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Human papillomavirus infection

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The human papillomavirus, well known as the etiologic agent of warts, has recently received much attention in the medical literature for its association with various cancers. This article discusses the virology, epidemiology, pathogenesis, immunology, clinical manifestations, and therapy for human papillomavirus infection. Some newer techniques for identifying human papillomavirus in tissue, based on recent advances in molecular biology, are also covered. Two final topics addressed are human papillomavirus infection in the immunocompromised host, including patients with acquired immunodeficiency syndrome, and the possible role of human papillomavirus in several different carcinomas. (J AM ACAD DERMATOL 1990;22:547-66.)

Warts, or verrucae, are benign epidermal proliferations that have been recognized for thousands of years. The ancient Greeks and Romans observed that anogenital warts were sexually transmitted.[1] Celsus (cited by Lutzner[2]) in the first century AD described three types of warts: "ficus" (fig), referring to genital warts; "thymion" (thyme plant), indicating the common wart; and "myrmecia" (anthill), meaning the deep plantar wart. Warts were regarded as infectious by the end of the nineteenth century and a viral etiology was suggested in 1907 when Ciuffo[3] demonstrated the transmission of warts by a sterile, cell-free filtrate of wart tissue. Strauss et al.[4] isolated crystalline viruslike particles from skin papillomas in 1949. The virus has subsequently been identified as a double-stranded DNA virus that belongs to the family *Papovaviridae*. Recently, the papillomavirus has enjoyed the medical limelight because a large body of research and literature implicates it in the development of some forms of human cancer. In view of this new twist to an ancient infection, it is important to be well versed in the biology, clinical manifestations, and therapy for human papillomavirus (HPV) disease.

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VIROLOGY

The papillomaviruses have traditionally been considered members of the family *Papovaviridae*, which includes polyomaviruses and the vacuolating agent, simian virus 40 (SV40). The latter two are well-studied oncogenic viruses that regularly produce a variety of tumors when inoculated into newborn rodents.[5] The papillomavirus contains double-stranded, circular, supercoiled DNA enclosed in an icosahedral capsid made up of 72 capsomers. The viral particle or virion has a molecular weight of approximately 5×10^6, of which 88% represents viral protein. The virus has no envelope and is resistant to ether inactivation, freezing, and desiccation. Papil-

Table I. HPV types and their clinical associations

HPV-1	Deep plantar warts, common warts
HPV-2	Common warts, flat warts
HPV-3	Flat warts
HPV-4	Common warts, plantar warts
HPV-5	EV
HPV-6	Genital warts, laryngeal papillomas
HPV-7	Common warts in meat handlers
HPV-8	EV
HPV-9	EV, keratoacanthomas
HPV-10	Flat warts
HPV-11	Laryngeal papillomas, genital warts
HPV-12	EV
HPV-13	Focal epithelial hyperplasia
HPV-14, -15	EV
HPV-16	Genital warts, bowenoid papulosis, cervical dysplasia, cervical carcinoma
HPV-17	EV
HPV-18	Genital warts, bowenoid papulosis, cervical dysplasia, cervical carcinoma
HPV-19 to 25	EV
HPV-26 to 29	Common warts, flat warts
HPV-30	Laryngeal carcinoma, genital warts
HPV-31, -32	Genital warts, bowenoid papulosis, cervical dysplasia, cervical carcinoma
HPV-33	Cervical carcinoma
HPV-34	Bowenoid papulosis, Bowen's disease
HPV-35	Cervical dysplasia, cervical carcinoma
HPV-36	EV
HPV-37	EV, keratoacanthomas
HPV-38	EV
HPV-39	Bowenoid papulosis, cervical carcinoma
HPV-41	Flat warts
HPV-42	Genital warts, bowenoid papulosis, cervical dysplasia, cervical carcinoma
HPV-43, -44	Genital warts, laryngeal papillomas
HPV-46, -47	EV
HPV-48	Bowenoid papulosis, Bowen's disease
HPV-49, -50	EV
HPV-51 to -54	Genital warts, bowenoid papulosis, cervical dysplasia, cervical carcinoma
HPV-55	Genital warts, laryngeal papillomas

Adapted from Beutner[7] and Gross.[15]

lomaviruses have some biologic differences from other papovaviruses and are now recognized as a distinct virus group.[6] The DNA genome of the papillomavirus has 8000 base pairs compared with 5000 found in the polyomavirus, with a correspondingly larger capsid diameter of 55 nm compared with 40 nm. Finally, papillomaviruses have never been successfully propagated in tissue culture whereas other papovaviruses have.

Animal papillomaviruses have been found in various hosts, including cattle, horse, deer, elk, sheep, dogs, rabbits, chimpanzee, and mice. An avian virus infecting the chaffinch has been described, the only nonmammalian papillomavirus.[7,8] With few exceptions, these viruses have been shown to be highly host specific.[9]

Serologic typing, as applied to some other human viruses, is not readily available for HPV. Antisera have been generated against viral capsid protein antigens. When disrupted virions are used as the antigenic source, an antiserum reacting to all HPV types is produced.[10-12] Even when intact virions are used, the resulting antisera show some cross-reactivity between HPV types[12,13] and are unable to distinguish reliably among different isolates.[6] Therefore DNA hybridization has been used as a means of separating different HPVs. By convention, viruses that hybridize by less than 50% with other known types are classified as a new type.[14] It is important to realize that 50% hybridization implies approximately 90% identity at the DNA sequence level.[1] If an isolate has greater than 50% DNA homology with a known type but a distinctive restrictive endonuclease pattern, it is designated a subtype alphabetically. To date there have been 55 HPV types identified and new types continue to be isolated.[7] For many of these types there are significant clinicopathologic correlations (Table I).

EPIDEMIOLOGY AND NATURAL HISTORY OF HPV INFECTION

Although the prevalence of warts in the general population is unknown, an incidence of 10% has been estimated for children and young adults.[16] In Great Britain, 10% to 25% of new patients who present to dermatologic clinics do so for treatment of warts.[17] The peak incidence of warts occurs between 12 and 16 years of age; 70% are common warts, 24% are plantar warts, and 3.5% are plane warts. Anogenital warts have increased in incidence in recent years as documented by a 28-year epidemiologic survey of patients from Rochester, Minnesota.[18] Between 1950 and 1978, Chuang et al.[18] noted a general increase in the average annual incidence rates of the disease for each consecutive 5-year interval examined, with an annual rate of 106.5 per 100,000 in the period 1975 through 1978. A report from the *Morbidity and Mortality Weekly Report*

documents a fivefold increase in the n umber of visits for condylomata acuminata from 1966 to 1981.[19] The incidence of HPV infections is increased in patients with depressed cell-mediated immunity; up to 43% of immunosuppressed kidney transplant patients have warts.[20]

The transmission of HPV to an uninfected person usually occurs by close contact with someone infected, although desquamated keratinocytes also may transmit the virus.[1] Small breaks in the skin may be necessary to inoculate HPV. This explains the frequent localization of warts to traumatized areas (hands, feet, knees) and the Koebner phenomenon seen with flat warts. Autoinoculation accounts for the local spread of warts and the appearance of apposed lesions on adjacent digits. Many factors are important in the infectivity of HPV, including the number of viral particles in the lesion(s) contacted (determined in part by lesion type and location), the degree of exposure to the lesion(s), and the host's defenses against HPV infection. Cell-mediated immunity, as will be discussed later, is believed to be important in the host response to HPV. Experimental inoculation studies have shown verrucae take 1 to 6 months to become apparent.[16]

Much of our knowledge about the infectivity and subsequent incubation period of HPV infection comes from the study of anogenital warts. One large, single center study followed 97 persons who had had sexual intercourse with those known to have genital warts at the time.[21] After 9 months 64% of them had developed genital warts. Similarly, Barrasso et al.[22] detected condylomata acuminata, papules, and acetowhite macules in 64.4% of 480 male sexual partners of women with cervical flat warts and cervical intraepithelial neoplasia. It appears that genital warts are less infectious the longer they are present. Oriel[21] found that men whose contacts developed warts had had their lesions for an average of 3½ months before sexual intercourse whereas men whose contacts remained free of warts had had theirs for an average of 12 months. The average incubation time in Oriel's study was 2.8 months (range 3 weeks to 8 months). De Jong et al.[23] quoted a range of 1 to 20 months.

In examining the possibility of genital warts arising from common warts, Oriel[21] found no difference in the incidence of common warts in men with or without genital warts (~18%). The recent availability of HPV typing also provides evidence against this route of transmission for most genital warts. Most genital warts contain HPV-6, -11, or -16 whereas most common and plantar warts contain HPV-1, -2, and -4 (Table I). However, there have been isolated reports of the detection of HPV-1 and HPV-2 in genital warts, supporting occasional nonvenereal transmission.[24,25]

Anogenital warts are also being reported with increasing frequency in children.[23,26] In this population, the route of transmission becomes of paramount concern in the assessment of potential child abuse. Although pediatric condylomata acuminata may be transmitted during delivery or from close nonsexual contact,[23] recent literature implicates sexual transmission in most cases. Herman-Giddens et al.[27] examined 11 girls younger than 12 years of age who presented with genital warts for the possibility of sexual abuse. Ten of the 11 patients had historic or physical evidence (vaginal trauma or concomitant infection) to confirm sexual abuse. Another group examined the genital warts of five children for the presence of HPV DNA by molecular hybridization.[28] In three patients HPV-6 was found, in one patient HPV-16, and in the remaining patient an HPV typed as 6 or 11. As these three types are commonly found in adult condylomata and not in common or plantar warts, transmission sexually or during delivery was supported. In three of the five cases sexual abuse was suspected. The authors concluded that transmission of genital warts to children is most often venereal but that "nonvenereal transmission should be considered when there is no evidence of child abuse, when the lesions are somewhat distant from the anus or introitus, and when the child is less than 9 months of age when the lesions first appear." (page 1132).[28] An American Academy of Dermatology task force on the subject of genital warts and sexual abuse in children (Norins et al.[29]) concluded that at least 50% of pediatric cases of genital warts can be documented by investigators as sexual abuse and that when anal or genital warts are found in children younger than 12 years of age, sexual abuse should be considered.

CLINICAL MANIFESTATIONS OF HPV

The clinical lesions that result from HPV infection can be divided into two broad categories, cutaneous and extracutaneous. The cutaneous lesions include common warts (verruca vulgaris), filiform warts, flat warts (verruca plana), plantar warts (including myrmecia and mosaic types), anogenital warts, and bowenoid papulosis. Extracutaneous le-

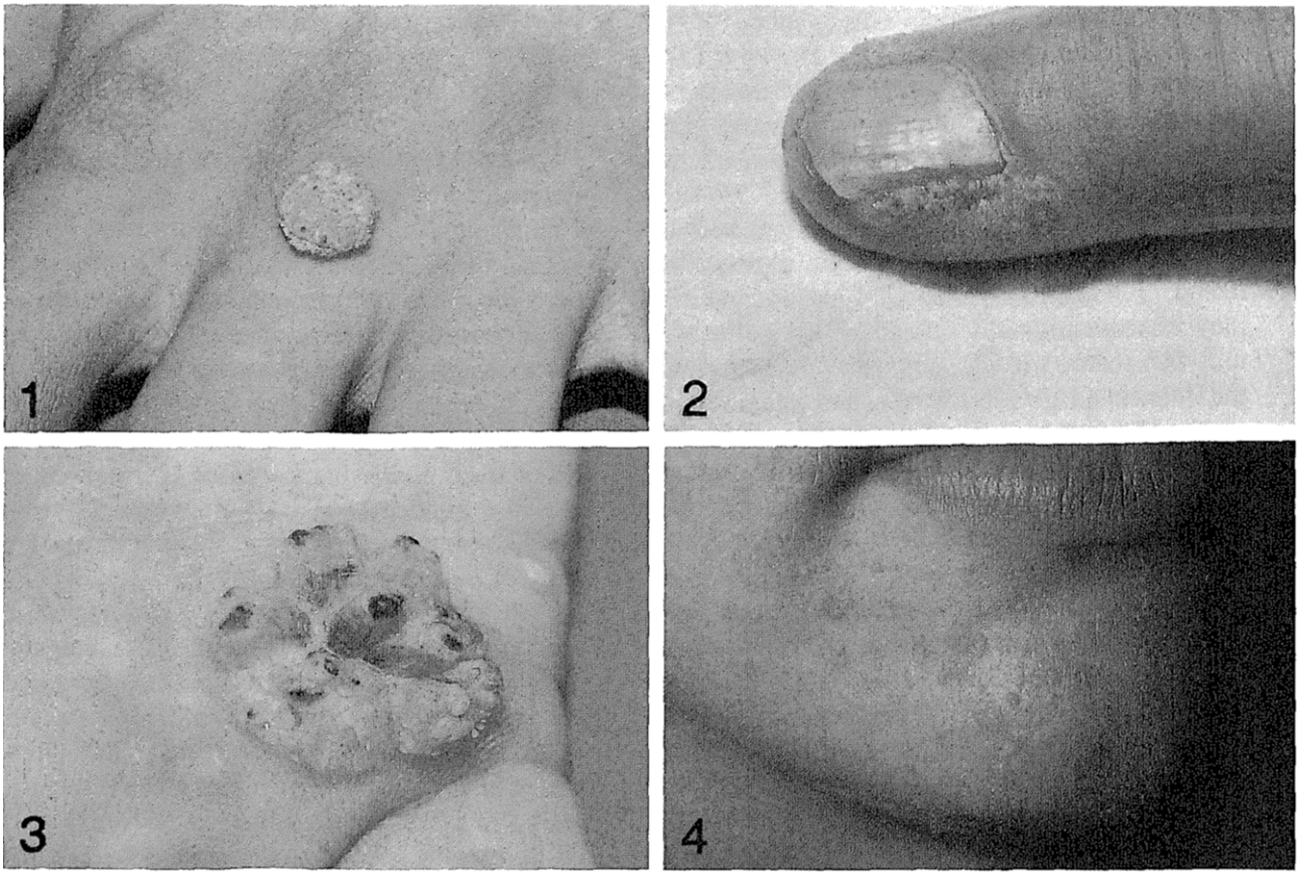

Fig. 1. Common wart on the back of the hand.
Fig. 2. Periungual wart with nail dystrophy.
Fig. 3. Common wart with cutaneous horn formation.
Fig. 4. Flat warts on the chin.

sions occur on orificial mucous membranes and include oral common warts, oral condylomata acuminata, focal epithelial hyperplasia, oral florid papillomatosis, nasal papillomas, conjunctival papillomas, laryngeal papillomatosis, and cervical warts (including exophytic, flat, and inverted types).

Common warts are rough, keratotic papules that may appear singly or grouped on any cutaneous surface (Fig. 1). They are most commonly located on the dorsal aspect of the hands and fingers and on the knees in children. Periungual warts may involve the hyponychium and nail bed and may cause a local nail dystrophy (Fig. 2). Although common warts can form at sites of trauma, the Koebner phenomenon is more common in flat warts. Butcher's warts, caused by HPV-7 as well as HPV types 1 through 4, are common warts that are found on the hands and fingers of meat cutters.[30] Occasionally, a wart can appear with an overlying cutaneous horn (Fig. 3) or as a long, slender filiform projection. Regression of warts and the associated clinical findings will be discussed later.

Flat warts are slightly elevated, smooth papules that are generally less than 5 mm. They range from flesh colored to gray or brown and usually occur as multiple lesions on the face, hands, and legs of children (Fig. 4). A linear arrangement of lesions, implying an isomorphic response, is common.

Plantar warts usually have a rough, keratotic surface studded with punctate black dots, representing thrombosed capillaries, and a peripheral rim of thickened skin (Fig. 5). When multiple warts coalesce into a large plaque, the term *mosaic wart* is used, whereas the myrmecia type of plantar wart refers to a deep, endophytic lesion. Plantar warts commonly occur beneath pressure ponts such as the heel or metatarsal heads and may cause pain with weight bearing. In patients with concomitant hy-

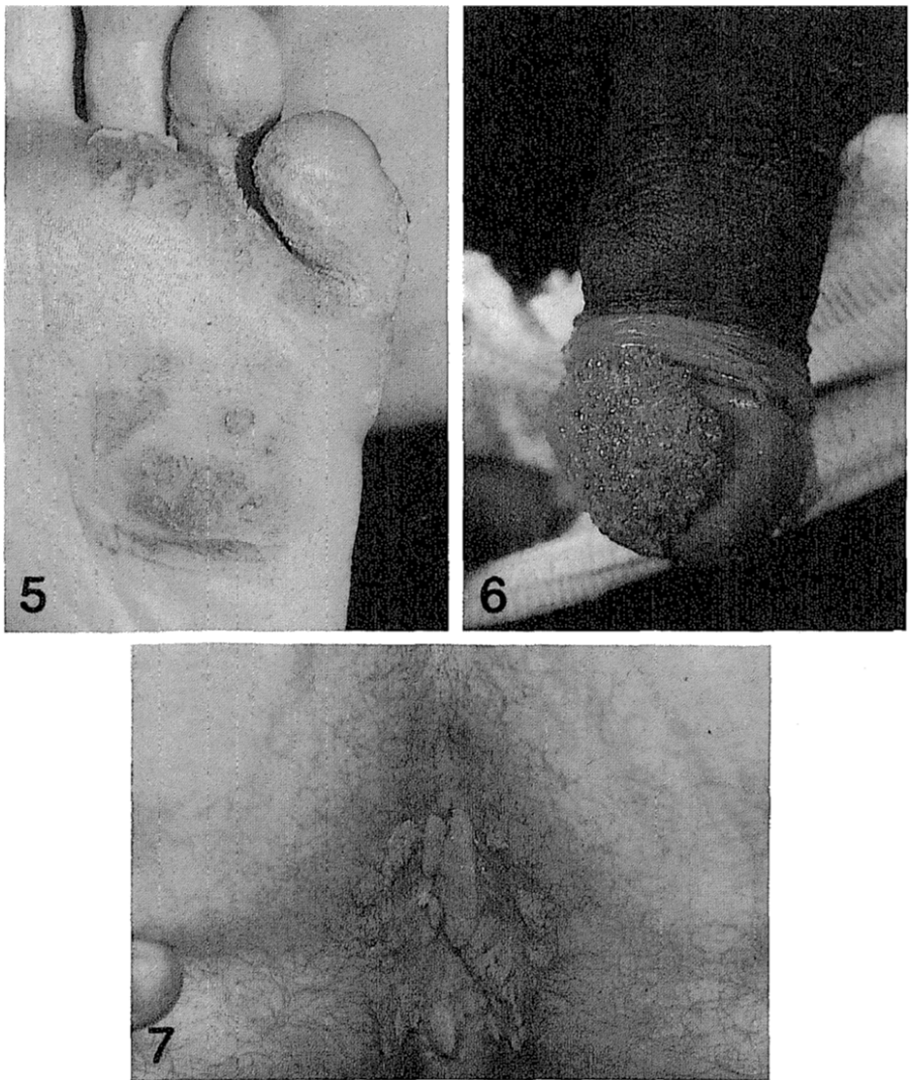

Fig. 5. Plantar wart.
Fig. 6. Condylomata acuminata involving the glans penis.
Fig. 7. Perianal condylomata acuminata.

perhidrosis, plantar warts are frequently widespread and refractory to therapy.

Anogenital warts can be categorized into hyperplastic, cauliflower-like lesions (condylomata acuminata), sessile papules, and keratotic, verruca vulgaris–like lesions. The hyperplastic types are typically soft, pink-to-flesh-colored lesions found on moist areas like the glans penis, inner surface of the prepuce, urethral meatus, anal mucosa, perianal area, and labia (Figs. 6 and 7). The sessile papules and keratotic lesions are seen on the penile shaft. The hyperplastic lesions can become large and exophytic, whereas the sessile papules tend to remain small. During pregnancy, condylomata acuminata can become large and have been reported to obstruct labor and even cause death from sepsis or hemorrhage.[31] Conversely, many cases of genital warts regress after birth.[21]

Recently, small, macular, and slightly elevated lesions have been detected on apparently normal penile skin after the application of 5% acetic acid and with the aid of magnification.[22,32,33] These lesions show histologic changes consistent with condylomata acuminata or intraepithelial neoplasia. Sedlacek et al.[32] examined 51 male sexual partners of female patients who had condylomata acuminata and performed biopsies of identifiable lesions. Of the 45 men with histologically confirmed condylomata,

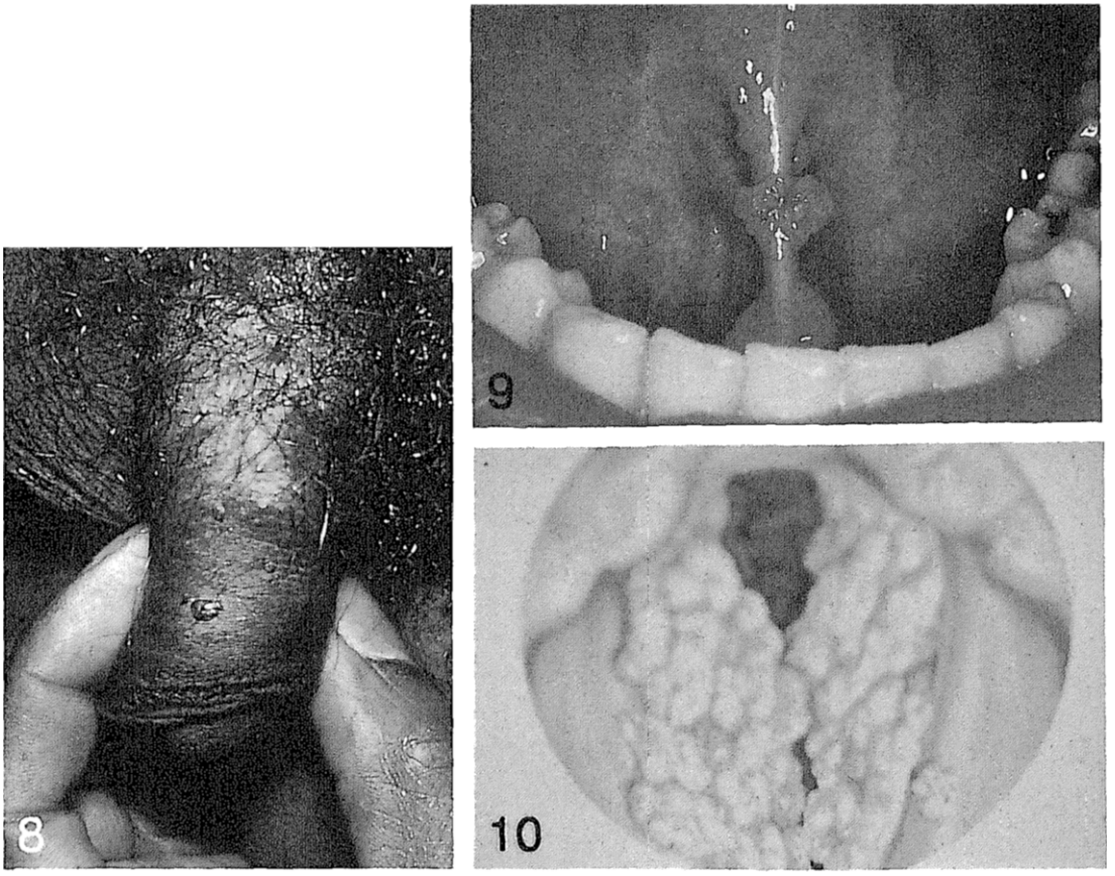

Fig. 8. Hyperpigmented lesions of bowenoid papulosis.
Fig. 9. Oral warts involving frenulum of the tongue.
Fig. 10. Juvenile laryngeal papillomatosis.

37 had lesions visible only after acetic acid application and magnification. Likewise, Barrasso et al.[22] identified 309 men with clinical evidence of genital HPV infection among 480 male sexual partners of women with cervical flat warts or intraepithelial neoplasia. Of these men, 204 (42.5%) had lesions detected only after the application of acetic acid. Therefore this is an important adjunctive diagnostic technique for the detection of HPV infection of the male genitalia.

In recent years, a disorder termed *bowenoid papulosis* has been described. It consists of multiple, small, verrucous or velvety, often pigmented papules that involve the anogenital region of young adults (Fig. 8).[34-36] Histologic examination reveals changes of carcinoma in situ suggestive of Bowen's disease. Observers of this condition report its behavior to be similar to that of condylomata acuminata. Lesions respond to conservative surgical removal, topical 5-fluorouracil, and even undergo spontaneous regression.[35-37] Ikenberg et al.[38] found HPV-16 DNA in 8 of 10 cases of bowenoid papulosis, evidence that this entity is yet another manifestation of papillomavirus infection. However, the benign nature of this condition has been questioned. HPV-16, as discussed later, has been linked to cervical dysplasia and neoplasia. In a study of 11 men and five women with bowenoid papulosis, three of the women had concomitant cervical intraepithelial neoplasia; of six female sexual partners of male patients examined, five had evidence of cervical HPV infection and two partners exhibited severe cervical dysplasia or carcinoma in situ.[39] In 11 of these 16 cases, HPV-16 was demonstrated. Bowenoid papulosis has also been reported to progress to Bowen's disease.[40]

Another newly described condition, vulvar papillomatosis, presents as a velvety, granular, or cobblestone-like surface of the vulvar vestibule.[41,42] On

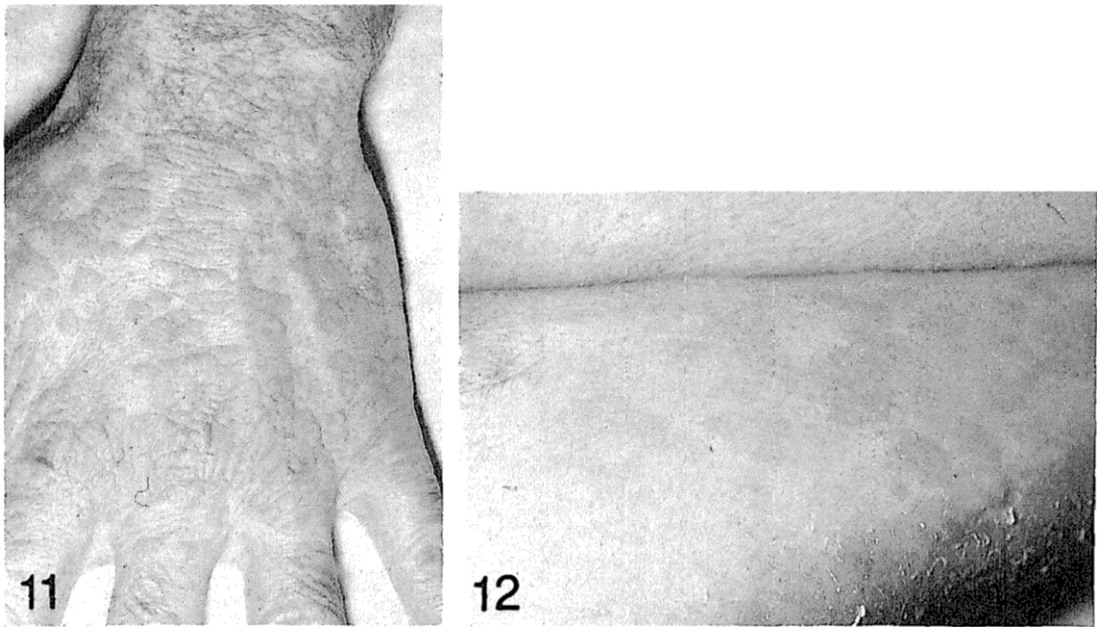

Fig. 11. Flat wart–like lesions of epidermodysplasia verruciformis. (Courtesy Dr. Doug Lowy, Bethesda, Md.)

Fig. 12. Pityriasis versicolor–like lesions of epidermodysplasia verruciformis. (Courtesy Dr. Doug Lowy, Bethesda, Md.)

colposcopic examination, these lesions have been colorfully described as "Arizona cactus–like projections," "camel hump–like projections," and "stony colonial pavement–like projections."[41] Histologically, these lesions demonstrate koilocytosis and with immunohistochemical techniques HPV antigen has been found in some. This diffuse HPV infection may manifest as vulvodynia.

Several extracutaneous HPV infections of mucous membranes are also recognized. Common warts that appear similar to their cutaneous counterparts can occur in the oral cavity, often on the hard palate (Fig. 9). Oral condylomata acuminata have been reported as well. Similarly, nasal and conjunctival papillomas are manifestations of HPV infection. In 1965 Archard et al.[43] described a condition they termed *focal oral hyperplasia,* involving the oral mucosa of American Indian children. The lesions were multiple, discrete, and confluent papules on the labial, buccal, and gingival mucosa as well as the tongue. Most lesions were of the same color as the adjacent mucosa. Subsequent cases have been described in other races, but the condition seems to be rare in whites. Recently, these lesions have been shown to contain HPV-13, a type unique to this condition.[44] Oral florid papillomatosis is characterized by white, vegetating cauliflower-like plaques on the oral mucosa of elderly patients. Whether this condition represents a type of verrucous carcinoma from the outset or rather is verrucous hyperplasia that may progress to carcinoma is the subject of debate.[45, 46] Although papillomavirus has been suspected as an etiologic agent, neither HPV particles nor DNA have been isolated from oral florid papillomatosis.

Laryngeal papillomas, unlike other benign lesions of HPV infection, are potentially life-threatening. These lesions involve the larynx but may also extend into the tracheal, bronchial, and pulmonary epithelia (Fig. 10).[47] Symptoms include hoarseness, aphonia, and stridor and may progress to respiratory distress. These papillomas may become sufficiently large to cause airway obstruction and death. The disease may present in infants or adults but is rarely seen in adolescents. The papillomas tend to regress spontaneously but recurrences and treatment failures are frequent. HPV-6 and HPV-11 have been frequently found in this condition. Because these are the types commonly isolated from anogenital warts, it is postulated that infants acquire the disease during birth from mothers with condylomata acuminata. Indeed, a correlation between mothers with

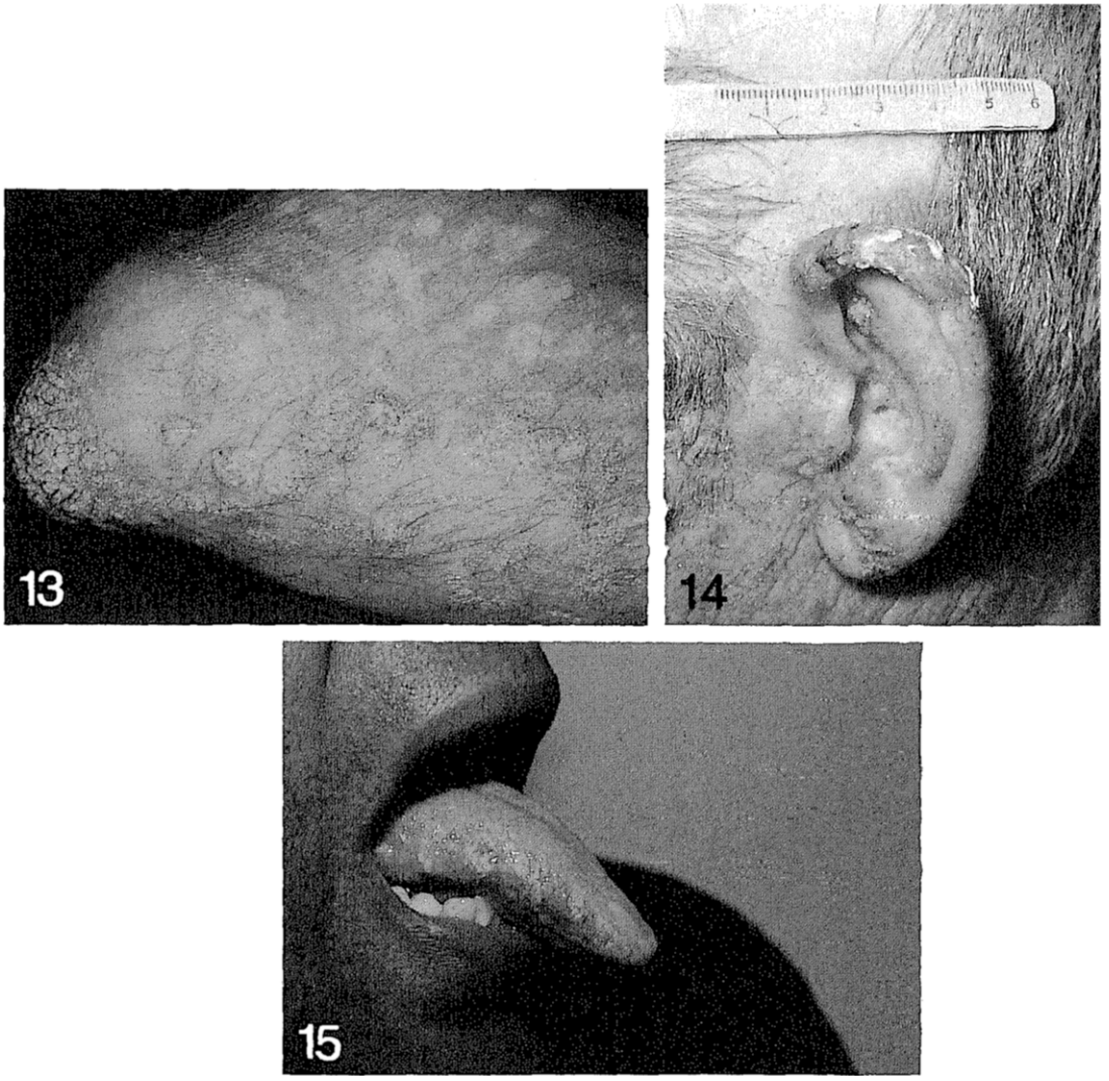

Fig. 13. Psoriasis-like lesions of epidermodysplasia verruciformis. (Courtesy Dr. Doug Lowy, Bethesda, Md.)

Fig. 14. Actinically induced squamous cell carcinoma in patient with epidermodysplasia verruciformis. (Courtesy Dr. Doug Lowy, Bethesda, Md.)

Fig. 15. Oral hairy leukoplakia.

condylomata acuminata and infants with laryngeal papillomas has been shown.[48] However, neonates have developed laryngeal papillomas after delivery by cesarean section, suggesting intrauterine infection.[47] This, coupled with the low incidence of laryngeal papillomatosis when compared with the incidence of condylomata in women of child-bearing age, casts doubt on the value of prophylactic cesarean section for pregnant women with overt genital condylomata.

Cervical condylomata have classically been thought of as exophytic, papillomatous lesions analogous to vulvar or penile condylomata. However, with the aid of acetic acid whitening and colposcopic examination, atypical or flat condylomata that appear as white patches have been described. These lesions are actually much more common than the papillomatous type.[49, 50] Although these lesions may show marked cytologic atypia and were first classified as cervical dysplasia or intraepithelial neoplasia, investigators found characteristic HPV cytopathic changes (koilocytes) within them and believed they were condyloma variants.[49, 51] Subsequent studies have confirmed their viral etiology by demonstrating HPV particles on electron microscopy, HPV antigen by immunohistochemistry, and HPV DNA within

some lesions.[50,52] Meisels et al.[49] reserve the term *inverted condyloma* for similar clinical lesions that histologically show an endophytic growth pattern.

Finally, HPV DNA has been demonstrated in the clinically normal skin adjacent to genital condylomata, indicating the presence of latent papillomavirus infection.[53] Furthermore, latent infection was associated with recurrent clinical disease after laser ablation of the original lesion in 67% of cases, compared with 9% recurrence in cases without evidence of latent infection.

EPIDERMODYSPLASIA VERRUCIFORMIS

Epidermodysplasia verruciformis (EV) is a rare, lifelong, cutaneous disorder characterized by persistent, refractory HPV infection manifesting as disseminated, flat, wartlike lesions and erythematous, hyperpigmented, or hypopigmented macules. EV was first described in 1922 by Lewandowsky and Lutz[54] and subsequently more than 200 cases have been reported. EV is believed to be a multifactorial disease with viral, genetic, immunologic, and extrinsic factors playing a role in its expression.[55] Ten percent of EV patients have consanguineous parents; in 10% of EV-affected familes, more than one sibling has the disease. An autosomal recessive pattern of inheritance has been suggested. The lifelong HPV infection in these patients is thought to result from a defect in cell-mediated immunity. Ultraviolet radiation probably plays a part in the development of skin cancer that occurs in about one third of EV patients.

The clinical onset of the disease may be from infancy to the second or third decade of life. Classically, two types of lesions are described: disseminated, flat wart–like lesions (Fig. 11) and erythematous, hyperpigmented, or hypopigmented (pityriasis versicolor–like) macules (Fig. 12). The former occur on the arms, legs, face, and back of the hands. They may become confluent, scaling plaques on the knees that resemble psoriasis (Fig. 13). The macular lesions occur on the face, neck, trunk, and arms. They are generally slightly scaly and tend to become confluent with polycyclic borders. As a rule palms, scalp, and mucous membranes are free of lesions.[56] Approximately one third of patients develop malignant degeneration of their cutaneous lesions, almost always occurring in sun-exposed areas such as the face, presternal region, and back of the hands (Fig. 14). The cancers are usually multiple and tend to be Bowen's disease or invasive squamous cell carcinoma with bowenoid features, although basal cell carcinomas occasionally occur. Squamous cell carcinoma in EV patients, like sun-induced squamous cell carcinoma in normal hosts, rarely metastasizes unless treated with x-radiation after which they tend to become more malignant.[57]

The skin lesions of EV almost never regress spontaneously and are almost always refractory to cure. Genetic counseling, avoidance of excessive sun exposure, and prompt detection and surgical excision of skin cancers are the mainstays of therapy. The benefits of interferon-α and systemic retinoids are currently being investigated.

At least 23 different HPV types occur in EV patients; 21 of these are found almost exclusively in these patients (HPV-3 and HPV-10 are found in EV patients as well as in common flat warts). The EV-specific HPV types include 5, 8, 9, 12, 14, 15, 17, 19-25, 36-38, 46, 47, 49, and 50. HPV-5 is the most common type isolated and often multiple types are found to infect a single patient. When carcinomas from EV patients are examined for papillomavirus DNA, HPV-5 is the predominant type detected. One group found HPV-5 in 21 of 28 tumors studied.[55] Other types found less frequently have been HPV-8, -3, -14, and -17. Patients with EV do not have an increased susceptibility to non-EV papillomavirus types.

PATHOGENESIS OF HPV INFECTION

A common feature of HPV-induced lesions is hyperplasia of the epidermis and it is therefore assumed that the virus stimulates the basal cells to divide. HPV replication is believed to be linked to the state of differentiation of the infected keratinocyte as viral DNA and viral particles are only detected in cells at or above the granular layer. The HPV DNA found in the cells of benign lesions is extrachromosomal and occurs as independent fragments called episomes. Some of this self-replicating viral DNA is incorporated into new virions. The amount of virus produced correlates to some extent with the type of lesion (plantar wart > common wart > anogenital wart) and the age of the lesion (new > old).

HISTOPATHOLOGIC FEATURES OF HPV INFECTIONS

The histologic features of common warts include acanthosis, papillomatosis, hyperkeratosis, and

parakeratosis.[58] The acanthotic rete ridges tend to point radially toward the center of the lesion. Vacuolated cells, with small, basophilic nuclei surrounded by a clear halo and pale cytoplasm, are found in the upper stratum spinosum and stratum granulosum. These contain few or no keratohyalin granules. Vertical tiers of parakeratosis are seen overlying the summits of the papillomatous elevations and granular cells with heavy, clumped keratohyalin granules are found in the valleys between the elevations. Plantar warts of the myrmecia type differ by having large, eosinophilic inclusions, shown to be keratohyalin, within the cytoplasm of the keratinocytes. The nuclei are retained in the stratum corneum and appear as basophilic round bodies surrounded by a clear halo. Flat warts tend to lack the papillomatosis and parakeratosis seen in common warts. They have a diffuse zone of vacuolated cells in the upper stratum corneum. In anogenital warts, the acanthosis is generally greater than in common warts and the rete ridges often display pseudoepitheliomatous hyperplasia. Vacuolated cells may be seen at lower levels of the stratum spinosum than in other types of warts. The histopathologic characteristics of EV are dependent on the HPV type involved. The flat wart–like lesions caused by HPV-3 are identical in their microscopic appearance to common flat warts. Lesions induced by HPV-5 display swollen keratinocytes with light blue cytoplasm that can appear foamy and nuclei ranging from small and pyknotic to large with marginated chromatin.

DETECTION OF HPV

HPV has been visualized and its intracellular location within wart tissue characterized by transmission electron microscopy.[59] The virions appear as a crystalline array of 55 nm particles within the nucleus. Plantar warts usually have the highest number of viral particles whereas common warts have few and flat warts are intermediate in number. HPV particles have been demonstrated in about half the condylomata studied but are absent in advanced cervical dysplasia and neoplasia. Virions have also been visualized in some oral and laryngeal papillomas.

Antisera have been generated to viral capsid antigens with tissue from clinical lesions. When intact virions from lesions infected with a single HPV type are used, a type-specific antiserum is developed, while detergent-disrupted virions produce a common antigen antiserum that cross-reacts with all HPV types. With these antisera in combination with immunohistochemical or immunofluorescence techniques, productive HPV infections (those in which intact virions are produced) can be demonstrated in lesional tissue. Tissue infected with HPV but not actively producing viral particles will be negative. Positive reactions are usually seen in the upper epithelial layer within the nuclei. Common warts react in approximately 90% of cases and approximately 50% of cervical condylomata show a positive reaction. In EV lesions, HPV antigen can only be found in benign lesions. Some oral and laryngeal papillomas react as well. Cervical carcinoma only rarely demonstrates a positive reaction.

Through recent advances in molecular biology, it has become possible to demonstrate the presence of HPV DNA within tissue of clinical lesions and to use it to identify the specific type of HPV involved. To accomplish this three important laboratory techniques have been instrumental: (1) nucleic acid hybridization, which allows the identification of specific DNA or RNA sequences by their ability to bind a complementary sequence; (2) cleavage of DNA at specific sites by restriction endonucleases; and (3) DNA cloning by the use of recombinant molecules in bacteria.[60] There are several methods in this new technology to identify HPV DNA. Southern blotting, first described in 1975,[61] involves extracting DNA from the tissue, cleaving it into variously sized fragments, and separating these fragments by agarose gel electrophoresis. The DNA is then transferred or blotted onto a nitrocellulose membrane where it is allowed to hybridize with a specific labeled DNA probe, which in this case is cloned HPV DNA. A newly described technique, the polymerase chain reaction, allows the targeted DNA sequences to be enzymatically amplified before Southern blotting.[62, 63] This modification vastly improves the sensitivity of the test to the point that a single molecule of HPV DNA can be detected in 10^5 cells. In the dot blot method, the extracted tissue DNA is denatured and blotted onto the membrane without prior cleavage or separation. This allows rapid screening with a number of HPV probes.[64] The filter in situ hybridization technique allows the examination of multiple samples at one time. Cytologic specimens are filtered onto nitrocellulose membranes, then hybridized with labeled probes. Although this technique is the easiest and least expensive to perform, it has a low sensitivity for specimens with few copies of HPV DNA per cell and may give

false-positive results.[65] In situ hybridization involves the use of labeled DNA probes to detect HPV DNA within formalin-fixed, paraffin-embedded, or frozen-tissue biopsy specimens.[66] The obvious advantages are preservation of lesional architecture and applicability to archival tissue. The polymerase chain reaction has also been used to amplify HPV DNA found in fixed, paraffin-embedded tissue.

The detection and typing of HPV in lesional tissue has greatly expanded our knowledge of the natural history of this viral infection as well as its significant clinical diversity. As this technology becomes readily available, a question that arises is when should the practicing dermatologist, away from the research setting, pursue these lines of investigation. In several clinical situations, a knowledge of the presence and type of HPV involved may be important. Patients with genital warts refractory to standard therapy should be considered for HPV typing to estimate the risk of subsequent malignancy for them as well as their sexual partners. This may guide the aggressiveness of further treatment. In pediatric patients with genital warts, HPV typing may also be beneficial in the evaluation of transmission route because sexual abuse is a primary concern. In this context, as with forensic blood typing, the test may exonerate but not definitively incriminate a suspected abuser. Anogenital squamous cell carcinoma and verrucous carcinoma should probably be studied for the presence and type of HPV involvement to characterize better the etiology of these tumors. Finally, patients with extensive, recalcitrant flat warts with or without tinea versicolor–like lesions or atypical papulosquamous lesions should be examined for EV-related HPV types because this diagnosis requires detailed counseling and clinical follow-up.

IMMUNOLOGY

Spontaneous regression of warts is well documented and occurs in approximately two thirds of warts on children when followed up for 2 years.[67] Clinical and pathologic features of regression differ when flat warts are compared with plantar and common warts.[20] Regressing flat warts frequently display clinical signs of inflammation and become pruritic, erythematous, and edematous.[68] As they involute, depigmented halos may appear around the lesions. Other flat warts on the body may become inflamed and involute, indicating a systemic reaction. Common warts however, do not involute in patients with regressing flat warts. Histologically, regressing flat warts show a lymphocytic perivascular infiltrate in the papillary dermis with spongiosis, exocytosis of mononuclear cells, and keratinocyte necrosis in the overlying epidermis, features suggestive of a cell-mediated immune reaction.[69] In addition, Iwatsuki et al.[70] have demonstrated OKT6-reactive cells in both the dermis and epidermis, of which some were in apposition with Leu-1–positive lymphocytes. The process resembles allergic contact dermatitis. Plantar and common warts, however, do not become clinically inflamed as they involute. Rather, their regression is often heralded by darkening, the presence of thrombosed vessels, and finally by the tendency for the wart to liquefy or desiccate.[71] When the lesion is examined histologically, thrombosis of small vessels in and around the regressing wart suggestive of an infarctive process is seen. The lymphocytic infiltrate associated with flat warts is absent. Both humoral and cell-mediated immune responses may occur in patients with warts, but the exact role of either in the resolution of warts is unknown.

Serum antibodies have been detected to both wart virus and wart tissue antigens with various techniques, including electron microscopic visualization, complement fixation, immunodiffusion, immunofluorescence, passive hemagglutination, immunoelectron microscopy, and radioimmunoassay.[20,72] However, most patients with active warts have no demonstrable antibodies. When found, antibodies tend to be of low titer IgM type directed toward wart tissue antigens. This poor antibody response may be due to the localization of the virus in the outer epidermis where it is sequestered from the immune system.[20] When patients with regressing warts have been studied, several investigators have found either IgG or IgG and IgM antibodies.[73-77] It has also been shown that warts present for less than 1 year will usually regress within 2 months if the wart-specific IgG antibodies develop.[75] This suggests that an IgG response is somehow necessary for wart regression. In general, the level of wart-specific antibodies is inversely related to the number of warts and duration of disease in a given patient. Because most studies of the humoral immune response to warts were conducted before the identification of different HPV types, the question of cross-reactivity was not addressed. This makes the interpretation of some of the data difficult as responses to different HPV types may vary.

Several studies have addressed the cell-mediated immune response to HPV infection and its possible role in wart regression. Chretien et al.[78] observed that patients with warts and those cured of warts had fewer circulating T cells when compared with age-matched controls. There was a significant increase in peripheral T cells in 11 of 13 patients after therapy. Another study looked at a group of children previously vaccinated with bacille Calmette-Guérin (BCG) and found that those with warts had a significantly lower incidence of positive tuberculin skin tests when compared with those without warts.[79] An in vivo intradermal skin test has been developed that uses purified formalin-inactivated HPV antigen derived from pooled warts.[80,81] Fifty-one percent of patients with active warts had positive delayed skin hypersensitivity responses and 73% of patients with a past history of warts responded, whereas in the control group only 6.3% were positive. The only clinical type of wart associated with a much lower hypersensitivity response (28%) was flat warts. The delayed hypersensitivity response varied with the duration of the wart; the highest frequency was seen in patients with warts present from 6 months to 2 years. Only 20% of patients with warts of more than 10 years duration had positive skin tests, suggesting an inability to mount the necessary response for regression. The cell-mediated immunity of patients with warts has also been assayed with the leukocyte migration inhibition factor test to measure lymphocyte responsiveness to stimulation with phytohemagglutinin and purified protein derivative.[82] Patients with warts were found to be less responsive than control subjects. Other studies have examined specific cell-mediated immunity to HPV by lymphocyte transformation and leukocyte migration inhibition in response to papillomavirus antigen.[83,84] Patients with a history of warts showed a greater reactivity than those with active warts and both groups were more reactive than control subjects. A role for natural killer cells and lymphokines in the immune response to HPV infection remains speculative.[85]

HPV INFECTION IN IMMUNOSUPPRESSED HOSTS

Further support for the role of the immune system in HPV infection is the behavior of warts in patients with immune deficiency states. Kidney transplant patients, receiving long-term immunosuppressive therapy, have a high frequency of warts. In one study of 200 unselected, consecutive renal allograft recipients, warts were noted in 43%.[86] A recent survey categorized kidney transplant patients into two groups on the basis of graft survival less than or greater than 5 years and found 20% of the former group had warts compared with 77% in the latter group.[87] Three patients had plaque lesions similar to those seen in EV. These lesions were all found to contain HPV-5/8 DNA, originally thought to be exclusively associated with EV. Another report described a kidney transplant patient who exhibited an EV-like syndrome, again with HPV-5 demonstrated in the lesions.[88] Van der Leest et al.[89] examined 48 wart specimens from kidney transplant recipients for HPV type with the Southern blot method of DNA hybridization. In samples positive for HPV DNA (90%), they found HPV-1 in 2%, HPV-2 in 56%, HPV-3 in 19%, HPV-4 in 47%, HPV-5 in 9%, and HPV-6 in 5%. One of their 36 patients had multiple red-brown, scaling lesions characteristic of EV; however, unfortunately typing for HPV-5 was not done in this patient. A significant finding was that 16 specimens contained more than one type of HPV, analogous to reports of multiple HPV types occurring simultaneously in EV patients.[90]

Like EV patients, kidney transplant recipients have a markedly increased incidence of sun-induced squamous cell carcinoma.[91,92] Boyle et al.[92] found both warts and squamous cell carcinomas to be increased significantly in a group of 94 kidney transplant patients when compared with control subjects. Moreover, when the transplant patients were stratified into high and normal sun exposure groups, the high exposure group had all the squamous cell carcinomas and a significantly higher incidence of warts (58% vs 26%). Kidney transplant patients are also at increased risk for genital tract neoplasia. Halpert et al.[93] evaluated the cervical cells of 105 female transplant recipients. Eighteen patients (17.1%) had evidence of HPV infection and 10 of these (9.5%) demonstrated cervical neoplasia. When compared with an immunocompetent cohort, the transplant patients had a 17-fold increase in the rate of HPV infection and a nine-fold increase in the rate of cervical neoplasia. Another study of 120 kidney transplant patients found warts in 48% and cancer in 5% (four with skin cancer and two with anogenital squamous cell carcinoma).[94] All six patients with cancer had warts. HPV-16 was detected in tissue from one of the patients with anogenital cancer. These studies suggest that immunocompromised kidney transplant recipients with HPV infection have a greater risk of malignant transformation than immunocompetent patients with similar infections.

Extensive warts have also been seen in patients with primary immunodeficiency diseases. Barnett et al.[95] documented extensive and persistent verrucae in three patients with ataxia telangiectasia, a patient with common variable immunodeficiency and mucocutaneous candidiasis, and a patient with selective IgA deficiency. Other immune diseases associated with warts include Wiskott-Aldrich syndrome, lymphocytopenia associated with generalized lymphatic hypoplasia, lymphedema and protein-losing enteropathy, and Bittner's syndrome.[20]

Warts may occur with increased frequency in patients with lymphoma, chronic lymphocytic leukemia, and Hodgkin's disease.[96,97] Morison[97] examined 633 patients with a variety of malignancies including multiple myeloma, Hodgkin's disease, malignant lymphoma, chronic lymphatic leukemia, systemic malignancy (carcinomas and sarcomas of various types), and basal cell carcinoma and 348 control subjects for the presence of viral warts. He found a striking increase in the incidence of warts in the patients with Hodgkin's disease, lymphoma, and chronic lymphatic leukemia (29.6%, 20.1%, and 17.6% respectively) compared with other malignancy and control groups (ranging up to 6.2%). Among patients in these high-risk groups, only a small percentage had their warts successfully removed. He postulated that cell-mediated immunity was important in both the prevention and resolution of warts because all three high-risk groups had some degree of cell-mediated immune deficiency whereas multiple myeloma patients with deficient humoral immunity had no more warts than the control group.

Several large studies have examined the prevalence and nature of HPV disease in patients with acquired immunodeficiency syndrome (AIDS) as part of general dermatologic surveys.[98-100] Valle[98] found that HIV-positive patients had significantly more new warts on the face, hands, and feet when compared with HIV-negative high-risk patients and normal control subjects. Verrucae, including flat warts, condylomata, and verrucae vulgares, were noted in 8% of AIDS patients and those with AIDS-related complex studied by Goodman et al.[99] One of their AIDS patients had multiple verrucae and a verrucous carcinoma on the penis that contained HPV-11 DNA determined by Southern blot technique. A recent case report described a similar patient with AIDS, who presented with widespread verrucous lesions on the hands, feet, and penis.[101] Although biopsy specimens from the hand lesions showed verruca vulgaris with or without some epidermal dysplasia, a specimen from the penis had features of verruca vulgaris associated with an intraepidermal neoplasm, believed to be most likely an evolving squamous cell carcinoma. This lesion contained DNA that hybridized to an HPV-11 DNA probe as well. In both these patients there appears to have been malignant transformation induced by an HPV type formerly believed to be benign. Kaplan et al.[100] looked at cutaneous findings in 217 HIV-positive patients and reported that patients with warts on their hands and feet frequently had a recurrence after removal; pigmented hemorrhagic facial warts were occasionally seen; and venereal warts were sometimes large and frequently recurrent. These large perianal condylomata acuminata are often difficult to treat and may require surgical or laser excision.[102]

Papillomavirus has also been reported in a mixed cutaneous infection seen in an AIDS patient.[103] This patient had a chronic vegetating plaque on the thigh from which herpesvirus was cultured, HPV antigen was demonstrated immunohistochemically, and septate hyphae were seen. Another condition seen in HIV-positive patients, oral hairy leukoplakia, was believed to represent a mixed infection with HPV and a herpes-type virus when first reported in 1984.[104] These lesions appear as white papules with a corrugated or "hairy" surface, most frequently located on the lateral borders of the tongue (Fig. 15). Immunoperoxidase staining with antibody to the core antigen of the papillomavirus group revealed a positive reaction in 77% of biopsy specimens studied, whereas with electron microscopy viral particles characteristic of *Herpesviridae* but not HPV were seen. The herpes-type virus in these lesions was subsequently identified as Epstein-Barr virus (EBV) by immunofluorescence technique to EBV antigens as well as by demonstration of EBV DNA by Southern blot hybridization.[105] However, further studies to document HPV by using various antisera to HPV antigens and both Southern blot and in situ hybridization methods for HPV DNA have been unsuccessful; it is now believed that oral hairy leukoplakia is due to EBV in the presence of HIV-induced immunosuppression.[106]

RELATION BETWEEN HPV INFECTION AND CANCER

Certain animal papillomaviruses produce lesions capable of malignant transformation. One of the first studied was the cottontail rabbit (Shope) papillomavirus that can experimentally induce in

domestic rabbits papillomas that progress to carcinoma in approximately 70% of cases.[107] This represents a threefold higher rate of malignant transformation compared with that seen in papillomas of the cottontail rabbit, thereby suggesting a possible role for genetic factors as well.[108] Another well-studied example is that of the bovine papillomavirus type 4 that causes alimentary tract papillomatosis of cattle. In this case, an environmental factor, grazing by the affected cattle in areas infested with bracken fern, is associated with malignant transformation of the papilloma.[109] Recently, several human carcinomas have been associated with HPV infection including cervical carcinoma, squamous cell carcinoma associated with EV lesions and warts in immunocompromised patients, carcinomas arising in the aerodigestive tract, verrucous carcinoma, and Bowen's disease.

The relation between HPV infection and human carcinoma has focused mainly on cancer of the uterine cervix. Historically, cervical cancer has long been linked with sexual activity. In 1842, Rigoni-Stern (cited in Koss[10]) analyzed cancer deaths in the city of Verona, Italy during a 79-year period and found that deaths caused by "cancer of the uterus" (now believed to represent primarily cervical cancer) were rare among virgins and nuns and common among married women and widows. From multiple subsequent epidemiologic studies, two important risk factors for cervical cancer have been identified: (1) young age at the onset of sexual activity and (2) multiplicity of sexual partners. These data implicated an infectious agent and syphilis, gonorrhea, *Trichomonas vaginalis,* and herpes simplex virus 2 have been considered. The preponderance of recent evidence, however, implicates HPV as the long-sought agent.

This association between HPV and cervical cancer is suggested by a number of lines of evidence that range from epidemiologic observations to findings based on recent advances in molecular biology. A major advance in the understanding of cervical HPV infection came with the recognition that the koilocyte, a long-described finding in certain cervical smears, was a specific cytopathic effect of HPV infection.[111,49] These are cells containing hyperchromatic nuclei with a large perinuclear cavitation and surrounding cytoplasm that is dense and often amphophilic. Meisels and Morin[112] analyzed results from more than 400,000 cervical smears received by the Saint-Sacrement Hospital in Québec from 1975 to 1979 and found cytologic evidence of cervical condylomata (koilocytes) in only 1.69% of the 234,715 women screened, whereas condylomatous cells were observed in 25.6% of dysplastic and neoplastic lesions. Investigators studying cervical cytologic characteristics have noted a range of nuclear atypia in the koilocytes. Atypia so marked as to suggest carcinoma in situ has been found in certain flat condylomata termed *atypical condylomata.*[50] These lesions appear to progress to malignant transformation at a rate higher than other cervical condylomata and may represent an intermediate step.

Recently developed DNA hybridization techniques have demonstrated the presence of HPV DNA in a variety of cervical lesions. HPV-6 has been found in various forms of carcinoma in situ and HPV-11 in a few cervical carcinomas. In general, however, these two types are associated with condylomata and lower grades of carcinoma in situ. More importantly, HPV-16 and HPV-18 have been repeatedly demonstrated in invasive cervical carcinoma. Gissmann et al.[113] found one or both of these types of HPV DNA in 57.4% of invasive cervical cancers. Another group, using HPV-16 and HPV-18 cloned directly from human cervical carcinoma, found these types in approximately 70% of cervical cancers.[114] Macnab et al.[115] detected HPV-16 sequences in 84% of cervical tumors and in 73% of samples of clinically and histologically normal tissue taken from sites 3 to 5 cm from the malignant tumors. HPV-33 and HPV-35 have now also been isolated from invasive cervical carcinoma. The HPV DNA found in cervical carcinoma is integrated into the host genome and differs from that found in benign intraepithelial lesions, which is extrachromosomal. Once integrated, the HPV DNA no longer produces virions. This is illustrated by indirect immunoperoxidase studies for HPV common antigen on cervical lesions, where staining is inversely proportional to the degree of epithelial atypia and is almost always negative in invasive cervical cancer. The integration of HPV DNA results in deregulated expression of two viral genes involved with transformation, E6 and E7, and provides further evidence for the role of HPV in cervical cancer.[6]

Much less studied are some of the other human cancers that have been associated with HPV infection. The increased incidence of actinically induced squamous cell carcinoma in EV patients and kidney transplant recipients has been discussed. An HPV origin, based on the demonstration of HPV antigen

or HPV DNA in tissue, has been suggested in the following types of squamous cell carcinoma: carcinoma of the nasal cavity and paranasal sinuses, laryngeal carcinoma, bronchogenic carcinoma, and esophageal carcinoma.[116] In a recent study of 10 periungual squamous cell carcinomas, HPV DNA was demonstrated in eight by dot blot hybridization and six hybridized with an HPV-16 probe.[117] Another group has isolated HPV-34 DNA from a lesion of Bowen's disease on the periungual region of a digit.[118] Abramson et al.[18] found HPV-16 DNA in all five cases of verrucous carcinoma of the larynx that they studied. A viral origin is suspected in other forms of verrucous carcinoma (oral florid papillomatosis, giant condylomata acuminata, and epithelioma cuniculatum) as well. Although not a true malignancy, keratoacanthoma has also been associated with HPV infection.[120, 121] The HPV types isolated from keratoacanthomas have been those heretofore associated only with EV patients.

THERAPY FOR HPV INFECTION

A comprehensive review of the therapy for warts is beyond the scope of this article. The time-honored physical (surgical, electrosurgical, cryosurgical, and laser) and chemical (salicylic acid, lactic acid, trichloroacetic acid, cantharidin, formaldehyde, and glutaraldehyde) destructive methods and chemotherapeutic agents (podophyllin, 5-fluorouracil, and bleomycin) are well known to all dermatologists. Equally familiar is the induction of a local allergic contact dermatitis with dinitrochlorobenzene or squaric acid dibutyl ester to stimulate an immunologic or at least inflammatory reaction to eliminate warts. In the area of genital warts, one of the most significant recent advances has been the detection of subclinical HPV lesions in both condyloma patients and their sexual partners with the use of 5% acetic acid application and magnification.[33] It is therefore important to examine and treat the sexual partners of patients with genital HPV infection. In view of the previously discussed spectrum of cervical disease related to HPV, female patients and the female sexual partners of patients should be referred for regular gynecologic examinations, including Papanicolaou smears.

Three newer treatment modalities will be discussed in more detail: topical podophyllotoxin, interferon, and sytemic retinoids. Podophyllotoxin is the purified active ingredient in podophyllin, a nonhomogenous, unstable plant extract derived from *Podophyllum peltatum* or *P. emodi.* In contrast to podophyllum resin, podophyllotoxin appears to be significantly less toxic with no systemic reactions reported as yet.[122] Several studies have documented the efficacy of 0.5% podophyllotoxin in ethanol applied by the patient at home for the treatment of penile warts. Von Krogh[123] reported a cure rate of 49% with this self-administered preparation applied twice daily for 3 days. In a subsequent study on the same preparation applied twice daily for 4 and 5 days, he found no significant improvement in efficacy but noted an increase in the frequency and severity of local irritation.[124] Beutner et al.[122] reported that 82% of genital warts treated with this regimen cleared compared with 13% in the placebo group. Recurrence, however, was observed in 34% of the previously resolved warts. Podophyllotoxin 0.5%, applied twice daily for 3 days per week for up to 6 weeks, was compared with 20% podophyllum resin, applied by a physician once a week for up to 6 weeks.[125] The former treatment was more effective and cleared the warts in 28 of 32 patients, whereas the latter cleared the warts in 12 of 19 patients. Side effects of topical podophyllotoxin at this dosage appear to be limited to local cutaneous irritation, for example, erythema, swelling, burning, and erosions. In most patients these signs and symptoms are mild and in all cases are transient and reversible. Therefore topically applied podophyllotoxin appears to be a relatively safe, efficacious therapy for penile warts that can be given to the patient for self-application.

Interferon is theoretically an attractive modality for the treatment of HPV infection for several reasons.[126] The recurrence of warts after destructive therapy is a well-documented and not infrequent event, occurring at rates ranging from 7.5% to 33%. As discussed earlier, the normal-appearing perilesional skin has been shown to harbor HPV, which would explain these recurrences. The antiviral activity of interferon should limit papillomavirus replication in this clinically normal, but infected skin as well as in lesional tissue. The antiproliferative effect of interferon should slow the rapidly dividing keratinocytes in some warts and dysplastic genital lesions. Finally, the immunomodulatory effects of interferon may augment the host's defensive response to HPV infections.

Several clinical trials have demonstrated the efficacy of interferon, primarily leukocyte-derived interferon-α, in the treatment of condylomata acuminata.[126-130] Eron et al.[127] conducted a ran-

domized, double-blind study that compared recombinant interferon alfa-2b with placebo in treating condylomata. They treated one to three warts per patient with intralesional injections of 1×10^6 IU of interferon or placebo three times per week for a total of 3 weeks. At follow-up 13 weeks after completion of therapy, 36% of the 125 patients receiving interferon had complete clearing of all treated warts compared with only 17% of the 132 placebo patients ($p < 0.001$). In another similarly constructed study interferon-α purified from human blood was injected into condylomata twice weekly for up to 8 weeks.[128] An even higher response rate was achieved; 62% of the 66 patients receiving interferon had complete clearing of treated warts compared with 21% of those receiving placebo ($p < 0.001$). In a multicenter double-blind study, intralesional recombinant interferon alfa-2 was compared in two dosages, 10^6 and 10^5 IU, with placebo in the treatment of a single lesion of condyloma acuminatum or verruca plantaris per patient.[129] These investigators found that for condylomata, only the higher dose of interferon was significantly better than placebo in clearing the warts; 53% of the 30 patients receiving high-dose interferon cleared compared with 19% of the 32 patients receiving low-dose interferon and 14% of the placebo patients. In the 100 patients with plantar warts, no significant benefit was observed from either dosage of interferon when compared with placebo.

Several uncontrolled studies have evaluated the benefit of systemic interferon, delivered either subcutaneously or intramuscularly, in the treatment of genital warts. Weck et al.[126] used interferon alfa-n1 derived from a human lymphoblastoid cell line to treat patients with resistant or recurrent condylomata acuminata in dosages ranging from 1 to 10×10^6 IU/m^2 administered initially on a daily basis followed by three times per week. The authors concluded that although doses of 5×10^6 IU/m^2 are highly effective, they are unacceptable because of the high incidence of side effects (discussed later). However, low doses of 1×10^6 IU/m^2 are well tolerated and have similar overall response rates. Another trial of daily subcutaneous doses of 5×10^6 IU of interferon alfa 2c noted complete response in five of seven patients with condylomata and in one of three patients with bowenoid papulosis.[130]

Interferon-β has also been used intralesionally[131] and intramuscularly[132] with some success in condylomata acuminata. Finally, interferon-α has been shown to be beneficial, although not curative, in two other HPV-related conditions, laryngeal papillomas[133] and EV.[134] Side effects of interferon therapy include fatigue, fever, chills, myalgias, headache, and malaise as well as a transient leukopenia. They can occur with intralesional as well as subcutaneous or intramuscular delivery, which implies systemic absorption with either route.

Retinoids are another theoretically promising modality for the treatment of HPV disease. Through mechanisms that are not yet clear, retinoids have been demonstrated to enhance both humoral and cell-mediated immunity.[135] These compounds are also well-known regulators of cellular differentiation. Because HPV replication appears linked to the state of keratinocyte differentiation, retinoids could potentially block the production of new viral particles. Finally, they are capable of preventing malignant transformation, a function theoretically applicable to HPV-induced neoplasia.

Several reports have documented beneficial results with systemic retinoids used for immunosuppressed patients with HPV disease. Lutzner et al.[136] treated a patient with EV who had flat wart–like lesions, hypopigmented, scaly plaques, and several cutaneous tumors with etretinate at a dosage of 1 mg/kg/day. After 2 months of therapy, most flat wart–like lesions were gone, the plaques had lost their scale and were starting to repigment, and the tumors had decreased in size. Another patient with sarcoidosis who developed extensive warts while taking systemic steroids, was given etretinate, 100 mg/day.[137] Although he responded dramatically, the warts recurred when the dosage was tapered below 30 mg/day. Similarly, a patient with chronic lymphatic leukemia who had extensive verrucae on the hands and fingers showed marked regression of the lesions when given etretinate, 1 mg/kg/day, only to relapse when the retinoid was discontinued.[138]

Obviously we have come a long way in our understanding of the biology and clinical manifestations of HPV infection but need to continue the pursuit of effective therapy for this common, but by no means trivial, infection.

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Answers to CME examination*

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Questions 1-33, Wieselthier JS, Koh HK. J AM ACAD DERMATOL 1990;22:381-401.

1. e (p 382, c 2, pa 3)
2. d (p 382, c 2, pa 4)
3. a (p 384, c 1, pa 3—c 2, pa 1)
4. e (p 385, c 2, pa 4—p 386, c 1, pa 1)
5. c (p 386, c 1, pa 1; p 390, c 1, pa 2)
6. d (p 385, c 2, pa 2)
7. b (p 389, c 2, pa 2)
8. d (p 396, c 1, pa 3)
9. c (p 396, c 1, pa 3)
10. c (p 382, c 2, pa 2; p 396; c 2, pa 4)
11. e (p 389, c 2, pa 1)
12. a (p 394, c 2, pa 3)
13. c (p 394, c 1, pa 2)
14. e (p 388, c 2, pa 1)
15. b (p 394, c 1, pa 3)
16. e (p 394, c 2, pa 5)
17. d (p 381, c 2, pa 2)
18. c (p 381, c 2, pa 2)
19. e (p 382, c 1, pa 1)
20. b (p 381, c 2, pa 2)
21. a (p 381, c 2, pa 2)
22. c (p 390, c 1, pa 2)
23. d (p 390, c 1, pa 2)
24. b (p 390, c 1, pa 2)
25. e (p 390, c 1, pa 2)
26. c (p 384, c 2, pa 2)
27. d (p 384, c 2, pa 2)
28. c (p 396, c 1, pa 1; pa 2)
29. a (p 386, c 1, pa 1)
30. b (p 386, c 1, pa 2)
31. c (p 386, c 1, pa 1; pa 2)
32. a, b, c, d, e (p 385, Ta III)
33. None of the answers is correct (p 387, c 1, pa 1; p 396, c 2, pa 6)

*p: page; c: column; pa: paragraph; Ta: Table.