Human Cervical Cancer as a Venereal Disease

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Summary

The operation of venereal factors in human cervical cancer is suggested by demographic and epidemiological data. Recent evidence supporting the genital herpesvirus hypothesis is consistent with this notion. A controlled epidemiological investigation has been undertaken on the role of the male coital partner in cervical carcinogenesis. An answer is sought to the question, "Is the risk of developing cervical cancer increased among the wives of men who at some other time were married to other women who developed cervical cancer?" With one-quarter of the study completed, a total of 14 marital clusters have been identified in which 2 or more wives of the same men developed cervical carcinoma. The expected number of such clusters is estimated to be 4.

Introduction

Prevention or control of a disease such as human cervical cancer requires intervention at the level of 1 or more elements in its natural history: (a) the etiological agent; (b) the host at risk; (c) the disease itself; and (d) the environment in which these elements interact.

At the present time, cervical cancer control activities are directed primarily at the human host and at the disease. Women, especially those at increased risk, are encouraged to undergo periodic cytological screening for the detection of the neoplasm or one of its precursors. In addition, effective therapeutic modalities are now available for the treatment of both invasive and intraepithelial carcinoma of the cervix. On the other hand, relatively less has been accomplished thus far in identifying the specific etiological agent or agents of the disease and in developing effective methods for modifying those environmental factors that operate to the advantage of the neoplasm.

In recent years, a consistent body of evidence has accumulated that suggests a possible role for the genital herpesvirus, HSV-2, in human cervical cancer. In view of this, it may be useful to review the known or suspected mechanisms of HSV-2 transmission in man and to speculate about cervical cancer prevention in terms of the environment in which the agent, host, and disease interact.

In this paper, evidence on the venereal nature of HSV-2 infections in man will be reviewed in the light of existing knowledge on other, more established, venereal diseases. Demographic and epidemiological data consistent with the notion that human cervical cancer behaves like a venereal disease will be cited. Published data on the possible role of the male in cervical carcinogenesis will be evaluated, with special reference to the herpesvirus hypothesis. Finally, preliminary findings from an ongoing investigation will be presented in support of a model of human cervical cancer as a venereal disease.

HSV-2 as a Venereal Disease

A wide variety of diseases are now regarded as venereal, i.e., "due to or propagated by sexual intercourse" (16). These include not only spirochetal and bacterial diseases (syphilis, gonorrhea, chancroid, and granuloma inguinale) but also a number of viral, protozoal, fungal, and parasitic conditions. The latter consist of herpes simplex, lymphogranuloma venereum, condylomata acuminata, trichomoniiasis, moniliasis, tinea cruris, scabies, and pediculosis, among others (102).

The relatively more serious venereal diseases, such as syphilis and gonorrhea, share a number of attributes. They usually occur among sexually active young adults who comprise the principal reservoir of infection through a venereal mode of transmission. The agent has a relatively short incubation period, and immunity to reinfection is absent or insubstantial. The considerable individual variation in susceptibility to infection may be related to characteristics of the agent, such as virulence, or to characteristics of the host, including genetic, constitutional, hormonal, or other factors.

The true incidence and prevalence of these diseases are unknown because of the difficulties in case ascertainment and because of the relatively high proportions of asymptomatic cases. Despite this, the numbers and rates at which both these diseases have been reported in recent years indicate a marked increase in their relative frequency (7, 26, 31, 42, 97). As will become evident below, genital herpetic infections share many of these characteristics.

Early Studies. It is not possible to identify with certainty the study that first demonstrated the venereal nature of HSV-2 infections in man. In his classical description of genital herpes, published in 1736, Jean Astruc not only classified the condition as a venereal disease but also noted its increased frequency among practicing homosexuals (36). Rollet, in 1869, was probably the first investigator to describe a specific venereal infection of the uterine cervix.
termed “blennorrhagie,” which was regarded by some contemporaries as herpetic in origin (84).

In a paper delivered at a meeting of the American Dermatological Association in Newport, R. I., in 1880, Greenough (29) noted that “the influence of the venereal act as the immediate cause of herpes progenitalis has [not] been given the importance that it deserves,” although he credited the French physician Doyon with having previously called attention to this problem. He emphasized that, in his practice, genital herpes was seen only in males, particularly young adults with histories of other venereal diseases. This conclusion was challenged in a subsequent paper by the German physician, P. G. Unna, who had also attended the Newport meeting. After reviewing earlier inferential evidence from the French literature, Unna assembled the records of genital herpes infections among patients seen at the Hamburg General Hospital (99). Over a recent 4-year period he was able to identify a total of only 17 males as compared with 423 females who were treated for herpes genitals in the venereal diseases department. He concluded that “women are just as susceptible to herpes as men are; there is no immunity from herpes for the female sex.”

Clinical Studies. Direct evidence concerning the venereal transmissibility of genital herpes infections derives from a number of observational studies on the sexual contacts of infected consorts. In many of these studies, clinical diagnoses of herpetic infections were made in the contacts and, sometimes, in the consorts, but serological measurements or virus isolations were not undertaken (35, 88). In other investigations, laboratory tests were performed on the contacts, the consorts, or both. Measurement of herpes antibodies, virus isolations, or cytological diagnosis through visualization of characteristic multinucleated giant cells in exfoliate smears were variously used (10, 14, 15, 19, 41, 51, 69, 75, 79, 91, 101). Special attention was usually given to the temporal relationships between the reported coital experiences and the subsequent manifestations of genital disease in contacts and consorts.

The most impressive clinical evidence on the venereal transmission of HSV-2, to date, is to be found in the investigations of Nahmias and Rawls and their respective colleagues. Eight female sex contacts of 7 male patients with virologically confirmed HSV-2 penile infections were examined within 1 week of the initial detection of the herpetic lesions in their consorts (69). Seven of the 8 contacts gave evidence of a current genital HSV-2 infection of either the vulva or the cervix. Genital herpesvirus was isolated from each of these 7 women.

Rawsl et al. (79) examined 30 female contacts of 30 males with clinically diagnosed genital herpes infections from a public venereal disease clinic. HSV-2 was successfully isolated from the penile lesions of 53% of the male patients and from the genital secretions of 33% of their female contacts. These rates were markedly in excess of the prevalence of HSV-2 infections in a control group of women from the same clinic.

Another approach to studying the venereal transmission of genital herpesvirus infections is exemplified by the observations of Tyler (98) on 200 military patients with penile lesions seen aboard a troopship shortly after exposure to Oriental prostitutes. Although the diagnosis of herpes genitals was arrived at by exclusion, the author concluded that “nearly all of these diseases must result from sexual intercourse.”

Inferential Problems. The studies just described, while far from conclusive, are not different in kind from most of the earlier clinical efforts to demonstrate the venereal transmission of such diseases as syphilis and gonorrhea. Even the controlled experimental studies, primarily of gonococcal infections, which have been conducted in human populations are not entirely free of inferential problems, if only because the infections were artificially induced by inoculation rather than by sexual intercourse (9, 57).

There is an analog in the studies of gonorrhea to the previously cited military investigation of herpes by Tyler. Holmes et al. (34) observed the occurrence of gonorrhea among a large group of naval personnel who admitted to sexual intercourse with a group of women whose prevalence of neisserial infection could be estimated. To account for the relatively low rate of venereal transmission observed (22%), these investigators suggested the possible effects of variations in such parameters as virulence of the agent, immunity of the exposed male, sensitivity of the serological tests used, and degree of mechanical exposure, among others. A quite similar situation may apply to the question of the venereal transmission of HSV-2.

There are several unique features of HSV-2 that probably influence its venereal spread and, in addition, confound studies of the same phenomenon. In view of latency, which is characteristic of herpetic infections, “it would be of interest to know whether secondary genital herpes follows the stimulation of a dormant virus left in the tissues after a primary infection of the area, or if new infectious herpetic material is introduced via sexual intercourse” (51). In very few of the clinical studies on the venereal transmission of HSV-2 is there an adequate differentiation between primary and secondary (or recurrent) herpetic infections. Thus, the postcoital manifestations of HSV-2 infections may, in fact, be venereal (i.e., due directly to the transmission of herpetic virions) or nonvenereal. The latter, in turn, may be either coitus related (i.e., due to the triggering of a clinical recrudescence by, or associated with, the coital act) or not coitus related (i.e., triggered by menstruation, hormone imbalance, fever, or other stresses unrelated to sexual intercourse) (73). All such recurrences, both endogenous and exogenous, cannot presently be differentiated from one another on serological or other grounds. Confounding the problem is the possibility that other venereal diseases such as gonorrhea may activate latent cervical herpes (6).

Another consideration, of possible relevance to the herpesvirus hypothesis in cervical cancer, stems from the fact that herpetic cervicitis is usually asymptomatic whereas penile herpes is an extremely painful and incapacitating, although self-limited, condition (14). Therefore, while infected males are extremely unlikely to engage in sexual intercourse during a productive herpetic infection, females with active cervical lesions may continue to do so. The relevance to cervical cancer risk of sexual intercourse or
abstention at a time when the cervical epithelium has been compromised by active herpetic lesions is presently unknown.

In their investigation of patients with clinically diagnosed primary and recurrent HSV-2 infections, Rawls et al. (79) successfully isolated virus 1 week or more after the infection from 75% of patients with primary lesions but from only 15% of those with recurrences. These observations suggest that the venereal transmission of HSV-2 is more likely to occur after an individual's primary infection than during the relatively brief periods of infectiousness following secondary recurrences. In other words, the principal reservoir may consist disproportionately of sexually active (and recently infected) teenagers.

The effect of changing sexual mores on the patterns of venereal transmission of HSV-2 is only now becoming evident. An example is afforded by the apparently increased prevalences of cunnilingus and fellatio which have been reported (102). Such practices also open up possibilities of the venereal transmission of oral herpesviruses which cannot be distinguished from HSV-2 on clinical or cytological grounds alone and which are differentiated imperfectly by most serological techniques in current use (45, 100).

That genital herpes is a venereal disease is also suggested by clinical studies of prostitutes (18, 29, 63, 99) and patients seen in venereal disease clinics (6, 37, 38, 48, 69). It is clear from such investigations that the prevalences both of clinically manifest disease and of serologically diagnosed infection are increased among the sexually promiscuous as compared with control population groups.

Animal Models. Evidence from animal models on the venereal transmission of HSV-2 is relatively meager. In 1923, Levaditi and Nicolau (52) mated 5 normal mature male rabbits with 1 female in whom herpetic vaginitis had been induced by intravaginal inoculation of herpesvirus recovered from human sources. On the 5th postcoital day, 1 of the 5 males developed a typical herpetic penile lesion. Inferences from these results to man are tenuous because of the small size of the experiment and, more importantly, because of the likelihood that the virus was, in fact, an oral type. In 1967, Nahmias et al. (72) mated uninfected male mice with females in whom vaginal HSV-2 infection had been produced by direct inoculation of undiluted virus with cotton pellets. They reported that "sexual transmission of genital infection was demonstrated when uninfected male mice placed in contact with infected females developed herpetic penile lesions." Unfortunately, no details on this interesting experiment were offered by the authors in the cited abstract and, to our knowledge, the details have not been elaborated in published papers.

Nahmias et al. (71) have also reported on the successful establishment of an HSV-2 genital infection in female Cebus monkeys. Although efforts at infecting rhesus and squirrel monkeys failed, 10 female Cebus monkeys did develop genital infections with a HSV-2 strain recovered from a human female patient. Intravaginal inoculations as performed in their earlier mouse study were followed by the appearance of typical herpetic lesions, successful isolation of the virus, and demonstration of rising titers of herpesvirus antibodies in the serum. However, venereal transmission of such infections to male monkeys mated with infected females has not yet been achieved. The latter, of course, would constitute evidence of the highest quality on the venereal transmission of HSV-2.

Nonvenereal Herpes. While there seems little doubt that HSV-2 infections are relatively prevalent among the sexually promiscuous, not much has yet been documented on herpetic infections among virgins or other sexually inactive persons. We are aware of only 1 specific citation in the literature, namely, the statement by Nahmias et al. (70) to the effect that they "have found that only one (3%) of 35 nuns had type 2 antibodies." No additional details concerning this interesting observation have been published by these authors, to our knowledge.

During the past 2 years, we have been conducting a survey of health and disease among several orders of religious nuns and their married female siblings. Data sources include personal interviews, medical record reviews, exfoliative cytology, and bleeding for serological analysis. A preliminary and quite incomplete review of the initial findings some months ago revealed the following prevalence rates of neutralizing antibodies to HSV-2: 58.6% among the nuns and 57.4% among their blood sisters. These findings must be interpreted very cautiously in view of the incomplete data upon which they are based. However, they do suggest the possibility of nonvenereal modes of HSV-2 transmission. This is further substantiated by the complete absence of trichomonads from the cervical smears of the nuns but not from those of their siblings.

That not all genital herpetic lesions should be attributed to venereally transmitted herpesvirus was succinctly put by Sharlitt (88), namely: "I profoundly trust that none will be so rash as to challenge the claim of celibacy or to impugn the professions of chastity or fidelity on the prima facie evidence of herpes genitalis." There is, of course, the fact of herpetic genital infections among infants and young children (49, 68, 89, 105). To some extent this is complicated by the question of transplacental transmission of HSV-2 in the newborn (24, 65, 103). Middelkamp et al. (84) reported on the successful transplacental transmission of herpes simplex virus in female rabbits given i.e. injections with high concentrations of the virus. While this work antedated the development of techniques for distinguishing between oral and genital herpesvirus types, it is likely that an oral virus type was used by these workers.

In any event, the weight of evidence to date suggests that most newborns are infected from active lesions in the maternal birth canal rather than hematogenously. Furthermore, the isolation of HSV-2 from the genital lesions of a 15-year-old girl with a virginal introitus (1) is instructive. The situation may be analogous with syphilis which generally follows a venereal mode of transmission, but which manifests itself in endemic nonvenereal forms as well (30).

Analogy of Cervical Cancer with Venereal Disease

In 1842, Rigoni-Stern (81) speculated that the susceptibility of the uterus to cancer in cloistered sisters and married
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women differed according to “the natural exercise of its functions.” His findings on the rarity of cervical cancer among nuns have since been confirmed by other investigators (21–23, 87, 95). Explanations offered for the unusually low risk of cervical cancer among Jewish women include their traditional sexual abstinence during the menses, circumcision of the male, undefined genetic factors, and reduced sexual promiscuity (46).

These populations at low risk stand in marked contrast to prostitutes and incarcerated women who may experience a 4- to 6-fold higher rate of cervical cancer than do other females (2, 43, 66, 76). In general, cervical cancer risk appears to vary inversely with socioeconomic class, however defined (17, 56).

**Coital and Marital Factors.** The data just cited on population groups at high and low risk of cervical cancer are consistent with a fundamental relationship of the disease with coital or venereal factors. Over the past 2 decades a number of epidemiological studies have been directed at the possible etiological roles of coitus, marriage, and pregnancy in cervical neoplasia. The findings are consistent with the operation of coital determinants in this disease. Mortality from cervical cancer is increased among the married and decreased among the never married of all ages (54). More importantly, cervical cancer incidence conforms to the same pattern (17, 32, 44).

In addition to mortality and incidence surveys, a number of controlled epidemiological investigations have been designed specifically to explore coital, marital, and parity factors in cervical cancer by means of personal interviews with cases and controls. Despite differences in definitions and specific parameters used, a positive association of cervical cancer with coitus and marriage has been repeatedly demonstrated. Mean age at 1st coitus is younger and the proportion initiating coitus early is greater among cervical cancer cases than among controls. These cases also tend to have had more coital partners on the average than other women. Furthermore, the proportion of cervical cancer cases denying coitus is essentially zero, while among controls it is small but definite.

The relationships of marital variables with cervical cancer are equally consistent. Women who develop cervical cancer are less likely to remain unmarried, they tend to marry for the 1st time at a younger age, and they are more likely to have had several marital partners than other women do. Age at 1st coitus appears to be more important than age at 1st marriage in differentiating between cervical cancer patients and controls. Another risk factor that implicates venereal elements in the disease is extramarital sexual practice by either the patient or her spouse (58, 78). Associations of cervical cancer with pregnancy, in large measure, appear to be secondary to the marital or coital determinants. These relationships have been discussed more fully elsewhere (45, 46, 58, 85, 86, 94).

**Penile Factors.** Inferences on cervical cancer as a venereal disease are strengthened by considerations of penile factors. In 1936, Handley (33) sought to relate the immunity of Jewish males to penile carcinoma to the decreased risk of cervical cancer among Jewish females. He attributed this to the practice of circumcision and the resulting protection against “mixed bacterial infections” of the cervix during coitus. A more direct approach to the relationship between cervical and penile cancer was undertaken by Martinez. Utilizing data from the Central Cancer Registry of Puerto Rico, this investigator noted an unusually high rate of cervical cancer among the wives of 889 men diagnosed as having penis cancer (59). A significant correlation between the death rates from cervical and penile cancer has been reported in Japan (50). Additional evidence on the possible role of the male coital partner in cervical carcinogenesis will be discussed subsequently.

**Associated Venereal Diseases.** That women with cervical cancer are more likely than expected to have syphilis has been known for many years (53). During the 1950’s at least 5 epidemiological studies yielded information on the prevalence of syphilis among cervical cancer patients (40, 55, 60, 83, 104). A positive association between the 2 diseases was consistently noted, but a more detailed examination of the data compelled one of the investigators “to assume the existence of a particularly potent carcinogenic factor among prostitutes—a factor which has no relation to syphilis” (83). Unfortunately, this work anedated the herpesvirus hypothesis, and one may only speculate on the extent to which HSV-2 might have constituted the hypothesized carcinogen.

Further evidence on the venereal nature of cervical cancer comes from the analysis of Beral (8) who compared mortality patterns for cancer of the uterine cervix with trends in incidence of syphilis and gonorrhea in the United Kingdom. She noted “striking associations between the temporal, social class, occupational and geographic distributions of these diseases.” These data suggest that exposure to sexually transmitted factors is an important determinant of cervical cancer.

Cytologists are also in agreement that trichomoniasis is relatively more prevalent among women with cervical dysplasia and carcinoma (13, 62). However, it is rather generally accepted today that the associations of both trichomoniasis and syphilis with cervical cancer are secondary, resulting from the relationship of each to sexual behavior.

The observed relationships of cervical cancer to coital practice, circumcision, syphilis, prostitution, and low socioeconomic class led a number of investigators to suggest the possibility of a venereally transmitted viral etiology for this neoplasm (5, 76, 85). Rawls et al. (80) succeeded in isolating HSV-2 from 4 smegma specimens of young male venereal disease clinic patients. Naib et al. (74) observed the development of cervical anaplasia (carcinoma or squamous atypia) in 23.7% of biopsied cervices giving cytological evidence of active herpetic infection.

At about the same time, a series of seroepidemiological studies involving the determination of neutralizing antibodies to HSV-2 in groups of women with and without cervical neoplasia were undertaken. In spite of the diversity of these studies, a positive association between cervical cancer and HSV-2 antibodies was evident (45). In more recent years, Aurelian et al. (4) have identified a tumor-specific antigen, AG-4, which is present in nearly all patients with cervical cancer, disappears following effective therapy, and reappears if the cancer recurs. It is also absent in most controls.
and in two-thirds of patients with dysplasia. Data associating HSV-2 with cervical cancer have been summarized in a recent paper and need not be further elaborated here (3). Additional findings concerning the specific role of the male coital partner will be discussed below.

**Male Role in Cervical Carcinogenesis**

As noted above, smegmal specimens of 4 young males in a venereal disease clinic yielded HSV-2. All 4 had penile herpetic lesions. This suggests a male role, although the virus could not be isolated from the smegma of the husbands of 22 women with cervical cancer (80). That males may serve as reservoir of HSV-2 is also suggested by the data of Centifanto et al. (11) who isolated the virus from the genitourinary specimens of 15% of 190 male patients seen at a urology clinic. None of the subjects had a previous known history of genital herpes (11). Successful isolations were obtained from the prostate, the vas deferens, and the urethra. Others have also reported on successful HSV-2 isolations from urethral discharges of men with nonspecific urethritis attending venereal disease clinics (27, 39). On the other hand, Traub et al. (96) were unable to isolate any virus from 144 cultured vas deferens specimens of patients undergoing vasectomy. These findings suggest that, if the male is the reservoir of herpetic infections, only certain regions of the genitourinary tract are involved.

For selected males to serve as asymptomatic carriers of HSV-2, they would most likely have to experience chronic infections rather than latent infections of the genitourinary tract. The reason is that, in latent herpetic infections, viral replication (and, therefore, viral isolation) does not occur except during the relatively brief periods of clinical recrudescence. However, because clinically symptomatic herpetic lesions of the penis are extremely painful, venereal transmission of the agent through sexual intercourse would rarely, if ever, take place. Therefore, it is the asymptomatic males with chronic low-grade herpetic infections of the genitourinary tract who are the more likely carriers and transmitters of the putative carcinogen.

Proceeding with this line of reasoning, one might speculate that the coital partners of women destined to develop cervical cancer would characteristically suffer from low-grade chronic herpetic genitourinary tract infections, whereas their consorts would undergo primary infection leading to the latent state which, on biochemical grounds, is potentially oncogenic (82). In turn, the male partners themselves would most likely have been infected by females with chronic herpetic infections, because the proportion of women at any given time with active primary infections is probably negligible.

Mention should also be made of 2 studies in which HSV-2 was isolated from the urinary sediment of women with known herpetic infections (61, 77). Virus recovery was more frequent among the patients with dysuria than among those without, suggesting that dysuria associated with genital HSV-2 infections may be caused by herpetic cystitis.

While, in the main, this discussion of the male role in cervical carcinogenesis has been oriented primarily toward HSV-2, an alternative theory consistent with a male role may also be cited. Coppleson and Reid (12) have postulated that malignant transformations of the cervix are most likely to occur when the epithelium is actively undergoing squamous metaplasia, such as in early adolescence and at 1st pregnancy. They suggest that DNA viruses might be involved but also that the spermatozoa themselves may be mutagenic in particular circumstances. Elaborating on their argument, Singer (90) hypothesizes that "the presence of an oestral-type mucus for long periods during the immediately post menarchial era—a period associated predominately with anovulation—provides an avenue for the facilitated entry of a potential mutagen by virtue of its open channel configuration." The likeliest candidate for such a mutagen, according to Singer, is the spermatozoon, which has far more DNA than the genital herpesvirus does.

**Ongoing Study of the Male Role in Cervical Cancer**

Since 1973, we have been conducting an epidemiological study of the role of the male in cervical carcinogenesis. The method involves direct observations on 2 large groups of women: 1 group married to men who, at some other time, had wives who developed cervical cancer, and a 2nd group married to men without such histories. The study seeks to answer the basic question, "Is the risk of developing cervical cancer increased among the wives of men who, at some other time in their lives, were married to other women who developed cervical cancer?"

The study begins with the identification of a large cohort of women who had pathologically confirmed epidermoid carcinoma of the uterine cervix during the past 20 years. The husbands of these women are investigated to the extent of identifying their previous and subsequent wives ("case" wives). A random sample of "control" wives, similar to the "case" wives in demographic and marital characteristics is then selected.

The cohorts of "case" and "control" wives are traced prospectively to death or survival as of a recent point in time. The ultimate risk of cervical neoplasia among the 2 cohorts is ascertained by interview, medical record review, and exfoliative cytological screening by means of a self-administered irrigation pipet. Cervical scrapings under direct visualization are obtained from all women with nonnormal irrigation findings. This approach affords a direct epidemiological test of the role of any venereally transmitted male factor in cervical cancer, whether viral, chemical, or otherwise.

To date, 4178 probands with cervical cancer have been identified, and their histopathological diagnoses have been confirmed. A total of 726 husbands of these probands have been studied and 858 "other" wives ascertained, of which 625 have been fully traced, cytologically screened (if alive), and their histories of cervical cancer elucidated. Among the latter, 14 "other" wives with cervical cancer have thus far been detected. This compares with a total of 4 cancers among the "control" wives. A flow diagram of the preliminary results of the study is presented in Chart 1. It may be seen that the prospective approach of this study had made it
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Chart 1
Case Probands Treated and Cervix Cancers Found

6,178

Probands
Identified

1,541

Probands whose
husbands married
only once and
single probands

726

Probands whose
husbands had 1
or more "other
wives"

1,019

Probands whose
husbands' marital
histories are still
unknown.

858

Number of
"other wives"

625

Traced

233

Not yet traced

28

Deceased

381

Interviewed

144

Not Yet
Interviewed

72

Refused

312

Irrigation
taken

69

Irrigation
not taken

57

Residing
in area

87

Residing
afar

14 cervical cancers in "other wives": observed
4 cervical cancers in "other wives": expected

possible to ascertain the development of cervical neoplasia among the deceased, the nonrespondents, and the other uninterviewed women as well as among those who have been interviewed and examined.

Some characteristics of the 14 marital clusters with cervical cancer that have been identified to date are presented in Table 1. Three of the husbands have each been married to 3 women. While these data are suggestive, their incompleteness must be emphasized. They are based on approximately one-quarter of the total probands that are to be followed.

Among the tentative implications of the present findings are the following: (a) certain males may venereally transmit a risk factor for cervical cancer in women; (b) HSV-2 appears to be the likeliest candidate for such a risk factor; (c) because HSV-2 prevalence greatly exceeds cervical cancer prevalence, a necessary condition for the herpesvirus hypothesis is that certain females be receptive hosts for the putative venereal carcinogen; (d) data from our Yugoslavian study suggest that an essential female host characteristic for effective venereal transmission is related to steroid hormone balance. Among the 350 cervical cancer cases studied, the proportion with any menstrual abnormality (in frequency, duration, quantity, or pain) was significantly less than among the 350 demographically similar controls (47).

The possible role of estrogenic hormones in cervical neoplasia is also suggested from the results of a number of clinical (20, 92) and laboratory animal (25, 28, 67, 93) studies; (e) a probable condition for this model is that the male role involve more than a 1-time transmission of the carcinogenic factor (e.g., primary HSV-2 infection). It is more likely an effect resulting from or exacerbated by multiple coital events at periods of life when conditions for donor transmission and host response are optimal; (f) the alternative hypothesis to explain our present findings, namely, that the male partners in these marital clusters somehow tend to
Table 1
Details on marital clusters of cervical cancer

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Age at marriage</th>
<th>Wife’s age at cervical cancer</th>
<th>Pathological diagnosis</th>
<th>Married to this husband</th>
<th>Married to another</th>
<th>Other</th>
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<tr>
<td>1</td>
<td>1st 19</td>
<td>39</td>
<td>In situ carcinoma</td>
<td>10</td>
<td>3</td>
<td>8</td>
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<tr>
<td></td>
<td>2nd 32</td>
<td>38</td>
<td>In situ carcinoma</td>
<td></td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1st 19</td>
<td>34</td>
<td>Squamous cell carcinoma</td>
<td>4</td>
<td>9</td>
<td>1</td>
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<tr>
<td></td>
<td>2nd 24</td>
<td>29</td>
<td>Squamous cell carcinoma</td>
<td></td>
<td>5</td>
<td>DK*</td>
</tr>
<tr>
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<td>3rd 29</td>
<td>29</td>
<td>Microinvasive carcinoma</td>
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<td>DK</td>
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<td>Squamous cell carcinoma</td>
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<td></td>
<td></td>
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<td></td>
<td>2nd 42</td>
<td>27</td>
<td>In situ carcinoma</td>
<td></td>
<td></td>
<td></td>
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<td>1st 22</td>
<td>47</td>
<td>Transitional cell carcinoma</td>
<td>28</td>
<td>1</td>
<td></td>
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<tr>
<td></td>
<td>2nd 56</td>
<td>43</td>
<td>Squamous cell carcinoma</td>
<td></td>
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* Years lived while unmarried, divorced, or widowed, between the 1st marriage indicated and diagnosis of cervical cancer.

** DK, data unavailable at the time of this report.

 marry women destined to develop cervical cancer, does not appear very likely.

Acknowledgments

I am grateful to Lucy Hare and her staff for their technical assistance.

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