Reprint from: ADOLESCENT MEDICINE: State of the Art Reviews
Volume 7, Number 1, February 1996, Philadelphia

Human Papillomavirus Infection

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Condyloma acuminata, or genital warts, is the anogenital expression of human papillomavirus infection (HPV), and is the most common viral sexually transmitted disease (STD) in the United States. If subclinical infection is considered, it is many times more frequent than any other STD. Its rapidly increasing frequency, with an estimated increase in incidence of 459% from 1966 to 1981,[5] has engaged the interest of epidemiologists; its role in the pathogenesis of cancer of the cervix has unleashed a great deal of research by basic scientists studying the mechanisms of this relationship. Primary care physicians are seeing more of these patients and are being encouraged to identify and treat HPV-infected males vigorously to reduce the rapidly rising rate of cervical cancer.[10] HPV infection in the male produces common and plantar warts. condyloma acuminata, and subclinical condyloma (also called flat condyloma) and is strongly associated with penile and anal carcinoma. It produces in women the same kinds of warts and condylomata, but also a cervical condition called squamous intraepithelial lesion (previously called cervical intraepithelial neoplasia), believed to be a precursor of carcinoma of the cervix.

HISTORY

Condyloma acuminata was a well-known disease in ancient Roman and Hellenic ages. *Condyloma* comes from the Greek "round tumor," and *acuminata* is from the Latin for "sharp points." Both of these seemingly exclusive descriptive terms are used because from a distance the condyloma looks like a round skin tumor, but up close the surface of most is irregular and multiple projections of wart tissue. The ancients knew both is venereal origin and that perianal condylomata were common among homosexual males. That condylomata occasionally underwent spontaneous remission was noted by the ancients, and Hippocrates recommended treatment by powdering them with alum and excisio.[22] Celsus (25 B.C.-50 A.D.) was probably the first to deduce that both common and plantar warts shared an etiology with genital warts, and in one Juvenal's *Satires* there is mention of a physician operating on anal warts.[1] At the time of the European outbreak of "malignant" syphilis at the end of the fifteenth century, there was no causal distinction between genital warts, syphilis, or gonorrhea, all of which were believed to be mere manifestations of a venereal poison. The infectious cause of condyloma acuminata was demonstrated in 1917 by the experimental transmission of the disease from penile condyloma tissue.[24] By 1920, a standard venereology textbook was recommending curetting them, with large lesions to be treated with topical formalin.[22] Topical podophyllin was first reported to be effective in 1942 by Kaplan.[16]

VIROLOGY

A wart is an epidermal tumor caused by HPV, one of the papovavirus family. It is now known that there are more than 60 specific types of HPV; nucleic acid hybridization studies are required to identify the type by its DNA. The differentiation has some clinical significance because common and plantar warts are generally associated with types 1 and 2; the lower genital tract tends to be infected with types 6, 11, 16, 18, and 32; and the external anogenital skin is usually infected with types 6 and 11. Cancer of the cervix is generally associated with either type 16 or 18. Type 11 is the usual cause of laryngeal disease of the newborn.

There are several kinds of nucleic acid hybridization tests for HPV differentiation: Southern blot hybridization, dot-blot hybridization, in situ hybridization of tissue sections, and the polymerase chain reaction (PCR). Schneider and Grubert[27] reviewed these methods with particular attention to their degree of sensitivity, specificity, and cost. The PCR is the most sensitive method and can detect as few as 10 to 100 copies of the genome, but this hypersensitivity can lead to false-positive results because of low-level contamination with extraneous HPV sequences.[29] Although a dot-blot hybridization test on a biopsy or endourethral swab specimen is available commercially to American physicians (Roche Diagnostic Laboratories throughout the United States), its cost, $104 (1995), and the fact that knowing the specific type does not affect the treatment plan make this a rarely used test outside of a research project. Unfortunately, the virus cannot be propagated in tissue culture.

IMMUNOLOGY

No reagents are available to test for either the body's humoral or cellular immune responses to HPV. Epidemiologic studies of HPV infection are therefore hampered by the lack of a type-specific antibody assay able to detect evidence of past infection. Warts do increase in size and number, however, when there are deficient numbers of T cells, and biopsy specimens of regressing warts show evidence of cellular immune response, so this is presumably the principal defense.[18]

EPIDEMIOLOGY

The first modern study demonstrating the sexual route of transmission of HPV was in 1954, when Barrett and colleagues[2] observed 24 women with genital warts, all of which had appeared within 4 to 6 weeks of the patients' husbands return form the Korean War. All of these men admitted to sexual contact with women in the Far East, and all of them had recently had penile warts.

It is now known, however, that visible warts are "only the tip of the iceberg." A West German study of normal men, mostly blood donors, tested exfoliated penile skin samples for HPV DNA.[14] It showed that 8% of 356 men between ages of 16 and 35 years had HPV DNA detected but only 2% of 174 men between 36 and 85 years of age. In another study of 80 male college students attending a college health service in Vermont, HPV-DNA was shown to be present in the exfoliated skin cells of 11%, and another 2% had clinically apparent condylomata.[11] This frequency can be compared with the much higher percentage of inapparent clinical infection in sexually active young women in the United States. Rosenberg and associates[26] reported a 54% prevalence rate of HPV DNA detected in Papanicolaou smears of women with multiple lifetime sexual partners who were attending an Adolescent Clinic in the Bronx, New York. They found that only 8% of the HPV-infected patients had clinically evident condyloma acuminata.

A review of the epidemiologic data by Koutsky and colleagues[19] in 1988 concluded that in the United States there was a 10% prevalence of genital HPV infection among men and women ages 15 to 49 years. One percent have condylomata, 2% have lesions visible only by magnification with a colposcope or magnifying glass, and 7% have clinically inapparent infection. Many of the latter, if tested for acetowhitening (see subsequently), might have become apparent as subclinical disease. In women, the presence of HPV DNA is inversely related to age, with the highest prevalence in those under 25 years of age.

HPV is readily transmitted during genital-genital contact, and moisture and abrasion of the epithelial surface probably enhance transmission. The incubation period varies from 3 weeks to 9 months or more, with the average being 3 months. There are anecdotal reports, however, of HPV infection appearing in one partner after several years of monogamy, suggesting the probability that on occasion the incubation period may be several years before visible disease is recognized. Transmission by fomites such as towels or toilet seats is believed to be possible but extremely infrequent because it is rarely seen in nonsexually active people such as children.

Most male sexual partners of women with condylomata or cervical cytology changes of HPV (i.e., *dysplasia* or squamous intraepithelial lesion) have clinically apparent condylomata if an acetoenhanced androscope is used to examine them.[25]

ONCOGENESIS

Many data link HPV infection to genital cancer, including the following:

1. Since the 1970s, it has been apparent that HPV could produce in the cervical epithelium a progression of cytologic changes from precancerous koilocytic lesions to dysplasias, intraepithelial neoplasia, and invasive carcinomas.[23]
2. It is known that carcinoma of the cervix has features of a STD because its major risk factors include having multiple sex partners and having first intercourse at an early age.[15]
3. More than 90% of cervical cancer specimens contain HPV genomes, 70% of them types 16 and 18[12] These genomes are also present in metastases.

4. There is an increased risk of cervical neoplasia in the consorts of men with penile condylomata.[4] An epidemiologic study of Hispanic women with cervical cancer showed that cases and controls did not differ in their number of sexual partners; however, the cancer patients were five times more likely to be married to a husband who reported having had 20 or more sexual partners than the control partners.[32]

5. Cervical cancer is nearly unknown among celibate Catholic nuns and other virgins [17]

6. Penile carcinomas contain HPV DNA in half of those sampled in one study[21]; 40% contained type 16 HPV and 9% type 18.

7. An epidemiologic study of patients with anal carcinoma revealed that histories of receptive anal intercourse and genital warts were both risk factors for its developments.[7]

Obviously the preceding data are far from accomplishing Koch's postulates regarding cause and effect, but the data definitely suggest that HPV is at least a major factor, or cofactor, in the pathogenesis of genital epithelial cancer. The previous data are enough evidence, however, to support those who argue that by vigorously treating men, the frequency of cervical cancer in women can be reduced in future years.[10]

CLINICAL MANIFESTATIONS

Classic condyloma acuminata are the most frequent form of genital warts (Fig. 1). They are soft and flesh-colored, have an irregular surface, and are 2 to 5 mm in diameter. They can appear anywhere on the anogenital area but are most common on the frenulum, the coronal sulcus of the penis, and inside the preputium. Papular warts are a subset of condyloma acuminata lesions; are usually multiple, 1 to 5 mm in diameter frequently darker than the surrounding skin, with a smooth surface; and are seen principally in relatively dry areas such as on the penile shaft. With androscopy, punctate red spots on the surface representing loop capillaries can frequently be seen, which are pretty well typical of HPV lesions, both classic condylomata and papular warts. Condyloma plana (or *flat condylomata*) are areas of either normal-appearing or slightly elevated skin that are acetowhite and that on biopsy demonstrate the histologic picture of HPV infection; these are considered to be subclinical infection.

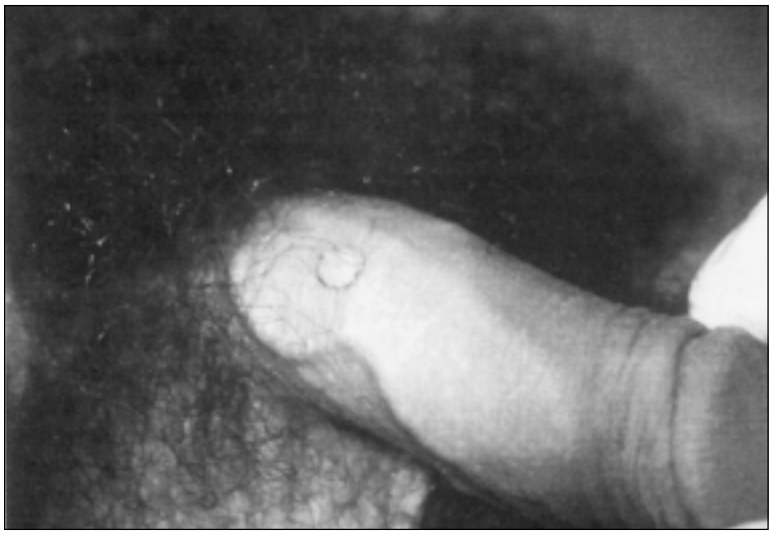

FIGURE 1. Classic condyloma acuminata lesion.

The presence of perianal condylomata does not indicate that rectal intercourse must have occurred because vaginal secretions containing the virus can easily reach the perianal region during heterosexual intercourse, and the virus seems to find moist areas, such as the perianal skin and under the prepuce, hospitable for its growth. The presence of exophytic condylomata visible in the urethral meatus does not warrant further urethroscopic investigation, as Rosenberg and colleagues[25] found no proximal urethral involvement in any of the 51 men they examined with endoscopy because of condylomata in this location.

The natural history of anogenital warts is that 17% of untreated warts spontaneously disappear by 16 weeks and 70% by 2 years.[30]

ANDROSCOPY

During the past decade, there have been several reports of the usefulness of the gynecologist's colposcope in examining the male patient suspected of having HPV infection, especially if preceded by the application of 5% acetic acid (i.e., household vinegar).[10,28] The combined procedure when used on male patients is called *acetoenhanced androscopy* and is indicated for all men whose sexual partners of either sex have been diagnosed with (1) condyloma acuminata, squamous intraepithelial lesion, or cervical cancer or (2) who present for a complete evaluation for a possible STD either because of an unprotected sexual contact or because they have clinically evident condylomata or other STD.

The importance of properly examining the male sexual partners of women with one of the above-mentioned lesions was demonstrated by Sedlacek and coworkers." His group examined 51 men who were the sexual partners of women who had biopsy-proven condyloma. Although only 8 of the 51 men had papules identified with the naked eye and confirmed histologically, all 51 demonstrated acetoenhanced lesions with androscopy, and biopsy showed the histologic changes of HPV infection in 45 of them. In another larger study of 199 male partners of HPV-infected women evaluated by Rosenberg and coworkers,[25] acetoenhanced androscopy revealed that 73% had evidence of HPV infection.

Androscopy Method

The patient, undressed from the waist down, lies on the examining table in the dorsal lithotomy position with his feet in the heel supports. A 5% acetic acid solution in a spray bottle is sprayed over the genitalia and perineum. The solution should be applied liberally, and the patient's buttocks should be on some absorbent material for comfort because he will have to lie there for 3 to 5 minutes before the examination commences as it takes that long for the "reaction" to occur. Most practitioners performing this procedure also soak a 4 x 4 gauze pad with the solution and wrap it around the penis to ensure continuing contact with the skin.

Using either a colposcope or a strong magnifying glass, the entire genital-scrotal- perianal area should be carefully searched for condylomata, which may or may not be acetowhitened; whitening of an area of otherwise normal-appearing skin indicates a subclinical infection (condyloma plana). Sometimes that white area has a slight thickened appearance under magnification. Many authors recommend obtaining a biopsy specimen of all but the most obvious genital warts on males[10,29]; however, most practitioners, including the author, rely on their vision, magnification, and the results of the acetic acid test to make the diagnosis. Unfortunately, not all condylomata turn white with acetic acid. In the author's experience, only about half of clinically obvious condylomata are acetowhite positive; however, the application of this solution has frequently identified small papules, which under magnification are obviously HPV infection but that would have been missed without this added test. Unfortunately, acetowhitening is not specific for HPV, and other skin conditions, such as an abrasion, eczema, or monilial dermatitis can give a false-positive test; however, the magnified surface scanning should readily distinguish whether this is condyloma. If perianal condylomata are observed, anoscopy should be performed.

Lesions that may be misidentified as condylomata include pearly penile papules (those normal coronal papules appearing during adolescence in perhaps 5% of males) and sebaceous and follicular hyperplasia, both producing 1 to 3 mm smooth swellings located on the proximal third of the penis, the latter usually having a hair emerging from it (sometimes so small it can be seen only with the androscope). Both of these lesions are perfectly normal.

The urethral meatus should also be examined by everting each side with the examiner's thumbs, allowing magnified inspection of up to a centimeter of the distal urethra, the location of most urethral condylomata.

It should be noted that minor degrees of acetowhitening of the scrotum (without abnormal thickening of the skin) are frequently seen and are best left unexplained and observed rather than biopsied. Rosenberg and coworkers[25] observed but did not treat 17 such patients and observed regression in 35% of them. This "condition," whatever it is, deserves further study.

TREATMENT

Although condylomata can disappear spontaneously after several months, aggressive treatment of clinical lesions seems likely to reduce the chance of further transmission. There is no scientific evidence of this, however, and the Centers for Disease Control in their 1993 STD Treatment Guidelines has actually suggested that their removal is primarily for cosmetic reasons.[6] As mentioned before, however, other authorities believe they should be treated aggressively in both men and women to reduce the frequency of cervical cancer.

For most primary care providers, the choice of a treatment modality for anogenital condylomata of the male rests between podophyllin, trichloracetic acid, 5-fluorouracil, or cryosurgery with liquid nitrogen. lntralesional injection of interferon has been studied in several randomized trials; not only was the remission rate not as good as the older methods, but also it has a 21 % to 25% recurrence rate, and the cost for a series of treatments was high, $1500 in 1990.[20] An even more expensive modality is carbon dioxide laser therapy. It requires local anesthesia, in the male, at least, and there is little evidence to suggest that its remission of recurrence rates are better than other much less costly treatments. It does, however, have a role in treating either extensive or refractory lesions.

Cryotherapy

Freezing the wart and a few small millimeters of surrounding tissue can induce remissions in most cases of condyloma in the male, although about a third of cases recur within the next 12 months. This should probably be the treatment of choice for most primary care practitioners.

Liquid nitrogen is the usual cryogen. The author's practice is to dip a cotton swab into a styrofoam cup containing some liquid nitrogen and then apply the swab to the lesion keeping it a frozen-white for 40 seconds. This is mildly painful for the duration of the treatment and for a few minutes thereafter. This treatment is repeated every 2 weeks until the wart is gone and the area smooth. It is theoretically important to include freezing of a small margin of normal-appearing tissue surrounding each wart because HPV DNA has been found in the skin as far out as 50 to 10 mm from the visible wart (Fig. 2).

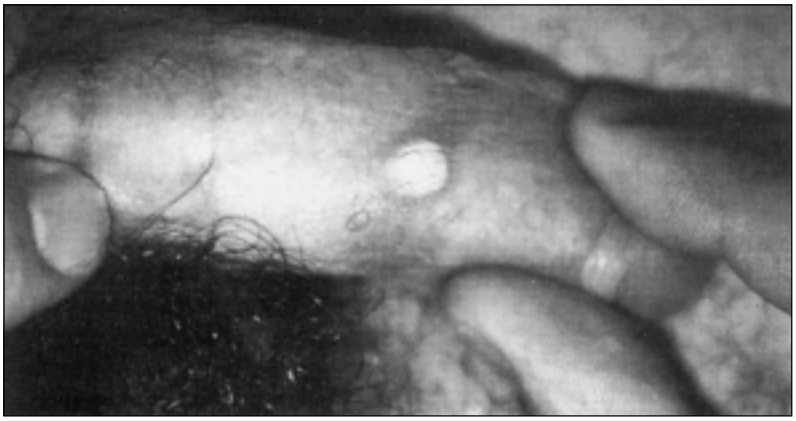

FIGURE 2. Frozen area including several millimeters of tissue surrounding the condyloma.

Over the next few days, the treated area will show signs of mild inflammation and will then probably blacken (Fig. 3). Treatment on a weekly basis is complicated by the presence of either acute inflammation or the blackening obscuring the size of the remaining wart, so 2-week intervals between treatments seem optimal. About a third of penile lesions require only one treatment before resolution, and almost all are gone with the above-mentioned regimen by 8 weeks. At that point, there is just an area of hypopigmentation (Fig. 4) left to identify where the treatment has been applied. This is most noticeable on dark-skinned patients, but even with them repigmentation occurs within a few months.

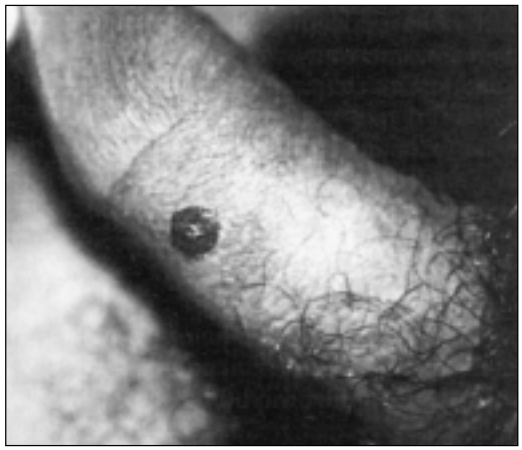

FIGURE 3.
Clinical appearance of treated area l week after cryosurgery.

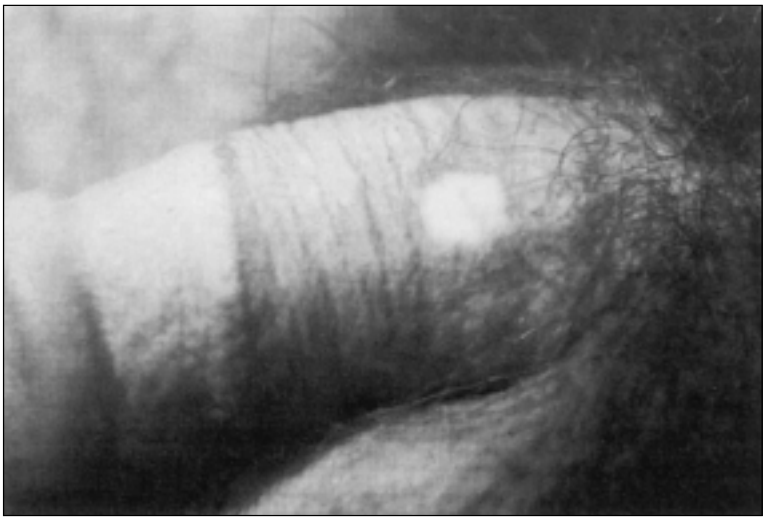

FIGURE 4. Hypopigmented area present 2 months after a series of cryosurgical treatments of condyloma.

Unfortunately, liquid nitrogen evaporates slowly in its container, and therefore it is not cost-effective for primary care physicians in solo or small group practices to maintain a supply. The development of a canister containing dimethyl ether and propane (Histofreezer®) for cryosurgery has eliminated this problem (Fig. 5). This closed container does not lose the cryogenic mixture by evaporation during storage between patients, and at least 15 patients can be treated with each canister. Its effectiveness is probably comparable to liquid nitrogen.[9] The device uses a disposable hollow applicator to carry the mixture down to the treatment head, and it is used as described previously.

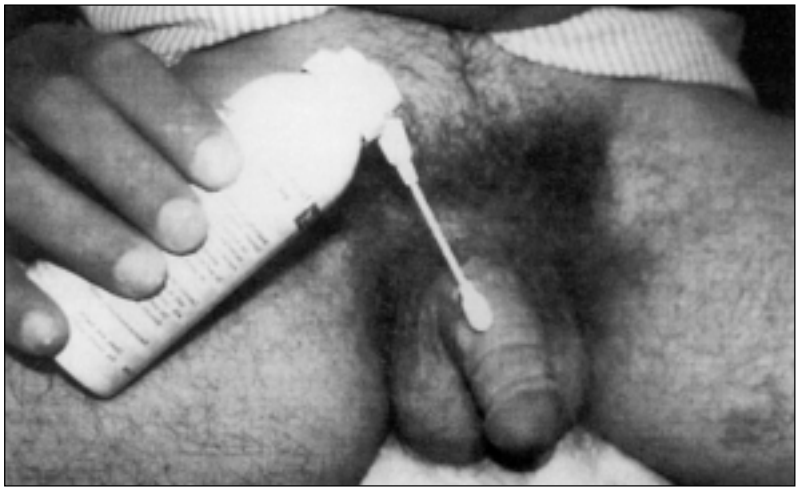

FIGURE 5. Cryosurgical unit (Histofreezer®) in position to begin treatment of condylomas. (Held by patient for demonstration purposes only.)

Podophyllin

Podophyllin resin is an extract from the May apple (mandrake) plant. It is perhaps the most widely used treatment for treating the male with condyloma; however, its cure rates have ranged from only 22% to 77%, with recurrence rates as high as 74%.[20] It is mainly effective on warts that are either located on mucosal tissue (meatus, anal canal) or other moist areas (perianal, preputium), and it is less effective for keratinized lesions (penile). The usual formulation is 25% in tincture of benzoin (Podofin), and this is touched to the lesion using a cotton-tip swab, taking care to use a new swab whenever it is dipped into the bottle containing the podophyllin solution to avoid possible cross-contamination. The patient is instructed to wash the solution off in 4 to 5 hours. Treatment is repeated weekly in the physician's office, and six or more treatments may be necessary. There is a milder inflammatory reaction than is seen with liquid nitrogen and much less discomfort.

Podophyllotoxin, one of the active components of the podophyllin resin (Condylox), has been approved by the Food and Drug Administration for self-application at home, but because of the possibility of systemic absorption is not recommended for perianal or mucosal lesions. Its efficacy is similar to podophyllin.[31] It is applied to the lesions every day for 4 consecutive days each week until either the lesion is gone or four weekly treatment segments are completed. Failure at that point to go into remission indicates another treatment modality should be tried.

Trichloroacetic Acid

Chemodestruction with acids such as trichloroacetic (TCA) has been used for many years in treating condylomata. Although TCA has been recommended as being suitable for home treatment (applying the acid to the lesion every other day until remission or 4 weeks have passed), because of the risk of skin irritation or ulceration, most physicians prefer to apply the caustic themselves on a weekly or twice weekly regimen. Other authors have abandoned the use of this form of chemodestruction because of the wide variety of more controllable therapies available.[3] One randomized clinical trial of TCA indicated that its effectiveness and and frequency of local adverse reactions were comparable to cryotherapy.[13]

5-Fluorouracil

Although the Food and Drug Administration has not approved the use of 5% 5-fluorouracil (5-FU) cream (Efudex) for condyloma, it is being used by physicians as a result of (uncontrolled) clinical trials, in which from 10% to 73% of patients with condylomata went into remission, as did 25% and 95% of men with urethral lesions. This antimetabolite drug is more commonly used to treat a variety of skin neoplasms and precancerous lesions such as actinic keratosis. It has been used by clinicians for treating urethral condylomata for 20 years since Dretler and Klein[8] in 1975 treated 2 such patients with 5% 5-FU by means of daily instillation of the cream and found that 19 of 20 visible visible condylomata were eradicated quickly, usually within 3 to 8 days. It can also be used on more routine anogenital condylomata, however, apparent or subclinical, with good effect.

METHOD

Urethra. Instill 0.5 ml of the 5% 5-FU cream using a tuberculin syringe without a needle, and "milk" it to the proximal Urethra. Use nightly after voiding for 3 nights, then every other night to tolerance or visible and symptomatic remission. Adjust the treatment frequency as indicated by individual patient response. The significant adverse effect is local irritation; to prevent irritation of the scrotum, a scrotal support with a penile aperture as well as a condom should be worn through the night and the adjacent thighs protected with petrolatum ointment.

External Skin and Anus. Apply a thin film at night to the lesion on 2 consecutive days per week or daily to tolerance. The adjacent skin also needs to be protected as previously with petrolatum ointment, a scrotal support, and a condom.

FOLLOW-UP

All patients with condyloma acuminata, as with patients with any STD, should be offered tests for other STDs at the time of diagnosis. In the author's practice, this consists of serologic tests for human immunodeficiency virus (HIV) and syphilis and a first-void urine sample with dipstick leukocyte esterase as a screen for gonococcal or chlamydial urethritis. If the dipstick is positive, an endourethral swab is obtained for culture (or DNA probe) for chlamydia and gonococcus. A discussion of safer sex practices is also indicated. After complete remission, the author advises patients to return for repeat examinations with acetoenhanced androscopy every 2 months until they have been in continuous remission for 12 months, after which their chance of relapse is quite low and they need to be seen only if there is a relapse.

It is not known whether men who have been in continuous remission for more than a year are contagious during sexual activity, and it is difficult to imagine the kind of clinical research that could settle the question. Because most regular male sexual contacts of women with HPV infection can also be found to have HPV infection using acetoenhanced androscopy, it could be argued that if acetoenhanced androscopic-negative men who had had a successfully treated HPV disease in the past were contagious forever, a greater number of them would have been found in studies of consorts, whereas studies repeatedly have found that *most* of the male partners have clinical or subclinical HPV disease (i.e., they are not "silent" transmitters of the disease).

The author advises sexual abstinence until the patient is in remission, then condoms should be worn to protect (to a degree) their sexual partners during the first year of remission. Continuing that advice after that depends on whether the physician believes in the likelihood of the "contagiousness-forever theory." The final answer to that question will have to await further epidemiologic studies.

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