clinical and virologic course of recurrent lesions among different patients and even within the same patient. These observations indicate several difficulties that must be considered in conducting careful antiviral trials in patients with herpes simplex genitalis.

GENITAL HERPES SIMPLEX VIRUS (HSV) infection is a commonly occurring venereal disease in the United States and in recent years has emerged as a public health problem of major proportions.[1] In the initial form of the disease, genital lesions can be painful and disabling; and complications such as urinary retention[2] and aseptic meningitis[3] may require admission to hospital. Recurrent disease is milder but may be associated with significant physical and psychologic morbidity. In pregnant women, active genital infection at the time of delivery can result in infection of the newborn infant during passage through the infected birth canal. In neonatal infection, mortality rates of 75 percent have been reported, with neurologic sequelae in most survivors.[4] Finally, HSV type 2 has been associated with and may have an etiologic role in carcinoma of the cervix.[5]

Because of the frequent occurrence and medical importance of genital HSV infections, many forms of therapy have been tried, including immunization with Bacillus Calmette-Guérin (BCG),[6,7] topical phototherapy with neutral red,[8-10] topical therapy with iododeoxyuridine alone,[11,12] iododeoxyuridine in dimethyl sulfoxide (DMSO),[13] or adenine arabinoside,[14,15] and systemic therapy with levamisole,[16] co-trimoxazole[17] or chlorpromazine.[18] With the possible exception of iododeoxyuridine in

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ABBREVIATIONS USED IN TEXT
DMSO = dimethyl sulfoxide
HSV = herpes simplex virus
pfu = plaque-forming units

DMSO,[13] none of these forms of therapy have proved effective in controlled clinical trials.

Several problems in the attempt to show antiviral efficacy are recognized, including the variable nature of the disease and the necessity of relying on subjective assessments to determine the effect of therapy. Our own studies[19] and those of others[9,12,14,15] indicate that lesion virology may provide a more accurate and objective assessment of disease severity. The purpose of this study was to define the clinical characteristics of herpes simplex genitalis lesions and to determine lesion virus titers in order to (1) identify those features of the disease that contribute to its variable course and (2) define more obective measurements of lesion severity for use in antiviral trials.

Patients and Methods

In May 1975, a clinic for the study of genital herpes was established in the clinical research center of the University of Utah Medical Center. In two years, 165 patients were referred for evaluation of which 130 were proved by viral isolation to have genital herpes, and 113 were included in the study. This group was then subdivided into women with initial disease (39 patients), women with recurrent disease (52 patients) and men with recurrent disease (22 patients). In women, initial disease was distinguished from recurrent disease by the absence of a history of previous disease and the presence of more severe and extensive lesions. Initial genital herpes in men was not observed. Referral was equally divided between private physician and public clinic sources.

Overall Study Design

At the initial interview, a complete history, physical examination and an informed consent were obtained. Women in whom the disease was occurring for the first time were evaluated by day 3 to 4 after the appearance of lesions. In all patients with a history of recurrent genital lesions, studies first were done to confirm HSV infection by virus isolation. Patients with proved herpetic disease were asked to return during the prodromal period or on the first day that lesions of their next episode appeared. All patients were requested to return for as many visits as possible during the observed episode. Of the total group of 113 patients with proved herpes genitalis, 72 patients appeared for one visit only, 17 patients had two visits, and 24 patients presented for three or more visits. Information gathered for each episode included a description of the prodrome, precipitating factors, location of lesions, and whether the episode was initial or recurrent. Information gathered for each daily visit included the number of lesions, stage of the lesions and the intensity of symptoms.

Lesion Evaluation

During all visits, lesions were classified into one of the following stages: no lesion (no physical evidence of a lesion but prodromal symptoms), vesicle, ulcer, crust or healed. Day 0 of the episode was defined as the day of physical onset of lesions. New lesions appearing at noncontiguous sites more than 24 hours after the eruption of the original lesions were followed as separate episodes. Pain was scored as objectively as possible using the following values: 1 = no pain, 2 = mild pain, 3 = moderate pain, 4 = severe pain.

Specimen Collection

A blood specimen was collected from every patient for syphilis serology (VDRL). A swab specimen was obtained from the cervix in women or urethra in men and streaked immediately onto Thayer-Martin medium for isolation of Neisseria gonorrhoeae. Specimens were processed by the routine diagnostic laboratories of the University of Utah Medical Center. In women with vaginitis, wet mounts and Gram stains of vaginal secretions were examined for the presence of Hemophilus vaginalis *clue* cells, Trichomonas vaginalis or Candida albicans. Papanicolaou smears were obtained for all women.

Dacron-tipped applicators were used to sample lesions for virus isolation and quantitation. When no lesion was present, the area indicated as tender by patients was abraded with a medium-moistened swab. Vesicles were unroofed and crusts removed before swabbing the lesion base. As much of the lesion area as possible was sampled. In women, after the lesions on the external genitalia were sampled, the labia were carefully and widely spread with fingers and a single sterile swab was passed through the introitus to sample both the vagina and cervix. A speculum was not used because pain was experienced by patients on introducing it into the vagina, and because passage of the speculum over introital lesions might result

in contamination of the vaginal walls and cervix. The swabs were immediately immersed in 1 ml of Eagle's minimal essential medium containing 50 μg per ml of gentamicin (Schering Corporation, Kenilworth, New Jersey), 10 μg per ml of amphotericin (Flow Laboratories, Rockville, Maryland) and 10 percent fetal bovine serum (Flow Laboratories). The specimens were frozen at −70°C within 30 minutes of collection.

Viral Assay

Virus was quantitated by the plaque titration method on fetal lamb kidney cells using techniques described previously.[19,20] Titers were expressed as total plaque-forming units (pfu) per specimen. First passage isolates of specimens were typed by a modification of the differential cytopathic effect technique described by Yang and co-workers[21] using chick embryo cells and fetal lamb kidney cells. Strains known to be type 1 or type 2 as determined by kinetic neutralization or immunofluorescence obtained from Dr. A. Nahmias (Emory University, Atlanta, Georgia) were included as controls.

Data Analysis

Data were programmed, stored and analyzed in the computers of the Department of Biophysics and Computing of the University of Utah College of Medicine. Only one *best* episode (most numbers of visits) was entered for each patient.

Results

Patient Population and Laboratory Data

At onset of disease, the mean age for women was 22 years and for men, 25 years (range 14 to 56 years). More than 95 percent of patients dated the onset of illness between 1972 and 1976. The mean age at first intercourse was 18 years in women and 15 years in men. The mean interval between first intercourse and the onset of genital herpes was four years in women and ten years in men. Approximately half of the patients had never been married, one quarter were married, and the remainder had been divorced one or more times. Of the women, 66 percent were using contraceptives, 10 percent had been sterilized and 24 percent used no contraceptive methods. Sixty-five percent of women and 80 percent of men had attended two or more years of college; some had pursued postgraduate studies. Marijuana was used more than once per week by 7 percent of patients. Only 4 percent of the patients reported periodic use of other common street drugs. However, most patients did admit to drug experimentation at least once in the past. None of the patients admitted to heavy alcohol consumption. None of the patients reported any significant medical or surgical illnesses, and none were taking any medication on a regular basis.

Findings on all physicial examinations made at time of first registering into the clinic were normal except for those in one man who was referred for evaluation of severe hypertension. Symptomatic vaginitis was noted in fewer than 10 percent of women; 40 percent of these were found to have either *clue* cells or trichomonads. Symptomatic moniliasis was unusual; only two women required treatment during the first two years of clinic operation. N. gonorrhoeae was not isolated from any of these patients. Four women had a positive VDRL; three of these were biologic false positive and one patient was subsequently treated for syphilis. Two patients were treated for condylomata accuminata and one for molluscum contagiosum. Cervical cytology showed some degree of inflammatory atypia in 19 percent of women and cells consistent with herpes infection in three women. No cervical lesions were observable in these latter three women. Two men described dysuria before and during a recurrence; results of routine and gonococcal cultures were negative.

Historical Data

A prodrome was noted by 46 percent of patients with recurrent disease. Characteristics of the prodrome were similar in women and men. Prodromal symptoms lasted more than 24 hours in 75 percent. Two thirds of those with prodromes had localized paresthesias consisting of itching, burning or a hypersensitivity of the skin surface at the site of the subsequent lesion. Prodromal neuralgia occurred in a quarter of patients, was always ipsilateral, and subsided shortly after the appearance of lesions. The buttock and groin were the most common sites of neuralgia but the thigh, calf, foot and scrotum were also involved. Two women noted unusual prodromes; one described a peculiar metallic taste in her mouth for several days before most recurrences and the other complained of pronounced irritability, lethargy and fatigue for 24 to 48 hours before the eruption of the lesions. Neither patient gave a history of oral herpes. Typical herpetic paresthesias and neuralgias were observed in two other women without any demonstrable lesions. These *false* prodromes usually occurred cyclically, often

in relation to the menses, and lasted 24 to 48 hours. Four women reported erythema multiformelike rashes that occurred periodically with recurrences.

Most women with recurrent disease (63 percent) did not identify a precipitating factor. Menses were related to the onset of an episode by 24 percent. A similar percentage of men (59 percent) did not identify a precipitating factor, but 32 percent related their episodes to intercourse.

There was little difference between men and women in the frequency or duration of recurrent lesions. Of the patients, 53 percent reported one or more recurrences per month; 33 percent reported recurrences every two to four months and 14 reported recurrences less frequently than every four months. Historically, the mean duration of recurrent episodes was seven days.

Clinical Observations

Dry-Skin Versus Wet-Skin Lesions. On dry skin surfaces, such as the labia majora, mons pubis, shaft of the penis, and thigh, individual lesions of both initial and recurrent disease in men and women were similar in appearance, duration and

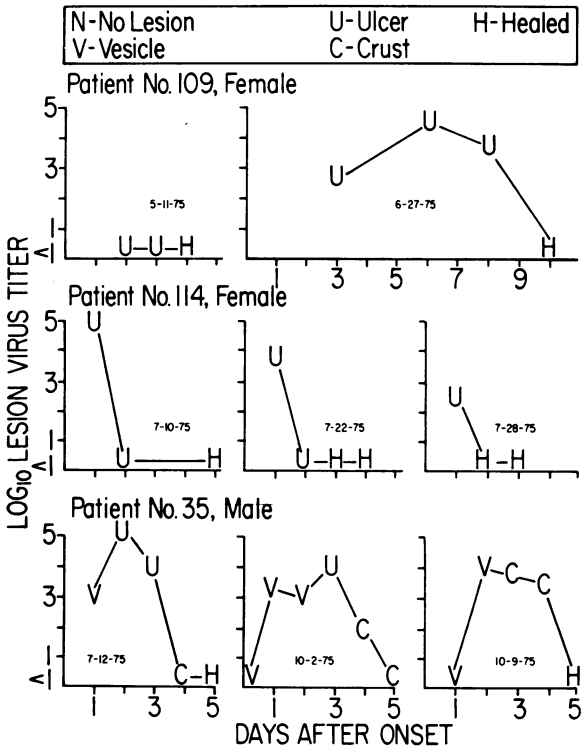

Figure 1.—Lesion stages and lesion virus titers in three patients with recurrent herpes simplex genitalis. The dates refer to the day of onset of each lesion.

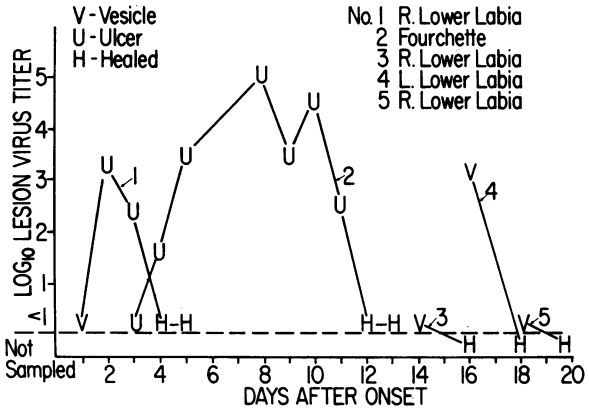

Figure 2.—Stages and virus titers of five separate lesions in a woman with recurrent disease over a 20-day period.

progression through the well-defined vesicular, ulcer, crust and healed stages that we observed in patients with recurrent herpes simplex labialis (Figure 1, Patient 35).[19] On dry skin, vesicles often persisted until the patient was seen. The ulcer stage was short, with a dry crust rapidly forming and reepithelialization progressing underneath the crust.

In chronically moist areas, such as the labia minora, introitus or fourchette in women and under the foreskin in uncircumcised men, lesion stages were not distinct because of maceration. The vesicular stage was rarely seen because vesicles quickly evolved into ulcers (Figure 1, Patients 109 and 114; Figure 2). Definite crusts were rarely seen. Instead, there was a gradual resolution of the inflammatory debris, with persistence of the ulcer and reepithelialization from the periphery of the lesion.

Initial Disease in Women. In women with initial disease, prodromal symptoms were unusual but, when present, consisted of paresthesias limited to the area where the disease would first erupt. Beginning at a localized focus, the vesiculo-ulcerative eruption spread in a wavelike fashion from the inital site across the external genitalia, thighs, buttocks, and frequently into the bladder, rectum and upper genital tract. Some lesions began healing while new ones erupted. In the moist skin areas, large, exquisitely tender ulcers formed with an erythematous, edematous base, giving the appearance of a second-degree burn. Systemic symptoms, described as *flu-like* with fever, headache, myalgia and abdominal pain, were present in 73 percent of patients. Four patients required admission to hospital: three for urinary retention and one for aseptic meningitis. Pain was severe.

The mean pain score (Figure 3) did not begin to decline until after day 9, and symptoms usually persisted for two weeks.

Recurrent Disease in Women. A third of women had only a single lesion; three quarters had no more than three lesions. The mean pain score was lower than in initial disease and declined to minimal levels by day 6 (Figure 4). Patients with multiple lesions had three patterns of lesion development: (1) A circumscribed, raised erythematous lesion formed with one or more vesicles or ulcers on its surface. The number of vesicles or ulcers was small—usually two or three, rarely as many as ten. Within the small anatomic area of recurrence, new vesicles would erupt while the initial ones were resolving. (2) A *cropping* pattern occurred in which the initial lesions resolved with complete healing of the skin. This was followed within hours to a few days by a second *crop* of lesions at the *same anatomic site* (Figure 1, Patient 114). (3) Less commonly, crops of lesions erupted at anatomically distinct sites around the external genitalia, the second crop beginning as the first was healing (Figure 2). For example, the anatomic areas could be mirror lesions of those on opposing labia, or they could be located at different sites on the same labia.

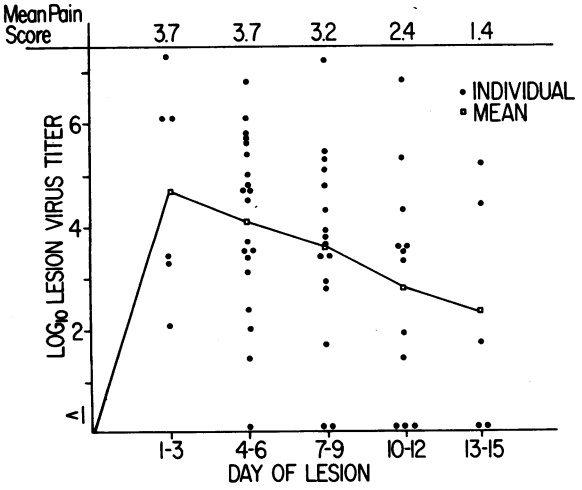

Figure 3.—Mean pain score and individual and mean lesion virus titers in 39 women with initial herpes simplex genitalis.

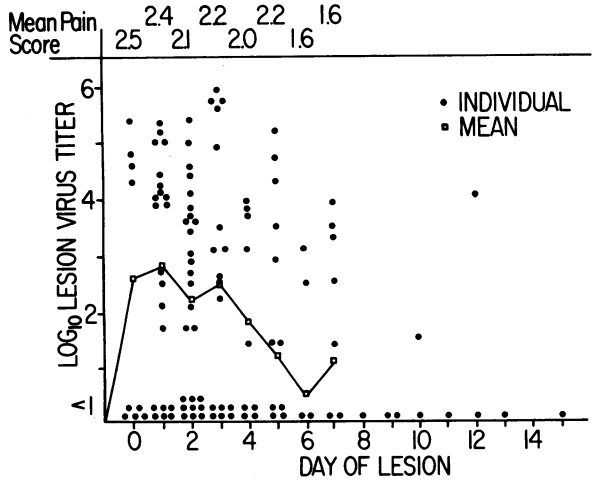

Figure 4.—Mean pain score and individual and mean lesion virus titers in 52 women with recurrent herpes simplex genitalis.

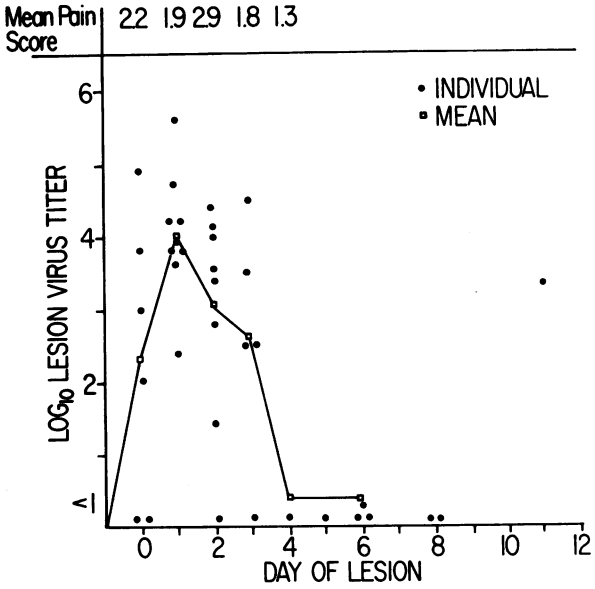

Figure 5.—Mean pain score and individual and mean lesion virus titers in 22 men with recurrent herpes simplex genitalis.

Some women with recurrent disease had ulcerations that were distinctly different from those that have been described previously.[22] Most common were linear ulcerations in the fourchette that superficially resembled inflamed excoriations. These occurred in 21 percent of women with recurrent disease and probably resulted from a combination of the tissue stresses peculiar to the fourchette and the continuous bathing of the area with purulent vaginal secretions. Less common was the herpetic chancre,[23] which was observed in two patients. These chancres were large, minimally tender ulcerations, up to 1 cm in diameter with sharply demarcated edges and a clean granular base. Results of darkfield examination and serologic testing for syphilis were negative. Herpes simplex virus was recovered from the herpetic chancre lesions in high titer.

Recurrent Disease in Men. Recurrent disease

in circumcised men followed a course similar to that described for recurrent herpes simplex labialis.[19] Fifty percent had no more than three lesions; 70 percent had no more than four lesions. The mean pain score through day 2 was similar to that in women with recurrent disease but declined to negligible levels by day 4 (Figure 5). Maceration of tissue was unusual unless the patient was not circumcised and the lesion was located under the foreskin.

Virologic Data

Individual and mean virus titers in 39 women with initial disease are shown in Figure 3. Only one patient was sampled on day 1 and few patients were seen before day 3. During the first three days, the mean virus titer was $10^{4.8}$ plaque-forming units (pfu) and virus was recovered from all specimens. Thereafter, titers declined in a linear fashion. A progressive increase in the number of virus-negative samples was not observed, since patients with healing lesions did not, as a rule, return for follow-up examinations. The patients who did return after day 9 were more likely to have symptomatic, virus-positive lesions. It is probable, therefore, that the mean virus titer for the entire group of 39 patients declined more rapidly than is indicated in Figure 3.

The titers of virus in women with recurrent herpes genitalis are shown in Figure 4. In contrast to the titers in initial disease, mean peak virus titers were in the $10^{2.5}$ to $10^{2.8}$ pfu range during the first three days of the illness, primarily because there were more patients with virus-negative lesions. Mean titers rapidly declined after day 3, although a number of patients continued to have virus-positive lesions. Only one of the 52 patients had virus isolated after day 7, the positive specimens indicated in Figure 4 on day 10 and day 12.

Virus titers in men with recurrent disease are illustrated in Figure 5. Virus titers increased from a mean of $10^{2.3}$ pfu on day 0 to $10^{4.0}$ pfu on day 1 but declined rapidly thereafter. Only one of the 22 patients had virus recovered from a lesion after day 3.

Pronounced variability in clinical staging of the lesion, virus titers and duration of virus excretion was noted among different patients and even between separate episodes in the same patient. Figure 2 illustrates the course of five separate and distinct recurrent lesions that occurred on the external genitalia of a woman over a 20-day period. The clinical and virologic evolution of each lesion was quite different. A vesicle was the initial stage in four of the lesions; virus was isolated from vesicle fluid in only one of these. Duration of the individual lesions varied from two to ten days and peak virus titers ranged from undetectable to $10^{5.0}$ pfu. In Figure 1 the clinical and virologic courses of eight separate episodes of recurrent herpes simplex genitalis in three different patients are illustrated. In one woman, patient 109, no virus was isolated in the first observed recurrent episode, while appreciable titers were recovered for six days during another episode six weeks later. Patient 114, a woman, had three separate and distinct episodes separated by only a few days. Although the patterns of virus excretion were similar for the episodes, the maximum virus titers were quite different. In patient 35, a man, the duration of virus excretion and peak virus titers from three separate episodes were quite similar.

One hundred isolates were typed: 81 percent were type 2 and the remainder type 1. Because of the small number of type 1 isolates, no attempt was made to distinguish differences in the clinical or virologic courses of illness due to the two serotypes. Both cervical/vaginal and external genital specimens were obtained from 93 recurrences in 52 women. Eighteen (19 percent) of the cervical/vaginal samples were positive in patients where the concomitant vulvar specimen also showed virus. Of the 18 positive cervical/vaginal isolates, 17 were type 2 and one was type 1.

Comment

Previous studies of herpes simplex genitalis have indicated that patients are largely from a lower socioeconomic group,[24] and have a high incidence of other types of venereal disease, particularly gonorrhea.[25-28] Most patients in this study were well educated and appeared to be from middle and upper socioeconomic groups. No cases of gonorrhea and only one case of syphilis were observed. Although our subjects with genital herpes may reflect the predominantly middle-class background of Salt Lake City, the patients with gonorrhea seen at our medical center are largely from a lower socioeconomic group. Our observations are consistent with those of Gardner and Kaufman,[29] which indicate that genital herpes is more of a problem than gonorrhea in patients of a private gynecologic practice. It may be that private patients with gonorrhea are not referred

to a medical center since the disease can be diagnosed and treated easily in an office setting, while patients with genital herpes are referred because methods for accurate diagnosis are not widely available and there is no effective therapy.

Moist-skin lesions (on labia minora, introitus and fourchette in women and under the foreskin in men) healed slowly from the periphery of the lesion and appeared to last longer than dry-skin lesions. The dry-skin lesions (on labia majora, mons pubis, shaft of the penis, skin of thigh, and the like), on the other hand, evolved rapidly through well-defined vesicle, ulcer and crust stages with healing progressing underneath the crust. The healed stage in moist lesions was more difficult to define because there was gradual disappearance of the lesion, while in dry lesions healing was usually heralded by loss of crust, an easily discernible event. Recurrent lesions in women appeared to be symptomatic longer than those in men (appreciable pain for six to eight days compared with three to four days) and to excrete virus longer (six to eight days compared with three to four days), perhaps because moist-skin lesions were more prevalent in women.

Women with initial genital herpes had lesion virus titers that were much higher than titers in those with recurrent disease during the early phase of illness (mean titers approximately $10^{4.5}$ pfu compared with $10^{2.5}$ pfu), had fewer virus-negative specimens (Figures 3 and 4) and excreted virus longer (13 to 15 days compared with 6 to 8 days). Quantitative lesion virology in women with genital herpes has not been previously reported, but other studies have noted duration of virus excretion similar to our observation.[9,13,15,34] Men with recurrent lesions had higher peak virus titers than women (mean $10^{4.0}$ pfu compared with $10^{2.5}$ pfu), but the duration of viral excretion was shorter (three to four days compared with six to eight days). Our virus titer results in men are similar to those observed by Goodman and co-workers.[14]

One of the most significant observations in our study is the notable variation in the clinical and virologic course of recurrences between different patients and even within the same patient. Figures 4 and 5 show the considerable scatter in virus titers from different patients on the same day of an episode. Figure 2 illustrates five separate crops of lesions that occurred at different anatomical sites in the same patient over a 20-day period. If this one patient had not been examined carefully and followed frequently, the recurrences might have been considered a single prolonged lesion with peak virus excretion on day 8 and lasting 20 days, rather than five separate lesions. Figure 1 illustrates the different clinical and virologic pattern not only between patients but also within the same patient. The lesions in these three patients recurred at the same anatomic site with a variable disease-free interval in between. From these data, the question of what reasonably constitutes a separate and distinct recurrent episode can be raised. More patients need to be examined and evaluated carefully to provide a definitive answer to this question.

There are many implications for antiviral clinical trials from the results in this study: (1) In many instances, and particularly with the dry-skin lesions, it is apparent that the natural healing process may begin within the first day or two after the onset of the episode. Topical antiviral therapy, therefore, must be applied as soon as possible after onset of a recurrence, preferably within 24 hours, in order to allow maximal opportunity for the compound to work. The fact that 46 percent of the patients have prodromal symptoms would be an aid in this regard. (2) The pronounced variability in the clinical and virologic course of recurrences between different patients dictates that a large number of patients be studied in order to identify any true differences due to drugs. (3) Because the character of recurrences in men differs appreciably from that in women, drug-placebo randomization and data analysis should be done separately by sex. (4) Because the clinical and virologic course of dry-skin lesions differs from that of wet-skin lesions, it may be that the results of treatment of these different types of lesions will have to be analyzed separately. (5) Since there is variation in severity of recurrences even within the same patient, previous episodes in the same patient cannot be used as a control. (6) The phenomenon of successive, separate crops of lesions at the same site or different anatomic sites in the same patient creates problems in the interpretation of data related to the reduction of severity of the episodes. For example, if only the site of the initially apparent lesion was treated (as was done with several of the trials of neutral red phototherapy), the appearance of new lesions at new untreated sites could be erroneously interpreted as drug failure. In addition, the appearance of new lesions at the same site that had received a course of topical therapy several days previously

could be interpreted as drug failure. The newly appearing lesions could be the result of additional virus from sacral ganglia rather than inability of the drug to inhibit replication of virus in the skin. (7) If frequency of recurrences is evaluated as a measure of antiviral efficacy, the definition of what constitutes a separate recurrence will need to be clarified, as mentioned above. (8) The definition of healing in moist-skin lesions may be difficult, since the ulcer slowly resolves by reepithelialization from the periphery. Lesion healing, since it may occur from one to two weeks after onset, is usually determined privately by the patient rather than during return clinic visits for evaluation by independent observers. In women, self-visualization of genital lesions is difficult, and the moist-skin lesions are more prevalent in women. The result may be unavoidable inaccuracies in determination of the endpoint of lesion healing. This is an unfortunate likelihood, since time to complete healing was the most sensitive clinical measurement evaluated in distinguishng between lesions of differing severity in patients with recurrent herpes labialis.[19] (9) As indicated by our data and the data of others,[22,26] the measurement of lesion healing may not be a valid assessment of *antiviral efficacy* in moist-skin lesions, since tissue maceration is common in these areas. (10) Finally, the data suggest that objective and quantitative measures such as lesion virus titers and duration of lesion virus excretion will be valuable in the attempt to assess antiviral efficacy.

The results of this study indicate that a carefully executed, adequately controlled clinical trial in patients with recurrent herpes simplex genitalis will not be an easy task. We were not so successful as we had hoped in getting patients to return for frequent and regular clinic visits, a problem noted in other studies of herpes simplex genitalis.[9,12,15] Such frequency and regular visits will be necessary in order to define precisely the duration of the various lesion stages, the time to complete healing, serial virus titers, "area under the virus titer curve" (titer hour-area), duration of virus excretion and other measurements that we were able to quantitate in patients with recurrent herpes simplex labialis.[19] We are attempting to conduct such a study at present. With the recent availablity of several promising antiviral compounds for the treatment of herpes simplex virus infections,[30,31] it is realistic to hope for successful therapy in the not-too-distant future. Detailed information concerning the natural history of herpes genitalis is a necessary step in the proper design of clinical trials.

REFERENCES

1. Nahmias AJ, Josey WE, Naib ZM, et al: Genital herpetic infection—The old and the new, chap 135, *In* Catterall RD, Nicol CS (Eds): Sexually Transmitted Diseases. London, Academic Press, 1976
2. Caplan LR, Kleeman FJ, Berg S: Urinary retention probably secondary to herpes genitalis. N Engl J Med 297:920-927, Oct 27, 1977
3. Craig CP, Nahmias AJ: Different patterns of neurologic involvement with herpes simplex virus types 1 and 2: Isolation of herpes simplex virus type 2 from the buffy coat of two adults with meningitis. J Infect Dis 127:365-372, Apr 1973
4. Nahmias AJ, Visintine AM: Herpes simplex, chap 5, *In* Remington JS, Klein JO (Eds): Infectious Diseases of the Fetus and Newborn Infant. Philadelphia, WB Saunders Co, 1976
5. Roizman B, Frenkel N: Does genital herpes cause cancer?—A midway assessment, chap 151, *In* Catterall RD, Nicol CS (Eds): Sexually Transmitted Diseases. London, Academic Press, 1976
6. Anderson FD, Ushijima RN, Larson CL: The treatment of *Herpesvirus hominis* type 2 genital infections with attenuated *Mycobacterium bovis* (BCG). Obstet Gynecol 41:639-640, Apr 1973
7. Bierman SM: BCG immunoprophylaxis of recurrent herpes progenitalis. Arch Dermatol 112:1410-1415, Oct 1976
8. Felber TD, Smith EB, Knox JM, et al: Photodynamic inactivation of herpes simplex: Report of a clinical trial. JAMA 223:289-292, Jan 15, 1973
9. Roome APCH, Tinkler AE, Hilton AL, et al: Neutral red with photoinactivation in the treatment of herpes genitalis. Br J Vener Dis 51:130-133, Apr 1975
10. Myers MG, Oxman MN, Clark JE, et al: Failure of neutral-red photodynamic inactivation in recurrent herpes simplex virus infections. N Engl J Med 293:945-949, Nov 6, 1975
11. Schofield CBS: The treatment of herpes progenitalis with 5 iodo-2′-deoxyuridine. Br J Dermatol 76:465-470, Nov 1964
12. Taylor PK, Doherty NR: Comparison of the treatment of herpes genitalis in men with proflavine photoinactivation, idoxuridine ointment, and normal saline. Br J Vener Dis 51:125-129, Apr 1975
13. Parker JD: A double-blind trial of idoxuridine in recurrent genital herpes. J Antimicrob Chemother 3 (suppl A):131-137, Mar 1977
14. Goodman EL, Luby JP, Johnson MT: Prospective double-blind evaluation of topical adenine arabinoside in male herpes progenitalis. Antimicrob Agents Chemother 8:693-697, Dec 1975
15. Adams HG, Benson EA, Alexander ER, et al: Genital herpetic infection in men and women: Clinical course and effect of topical application of adenine arabinoside. J Infect Dis 133 (suppl):A151-A159, Jun 1976
16. Kint A, Coucke C, Verlinden L: The treatment of recurrent herpes infections with levamisole. Arch Belg Dermatol 30:167-171, Jul-Sep 1974
17. Laird SM, Roy RB: Treatment of primary attacks of genital herpes with co-trimoxazole. Br J Clin Pract 29:37-42, Feb 1975
18. Chang T-W: Suppression of herpetic recurrence by chlorpromazine. N Engl J Med 293:153-154, Jul 17, 1975
19. Spruance SL, Overall JC Jr, Kern ER, et al: The natural history of recurrent herpes simplex labialis: Implications for antiviral therapy. N Engl J Med 297:68-75, Jul 14, 1977
20. Kern ER, Overall JC Jr, Glasgow LA: *Herpesvirus hominis* infection in newborn mice—I. An experimental model and therapy with iododeoxyuridine. J Infect Dis 128:290-299, Sep 1973
21. Yang JPS, Chiang WT, Gale PL, et al: A chick-embryo cell microtest for typing of *Herpesvirus hominis*. Proc Soc Exp Biol Med 148:324-328, Feb 1975
22. Kaufman RH, Gardner HL, Brown D, et al: Herpes genitalis treated by photodynamic inactivation of virus. Am J Obstet Gynecol 117:1144-1146, Dec 15, 1973
23. Chang T-W, Fiumara NJ, Weinstein L: Genital herpes: Some clinical and laboratory observations. JAMA 229:544-545, Jul 29, 1974
24. Josey WE, Nahmias AJ, Naib ZM: The epidemiology of type 2 (genital) herpes simplex virus infection. Obstet Gynecol Surv 27:295-302, Apr 1972
25. Beilby JOW, Cameron CH, Catterall RD, et al: *Herpesvirus hominis* infection of the cervix associated with gonorrhoea. Lancet 1:1065-1066, May 18, 1968
26. Amstey MS, Balduzzi PC: Genital herpesvirus infection: Diagnosis and significance. Am J Obstet Gynecol 108:188-193, Sep 15, 1970
27. Nahmias AJ, Von Reyn CF, Josey WE, et al: Genital herpes simplex virus infection and gonorrhoea: Association and analogies. Br J Vener Dis 49:306-309, Jun 1973
28. Jeansson S, Molin L: On the occurrence of genital herpes simplex virus infection: Clinical and virologic findings and relation to gonorrhoea. Acta Dermatol Venereol (Stockh) 54:479-485, no. 6, 1974
29. Gardner HL, Kaufman RH: Herpes genitalis: Clinical features. Clin Obstet Gynecol 15:896-911, Dec 1972
30. Merigan TC (Ed): Antivirals with Clinical Potential. Chicago, The University of Chicago Press, 1975
31. Oxford JS, Drasar FA, Williams JD (Eds): Chemotherapy of herpes simplex virus infections. J Antimicrob Chemother 3: supp A, Mar 1977