

# GENITAL INFECTION WITH TYPE 2 HERPES VIRUS HOMINIS\*

## A COMMONLY OCCURRING VENEREAL DISEASE

BY

A. J. NAHMIA, W. R. DOWDLE, Z. M. NAIB, W. E. JOSEY,  
D. McLONE, AND G. DOMESCIK

*From the Departments of Pediatrics, Preventive Medicine, Pathology, Gynecology and Obstetrics,  
Emory University School of Medicine;*

*Laboratory Program, National Communicable Disease Center, Public Health Service, U.S. Department of Health,  
Education and Welfare;*

*and the Fulton County Health Department, Atlanta, Georgia, U.S.A.*

Although genital herpetic infections in males and females have been recorded for more than two centuries (Hutfield, 1966), their venereal mode of transmission has not been universally accepted (Diddle, Williamson, and Gardner, 1963; Yen, Reagan, and Rosenthal, 1965; Hutfield, Wasley, and Gray, 1967). Interest in genital herpetic infections has been reawakened as a result of recent findings indicating that most strains of *Herpes virus hominis* (HVH) recovered from the genitalia differ antigenically and biologically from HVH strains commonly infecting non-genital sites (Dowdle, Nahmias, Harwell, and Pauls, 1967; Schneweis, 1967; Rawls, Laurel, Melnick, Glicksman, and Kaufman, 1968a; Nahmias and Dowdle, 1968). The importance of genital HVH in the mother as the source of neonatal herpes (Nahmias, Josey, and Naib, 1967a) and the possible relation of such infections to cervical cancer (Naib, Nahmias, and Josey, 1966; Josey, Nahmias, and Naib, 1968; Rawls, Tompkins, Figueroa, and Melnick, 1968b; Naib, Nahmias, Josey, and Kramer, 1969) have further stimulated clinical, epidemiological and laboratory investigations.

In this report we present studies providing further support for the venereal mode of transmission of genital HVH infection. Studies are also presented on patients attending a venereal disease clinic and a general municipal hospital which point to the common occurrence of such infections in males and females and emphasize their frequent prevalence in teenagers. In addition, further

experience is reported here on antigenic typing of HVH from male and female genital sites.

### Material and Methods

#### Study Groups

One study group included male and female patients who presented to the Fulton County Venereal Disease Clinic with genital lesions which appeared to be herpetic on clinical examination. Clinical suspicion was based on the presence of vesicular or ulcerative lesions (with a history of "blisters") occurring usually in clusters on the penis. In the female patient, lesions were present chiefly on the labia, occasionally with associated involvement of the perineal areas, thighs, or buttocks. In many cases, when external lesions were present, the cervix was also involved; the appearance of such cervical lesions has been described previously (Josey, Nahmias, Naib, Utley, McKenzie, and Coleman, 1966).

Another study group comprised women attending Grady Memorial Hospital, a general municipal hospital, over a 4-year period (July, 1963, to June, 1967). Cytological detection of herpetic infection—multinucleated giant cells and intranuclear inclusions—was made on cervico-vaginal smears obtained routinely for cancer detection (Naib and others, 1966, 1969). Studies to ascertain the specificity of the cytological method of detecting HVH infection have been reported previously (Nahmias, Naib, Josey, and Clepper, 1967c). Almost all the cases in women detected in this manner lacked clinical signs of herpetic disease of the external genitalia, vagina, or cervix.

#### Prevalence of Genital Herpes in Venereal Disease Clinic

For a 6-month period, June to November, 1967, an attempt was made to obtain virus cultures on all patients

\*Received for publication March 5, 1969.

coming to the Venereal Disease Clinic with genital lesions suspected of being herpetic. During the same period, the prevalence of herpetic disease was compared with that of gonorrhoea, syphilis, and other venereal diseases (chancroid, lymphogranuloma venereum, and granuloma inguinale).

**Virological Isolation and Typing of Genital Strains**

Swabs from genital lesions or apparently non-infected genital sites, such as the cervix, were placed in Hanks's buffered salt solution containing 200 units penicillin and 100 µg. streptomycin/ml. These specimens were then inoculated into primary rabbit kidney tissue culture tubes. 160 viruses recovered in this manner from male or female genitalia were typed. A micro-neutralization test (Dowdle and others, 1967) was used to type 101 of these strains; the results of typing 55 of these isolates have been reported previously (Nahmias and Dowdle, 1968). An immunofluorescent test was used to type 125 additional genital isolates, including isolates submitted for typing by other workers. The immunofluorescent test has been found to give identical results with 96 strains previously typed by the micro-neutralization test (Nahmias and others, 1969).

**Contact Studies**

Female patients had previously been found to carry the virus for several days or weeks (Nahmias and others, 1967b), but lesions from which HVH can be cultured in males do not persist as long. We therefore decided to study female contacts of infected males rather than male contacts of infected females. Within 1 week of the initial detection of penile herpetic lesions in seven males, eight female contacts were investigated. Studies of the males and their contacts included clinical observations, virological studies as noted above, and serological tests using previously described techniques (Nahmias, Dowdle, Naib, Josey, and Luce, 1968).

**Results**

**Age Distribution of Cases Studied**

Genital lesions in 112 cases were clinically suspected of being caused by HVH. As shown in Table I, viral isolation was made in 73 (65 per cent.) of these cases. Viral recoveries were made more readily (74 per cent.) in female cases than in male patients (56 per cent.). Table I also shows that

teenagers represented approximately one-fourth of the males and one-half of the females studied and confirmed virologically. The teenage group represented approximately one-fourth of all females tested cytologically, as well as one-fourth of those with positive cytological findings for HVH (Table II). It thus appears from both the virologically studied group (Table I) and the cytologically studied group (Table II) that genital herpetic infection is frequent in teenage females.

TABLE II  
GENITAL HERPETIC INFECTION IN FEMALE PATIENTS DETECTED BY CYTOLOGICAL CERVICO-VAGINAL SMEARS (JULY 1963 TO JUNE 1967)

| Age (yrs)   | No. with Positive Cytological findings for HVH | Total No. Screened | Per cent. Positive |
|-------------|--|--------------------|--------------------|
| 13 to 19    | 55   | 9,471              | 0.58               |
| 20 and Over | 145  | 30,843             | 0.47               |
| Total       | 200  | 41,614             | 0.48               |

**Prevalence of Genital HVH in Venereal Disease Clinic**

Table III (overleaf) shows the male and female patients examined at the Venereal Disease Clinic over a 6-month period. The diagnosis of HVH was suspected on clinical grounds in 30 males and in 43 females. The virus was isolated from 17 (57 per cent.) of the male patients and 31 (72 per cent.) of the female patients. Table III shows that suspect herpes cases comprised 1.2 per cent. of all infections recorded in patients at the Venereal Disease Clinic and virologically confirmed cases represented 0.8 per cent. Virologically confirmed HVH infections were second only to gonorrhoea in women, causing 5.7 per cent. of all infections affecting the female genitalia. In males, genital HVH was the third most common genital infection observed, comprising 0.3 per cent. of the total number of cases observed during that period. The comparative prevalence of clinically suspected cases

TABLE I  
CLINICALLY SUSPECT AND VIROLOGICALLY CONFIRMED GENITAL HERPETIC INFECTIONS, BY AGE AND SEX

| Age (yrs)   | Males         |          | Females |          | Total   |          |
|-------------|---------------|----------|---------|----------|---------|----------|
|             | Suspect       | Positive | Suspect | Positive | Suspect | Positive |
| 13 to 19    | 10            | 7        | 28      | 22       | 38      | 29       |
| 20 and Over | 44            | 23       | 30      | 21       | 74      | 44       |
| Total       |               |          |         |          |         |          |
|             | No. Per cent. |          |         |          |         |          |
|             |               | 54       | 30      | 58       | 43      | 112      |
|             |               | 56       | 56      | 74       | 74      | 65       |

TABLE III  
PREVALENCE OF VENEREAL DISEASES IN VD CLINIC (JUNE TO NOVEMBER, 1967)

| Infection                    |                       | Males      | Females    | Total      |
|------------------------------|-----------------------|------------|------------|------------|
| (1) Gonorrhoea               |                       | 5,397      | 469        | 5,866      |
| (2) Herpes                   | (Suspect)<br>Positive | (30)<br>17 | (43)<br>31 | (73)<br>48 |
| (3) Syphilis                 | Primary<br>Secondary  | 50<br>30   | 12<br>30   | 62<br>60   |
| (4) Other Venereal Diseases* |                       | 43         | 6          | 49         |
| Total                        |                       | 5,537      | 548        | 6,085      |

\*These include chancroid, lymphogranuloma venereum, and granuloma inguinale.

is 8 per cent. in females and 0.54 per cent. in males.

#### Antigenic Typing of Genital HVH Isolates

Table IV presents the results of antigenic typing of 64 HVH isolates from male genitalia and 162 from female genital sites. In all the adult males the isolate from the penile lesions belonged to Type 2. As reported previously (Nahmias and others, 1968),

a Type 1 HVH was recovered from penile lesions and mouth of a 3-year-old child. Type 2 HVH strains were recovered from various sites of the genital tract in 155 females. Type 1 HVH was recovered from vulva or cervix in seven female patients; in three of these (two adults and one 8-year-old girl), Type 1 HVH was also recovered from the mouth.

TABLE IV  
ANTIGENIC TYPE OF HVH RECOVERED FROM GENITAL INFECTIONS IN 226 PATIENTS, BY SEX

| Sex    | Site of Isolation | Type 1 | Type 2 |
|--------|-------------------|--------|--------|
| Male   | Penis             | 0      | 63     |
|        | Penis and mouth   | 1      | 0      |
|        | Total             | 1      | 63     |
| Female | Vulva             | 4      | 81     |
|        | Vagina, cervix    | 0      | 73     |
|        | Vulva and mouth   | 2      | 1      |
|        | Cervix and mouth  | 1      | 0      |
|        | Total             | 7      | 155    |
| Total  |                   | 8      | 218    |

#### Contact Studies of Males with Penile Herpetic Lesions

Seven men with HVH Type 2 penile lesions were questioned about female contacts in the previous week. Eight females were interviewed and studied within 1 week of the detection of infection in their male contacts. Table V shows that three women (f, g, h) had clinically recognizable vulval lesions and that five (a-e) did not demonstrate external genital lesions. In three cases (f, g, h) with external lesions, the cervix appeared clinically involved and HVH Type 2 was isolated from all three (two from the cervix and one from the vulva). In the cases of five other women (a-e) with no external genital

TABLE V  
STUDIES ON FEMALE CONTACTS OF MALES WITH PENILE HERPETIC LESIONS

| Identifying Letter | Males     |                            | Female Contacts    |           |                           |                 |                 |                 | Primary Genital Infection* |
|--------------------|-----------|----------------------------|--------------------|-----------|---------------------------|-----------------|-----------------|-----------------|----------------------------|
|                    | Age (yrs) | Primary Genital Infection* | Identifying Letter | Age (yrs) | Evidence of HVH Infection |                 |                 |                 |                            |
|                    |           |                            |                    |           | Vulva                     |                 | Cervix          |                 |                            |
|                    |           |                            |                    |           | Clinical Lesion           | Virus Isolation | Clinical Lesion | Virus Isolation |                            |
| A                  | 22        | No                         | a                  | 18        | 0                         | NT              | +               | +               | No                         |
| B                  | 18        | No                         | b                  | 17        | 0                         | NT              | +               | +               | Yes                        |
| C                  | 30        | No**                       | c                  | 22        | 0                         | NT              | 0               | +               | No                         |
| D                  | 19        | No                         | d                  | 16        | 0                         | NT              | 0               | 0               | Yes                        |
| E                  | 19        | Yes                        | e                  | 19        | 0                         | NT              | 0               | +               | Yes                        |
| F                  | 28        | Yes                        | f                  | 19        | +                         | NT              | +               | +               | No                         |
| G                  | 21        | No                         | g                  | 20        | +                         | NT              | +               | +               | No                         |
|                    |           |                            | h                  | 18        | +                         | +               | +               | 0               | Yes                        |

\*Primary = 4-fold or greater rise in Type 2 HVH antibody titre in convalescent serum.

\*\*Patient also gave history of penile herpetic lesions 6 months earlier.

NT = Not tested.

lesions, the cervix appeared clinically involved in two (a, b). In these two women, as well as in two others (c, e), HVH Type 2 was isolated from the cervix; one of these women was found to have developed vulval lesions when re-examined one week later. Serological studies on the males and their female contacts revealed that two males (E, F) had primary infections (4-fold or greater rise in Type 2 antibody titre in convalescent serum), whereas four females (b, d, e, h) had serological evidence of primary genital HVH infection.

### Discussion

The results obtained on antigenic typing of isolates from the genital tract suggest strongly that HVH Type 2 has a special genitotropism. It has also been shown that HVH Type 1 can on occasions infect the genitalia of humans (Table IV), and this infection has also been demonstrated in mice (Nahmias, Naib, Highsmith, and Josey, 1967b). However, present indications are that the mode of transmission of the two HVH types differs, with HVH Type 1 being primarily spread by nonsexual means (Nahmias and Dowdle, 1968).

Supporting the concept of venereal transmission of HVH Type 2 are the findings that seven of eight female contacts of seven males with penile herpes had evidence of a current genital HVH Type 2 infection. Serological studies suggest that males were the apparent source of genital infection to four female contacts (Table V), whereas females appear to have been the source of infection for two of their male contacts. Of particular interest is the observation that in four of the female contacts the diagnosis would have been missed if material from the cervix had not been examined and cultured. In other studies (Josey and others, 1966), the cervix has often been found to be infected in the absence of external genital involvement, suggesting that the cervix is often the initial site of genital herpes in the female.

Other workers have reported occasional instances of the occurrence of genital HVH in contacts of infected consorts (Sharlit, 1940; Slavin and Gavett, 1946; Lazar, 1955; Duxbury and Lawrence, 1959). Experimental studies in rabbits (Levaditi and Nicolau, 1923) and mice (Nahmias and others, 1967b) provide further support for the venereal mode of transmission of genital herpes. Therefore, the concept that genital herpes in the adult is the result of the trauma of coitus reawakening an infection developed in childhood (Yen and others, 1965; Hutfield and others, 1967) is doubtful, particularly since genital HVH Type 2 infection in children (Nahmias and others, 1968) is infrequent compared to its occurrence in teenagers and adults.

Greenough (1881) reported a high incidence of genital herpes in males with histories of other venereal infections. The prevalence of genital HVH in prostitutes was first noted by Unna (1883). Unna also found the incidence in several thousand women admitted to the female syphilitic department at the Hamburg General Hospital between 1878 and 1881 to be around 8 per cent., whereas in males, the incidence was approximately 1 per cent. It is of interest that 84 years later, we have found the incidence of clinically diagnosed genital herpes to be remarkably similar (8 per cent. in females and 0.5 per cent. in males). Virologically confirmed cases gave a slightly lesser incidence. It is probable that the incidence of genital herpes infection in women is actually higher than that observed by Unna and by ourselves, since only patients with clinical lesions were studied; we did not attempt to carry out cultural studies in all women attending the VD Clinic. In studies of women with no external genital herpetic lesions attending venereal disease clinics, Beilby, Cameron, Catterall, and Davidson (1968) and Kleger, Prier, Rosato, and McGinnis (1968) found the incidence of HVH isolations from cervical specimens to be 3.8 and 1.6 per cent. respectively, Beilby and others (1968), however, found cervical involvement in six of the eight women with positive HVH isolation.

The prevalence in males is probably greater than virological confirmation indicates. Recovery of HVH is more difficult in males than in females (Table I). This may be due to the greater difficulty in isolating the virus from ulcerative than vesicular lesions. Vesicles were more commonly found in female than in male patients at the time of examination.

The frequent finding of genital herpetic infection suggests strongly that many cases are being misdiagnosed in venereal disease clinics. The differential diagnosis of genital herpetic infections has recently been reviewed (Hutfield, 1968; Josey, Nahmias, and Naib, 1969). Barile, Blumberg, Kraul, and Yaguchi (1962), in a study of U.S. Armed Forces personnel in Japan, have emphasized the frequent misdiagnosis of genital HVH infection and have offered additional evidence for its venereal transmission. All of their patients with penile herpes admitted recent sexual exposure, but the virus could not be demonstrated in 47 patients who had abstained from sexual intercourse for a minimum of 30 days before examination.

Herpetic genital infection commonly affects teenagers as do other venereal diseases (Kampmeier, 1968). Serological studies conducted in over 150 cases of genital HVH infections have shown that about one-third are primary, that is, occurring in

patients with no previous exposure to either Type 1 of Type 2 HVH. Most of the primary infections occurred in teenagers. Genital Type 2 infections could occur in patients with a history of cold sores who already had Type 1 antibodies in their acute serum, but whether re-infection with Type 2 HVH can occur in an individual with previous Type 2 genital infection remains to be determined.

### Summary

Further evidence for the venereal transmission of genital infection with *Herpes virus hominis* (HVH) is presented. This includes:

- (1) The finding that seven out of eight female contacts of seven males with penile herpetic infection showed evidence of a current HVH genital infection;
- (2) The observation that 63 of 64 HVH isolates from male genitalia and 155 of 162 from the female genital tract were Type 2 HVH.

Studies on the relative prevalence of overt genital herpetic infection in a venereal disease clinic have revealed that about 6 per cent. of female patients and 0.3 per cent. of male patients had virologically confirmed herpes. HVH was the most common cause of genital lesions (vesicles and/or ulcers) found in women and was second only to primary syphilis as the cause of such lesions in males. Teenagers have been found to account for one-fourth to one-half of patients with genital herpetic infections studied at the venereal disease clinic and in a general municipal hospital.

This work was supported in part by a contract (DADA17-68-C-8141) from the U.S. Army Medical Research and Development Command. We wish to express our gratitude to Miss C. Luce, Miss R. Harwell, and Dr. J. Kramer for their assistance with these studies.

### REFERENCES

- BARILE, M. F., BLUMBERG, J. M., KRAUL, C. W., and YAGUCHI, R. (1962). *Arch. Derm. (Chicago)*, **86**, 273.
- BEILBY, J. O. W., CAMERON, C. H., CATTERALL, R. D., and DAVIDSON, D. (1968). *Lancet*, **1**, 1065.
- DIDDLE, A. W., WILLIAMSON, P. J., and GARDNER, W. H. (1963). *Obstet. and Gynec.*, **22**, 739.
- DOWDLE, W. R., NAHMIA, A. J., HARWELL, R. W., and PAULS, F. P. (1967). *J. Immunol.*, **99**, 974.
- DUXBURY, A. E., and LAWRENCE, J. R. (1959). *Med. J. Aust.*, **2**, 250.
- GREENOUGH, F. B. (1881). *Arch. Derm. (N.Y.)*, **7**, 1.
- HUTFIELD, D. C. (1966). *Brit. J. vener. Dis.*, **42**, 263.
- (1968). *Ibid.*, **44**, 241.
- , WASLEY, G. D., and GRAY, E. (1967). *Ibid.*, **43**, 48.
- JOSEY, W. E., NAHMIA, A. J., and NAIB, Z. M. (1968). *Amer. J. Obstet. Gynec.*, **101**, 718.
- , —, — (1969). *Clin. Obstet. Gynec.*, **12**, 161.
- , —, —, UTLEY, P. M., MCKENZIE, W. J., and COLEMAN, M. T. (1966). *Amer. J. Obstet. Gynec.*, **96**, 493.

- KAMPMEIER, R. H. (1968). *Hum. Sexuality*, **2**, 14.
- KLEGER, B., PRIER, J. E., ROSATO, D. J., and MCGINNIS, A. E. (1968). *Amer. J. Obstet. Gynec.*, **102**, 745.
- LAZAR, M. P. (1955). *A.M.A. Arch. Derm.*, **72**, 272.
- LEVADITI, C., and NICOLAU, S. (1923). *C.R. Acad. Sci. Paris*, **176**, 146.
- NAHMIA, A. J., CHIANG, W., DEL BUONO, I., and DUFFEY, A. (1969). *Proc. Soc. exp. Biol. (N.Y.)*, **132**, 386.
- and DOWDLE, W. R. (1968). *Progr. med. Virol.*, **10**, 110.
- , —, NAIB, Z. M., JOSEY, W. E., and LUCE, C. F. (1968). *Pediatrics*, **42**, 659.
- , JOSEY, W. E., and NAIB, Z. M. (1967a). *J. Amer. med. Ass.*, **199**, 164.
- , NAIB, Z. M., HIGHSMITH, A. K., and JOSEY, W. E. (1967b). *Pediat. Res.*, **1**, 209.
- , —, JOSEY, W. E., and CLEPPER, A. C. (1967c). *Obstet. and Gynec.*, **29**, 395.
- NAIB, Z. M., NAHMIA, A. J., and JOSEY, W. E. (1966). *Cancer*, **19**, 1026.
- , —, —, and KRAMER, J. H. (1969). *Ibid.*, **23**, 940.
- RAWLS, W. E., and LAUREL, D., MELNICK, J. L., GLICKSMAN, J. M., and KAUFMAN, R. H. (1968a). *Amer. J. Epidem.*, **87**, 647.
- , TOMPKINS, W. A. F., FIGUEROA, M. E., and MELNICK, J. L. (1968b). *Science*, **161**, 1255.
- SCHNEWEIS, K. E. (1967). *Dtsch. med. Wschr.*, **92**, 2313.
- SHARLIT, H. (1940). *Arch. Derm. Syph. (Chicago)*, **42**, 933.
- SLAVIN, H. B., and GAVETT, E. (1946). *Proc. Soc. exp. Biol. (N.Y.)*, **63**, 343.
- UNNA, P. G. (1883). *J. Cutan. vener. Dis.*, **1**, 321.
- YEN, S. S. C., REAGAN, J. W., and ROSENTHAL, M. S. (1965). *Obstet. and Gynec.*, **25**, 479.

### Infection génitale avec le virus herpétique humain type 2

#### SOMMAIRE

On présente des preuves supplémentaires de la transmission vénérienne de l'infection générale par le virus *Herpes hominis* (HVH). Ceci repose sur:

(1) La constatation que sept partenaires féminines sur 8 de 7 hommes atteints d'infection herpétique de la verge présentèrent une infection génitale herpétique évidente d'aspect courant.

(2) L'observation que 63 des 64 virus *Herpes hominis* isolés des voies génitales masculines et de 155 des 162 isolés des voies génitales féminines étaient du type 2.

Des études sur la prévalence relative de l'infection herpétique génitale manifeste dans une clinique vénérérologique a révélé qu'environ 6 pour cent des malades femmes et 0,3 pour cent des malades hommes avaient un herpès confirmé virologiquement. HVH fut la cause la plus fréquemment observée des lésions génitales (vésicules et/ou ulcérations) chez les femmes et seule la syphilis primaire se plaçait avant comme cause de telles lésions chez les hommes. Les moins de 20 ans ont été trouvés comme représentant un quart à une moitié des malades atteints d'herpès génital étudiés à la clinique vénérérologique et dans un hôpital municipal général.