Papillomavirus Infection of the Anogenital Region: Correlation Between Histology, Clinical Picture, and Virus Type. Proposal of a New Nomenclature

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The clinical and histologic picture of 84 anogenital condylomatous and condyloma-like lesions of both sexes were analyzed in an effort to establish a correlation to the different papillomavirus (PV) types. The presence of human papillomavirus (HPV)-specific DNA sequences was confirmed through molecular hybridization and the presence of PV structure antigens was verified in thin sections by means of a group-specific anti-PV-antiserum using the peroxidase-antiperoxidase (PAP) technique.

Three distinct clinical forms harboring distinct HPV types were distinguished: (1) Condylomata acuminata in which HPV-6 DNA was present in 37 of 59 samples and HPV-11 DNA in only 13 of 59 samples. HPV-16 DNA was not detected at all and 9 condylomatous lesions remained unclassified. (2) Flat condyloma-like lesions, where HPV-6 and HPV-11 were associated with lesions of low epidermal atypia in 8 and in 2 of 18 cases, respectively, and where HPV-16 was associated exclusively with 6 of 18 such lesions with severe atypia, called bowenoid papulosis. (3) Pigmented papules where HPV-16 was detected twice in lesions of bowenoid papulosis and HPV-11 in 2 of the benign pigmented lesions. The fourth clinical manifestation of genital papillomavirus infections—the so-called condylomata plana—was not available for virologic analysis.

Histologically 5 different koilocytotic features were determined which could not be correlated either with one of the clinical pictures or with a specific PV type. HPV-16, however, was found frequently in non-koilocytotic lesions exhibiting the features of severe epithelial atypia known in bowenoid papulosis. The existence of PV structure antigens in these lesions could not be verified using the indirect immunoperoxidase—PAP-technique—in contrast to the koilocytotic lesions where clear evidence of the presence of HPV was proved in 36 of 56 (64.3%) of the cases.

Human papillomaviruses (HPV) have been identified in a wide range of epithelial or fibroepithelial proliferations of the skin and mucosae. HPV on the skin lead to common, flat or plantar warts and flat pityriasis versicolor-like lesions in epidermodysplasia verruciformis. Distinct papillomavirus (PV) types of the oral mucosa have been associated with lesions such as oral papillomas, focal epithelial hyperplasia (Morbus Heck) [1], and recently with leukoplakias [2]. In addition, no further

doubt exists on the HPV-etiology of laryngeal papillomatosis [1]. In the genital region HPV have been demonstrated in benign lesions such as condylomata acuminata [3] and in dysplasias and malignant tumors of the internal and external female genital tract [4]. The following virus types were demonstrated in different lesions: HPV-2 [5], HPV-10-like DNA [6], HPV-6, and HPV-11, the latter being likely responsible for most of the exophytic condylomata acuminata [7] including the giant condylomas (M. Boshart, personal communication). These verrucous carcinomas (Buschke-Löwenstein tumors) do not usually metastasize and it has been reported that malignant conversion occurs only after a long period. HPV-11 was present in about 5% of cervical carcinomas investigated in comparison to 65% of cases with respect to HPV-16 and HPV-18 [4,8,9]. HPV-16-related DNA was found recently in genital Bowen's disease and in bowenoid papulosis of both sexes [10,11]. HPV-6 and HPV-11 appear to be related to benign proliferations whereas HPV-16 and HPV-18 DNA are found preferentially in carcinomata in situ, in invasive carcinomas of the cervix, and in some cancer biopsies of the vulva and penis [1; H. Ikenberg et al, in preparation].

Classical condylomata acuminata do not, in general, present diagnostic problems, in contrast to other uncharacteristic anogenital HPV-related lesions which are difficult to differentiate clinically from dysplasias of the anogenital skin. In the past, condylomata acuminata mainly were examined clinically and morphologically. Now the identification and molecular cloning of a large number of HPV types together with molecular hybridization of DNA extracted from tumors provide the investigator with new tools for the examination of such lesions.

Since the individual HPV types may differ widely in their oncogenic potential [1], it is of great practical interest to search for a correlation between the histologic picture and the HPV type in condylomatous and premalignant lesions. This study deals with condylomatous and condyloma-like lesions of the genital tract, perianal skin, and anal mucosa of both sexes, whereas in earlier reports only lesions of the female genitalia were discussed [12–14].

MATERIALS AND METHODS

Tissue and Subjects

A total of 189 anogenital wart samples of varying localization from 145 individuals were examined clinically and histologically. The patients were male and female individuals from the dermatologic and gynecologic outpatient clinics of the University of Freiburg. The precise origin of the lesions is summarized in Table I.

The tumors were removed by scalpel or scissors after local anaesthesia. Each biopsy was divided in two: one portion was reserved for light microscopy and immunocytochemical verification of PV structural antigens, and the other portion was snap-frozen in liquid nitrogen and stored at −70°C for virus classification.

Histologic and Cytologic Studies

After fixation in phosphate-buffered 4% formalin, the samples were embedded in paraffin, cut into 4–5 μm-thick sections and stained with hematoxylin and eosin (H & E) or toluidin blue.

A histologic grading was performed according to criteria previously described [15]:

TABLE I. *Origin of morphologically and virologically examined genital warts*

Clinical type	Total number	Male patients						Female patients				
		Genital mucosa		Anal mucosa	Penile skin	Groin	Perianal skin	Genital mucosa		Anal mucosa	Vulva skin	Perianal skin
		Glans	Urethra					Introitus vaginae	Portio uteri			
Condyloma acuminatum	130 (59)	31 (11)	6 (0)	10 (4)	6 (5)	1 (1)	43 (22)	4 (2)	1 (0)	4 (1)	3 (3)	21 (10)
Flat condyloma-like lesion	22 (18)	12 (10)	1 (0)	1 (0)							8 (8)	
Pigmented papular lesion	32 (7)	2 (1)			7 (2)	9 (2)		2 (0)			7 (1)	5 (1)
Condyloma planum	5 (0)								5 (0)			

Figures in parentheses indicate the number of biopsies tested histologically and for the presence of HPV.

I. *Mild atypia:* There is some increased proliferation of basal cells. The nuclei become more widely separated from one another. Individually keratinized cells and mitotic figures are restricted to the basal layer.

II. *Moderate atypia:* Increased cellularity and cellular disarray extending through approximately two-thirds of the thickness of the epithelium are observed. Individual keratinized cells and mitotic figures above the basal layer are seen infrequently.

III. *Severe atypia:* Cellular atypia exists throughout more than two-thirds of the full thickness of the epithelium. Individually keratinized cells and mitotic figures above the basal layer are seen occasionally.

Peroxidase-Antiperoxidase (PAP) Staining

After deparaffinization 4 μm-thick sections were sequentially incubated with: (1) normal swine serum at a dilution of 1:20 for 20 min; (2) a primary antiserum (dilution 1:100 and 1:500 for 1 h), cross-reactive against the common structural antigens of PV [16], prepared in rabbits through immunization against sodium dodecyl sulfate (SDS)-disrupted bovine papillomavirus (BPV) type 1 virions (gift of W. D. Lancaster, Georgetown University, Washington D.C.); (3) swine antirabbit immunoglobulin at a dilution of 1:10 for 1 h; and (4) rabbit-PAP complex (peroxidase-antiperoxidase soluble complex, purchased from Dako Corp., California) at a dilution of 1:100 for 30 min. Washings between steps 1, 2, 3, and 4 were performed with phosphate-buffered saline (pH 7.4). After a further washing with 0.5 M Tris-HCl (pH 7.6) the reaction was developed by 0.05% DAB (3',3'-diaminobenzidine), 0.01% hydrogen peroxide in Tris-HCl (pH 7.6) for 4–8 min and counterstained with hematoxylin, e.g., embedded in Permount (Fisher Scientific, Compton, New Jersey). This procedure was performed on each of the 3 sections taken from each biopsy.

The following controls were run concurrently with the testing of the condylomatous tissues: (1) human foreskin, normal vulvar skin, and skin from the forearm not reactive with SDS-BPV 1 (negative controls), and (2) sections of a virus particle positive HPV-1-induced plantar wart, which served as a positive control.

Extraction of Cellular DNA

The tissues were thawed, ground with sea sand, suspended in 10 mM Tris, 1 mM EDTA pH 8.1, 1% SDS, and digested with 100 μg/ml proteinase K for 1 h at 37°C. They were then deproteinized twice with phenol, once with chloroform isoamylalcohol (24:1), dialyzed overnight against 10 mM Tris, 1 mM EDTA pH 8.1, and treated with 20 μg/ml RNAse for 1 h at 37°C. After another extraction with phenol and with chloroform isoamylalcohol (24:1) the DNA was precipitated with 0.3 M ammonium acetate and 2 vol of 100% ethanol at 70°C and washed with 70% ethanol.

Labeling of HPV DNA

HPV-6 was cloned from a genital wart into pBR 322 [17]. HPV-11, which was identified from a genomic library of a laryngeal papilloma constructed in lambda 1 47 [18], was subcloned in pBR 322 at the single Bam HI site. HPV-16 was first cloned from a cervical carcinoma [4]. The DNAs were labeled with [α-^{32}P]TTP using the nicktranslation procedure to a specific activity of 10^8 cpm/μg [7].

Blot Hybridization

The DNA was digested with restriction endonucleases (Bethesda Research Laboratories) under controlled conditions. Whenever possible 10 μg of DNA was used. The DNA fragments were separated in 1% agarose gels and transferred onto nitrocellulose filters using Southern's procedure [19].

Nitrocellulose filters containing the unlabeled DNA were preincu-

bated for 16 h at 42°C in 0.75 M NaCl/0.075 M sodium citrate, 20% or 50% formamide, respectively, 0.2% Ficoll, 0.2% polyvinyl pyrrolidone, 0.2% bovine serum albumin, and 0.5 mg/ml denatured yeast tRNA.

Hybridization was executed for 3 days at 42°C with approximately 2 ng $\cong$ 2 × 10^5 cpm/cm^2 nitrocellulose ^{32}P-labeled viral DNA under the same conditions, however, with 0.1 mg/ml denatured tRNA. Filters were washed for 3 × 30 min in 0.30 M NaCl/0.03 M sodium citrate/ 0.1% SDS at the appropriate hybridization temperature, covered with Saran wrap, and exposed to a Kodak x-ray film at −70°C using an intensifying screen for 1–14 days.

Hybridizations were carried out at 20–40° below the melting temperature (T_m) of HPV DNA (applying formulas used by Schildkraut and Lifson [20] and McConaughy et al [21]): $T_m = 81.5 + 16.6$ (log Na$^+$) + 0.41 (%G + C) + 0.72 (% formamide). The G + C value of HPV DNA was taken as 40% [22]. In general, filters were hybridized under conditions of low stringency (40°C below T_m), kept moist before and during exposure, rewashed under well-controlled conditions (20°C below T_m), and exposed again.

RESULTS

Clinical Findings

A total of 189 biopsies of condylomatous and condyloma-like lesions from male and female patients were studied clinically and histologically (Table I). The mean age of the male patients was 30.45 years and that of the female patients 30.24 years. Four wart types were differentiated clinically: (1) classical condylomata acuminata including giant condylomas, (2) flat condyloma-like lesions, (3) pigmented papules, and (4) condylomata plana.

Classical condylomata acuminata: This papillomatous growth type was found in 130 instances both in the anogenital skin and in the mucosa of the urethra, vagina, cervix uteri, as well as of the anorectum. The surface of the tumors was more or less hyperkeratotic and verrucous and, as in the case of giant condylomas, imitating often a cock's comb-like arrangement. Prominent capillaries were visible only where hyperkeratosis was absent. Usually these condylomatous tumors were multiple, however, solitary tumors were also observed.

Flat condyloma-like lesions: In 22 cases slightly elevated papules or plaques featuring either a smooth or irregular surface were found on the vulvar, penile, and anal epithelia.

Pigmented papules: These pigmented lesions showed no similarity to condylomata acuminata but resembled seborrheic warts and were detected in 32 individuals. The preferential location was on the inguinal folds and the penile, pubic, vulvar, or perianal skin.

Condylomata plana: Condylomata plana—flat leukoplakia-like lesions—were disclosed in the mucosa of the portio of 5 female patients. Identification of these warts often was possible only after applying acetic acid or Lugol's solution as routinely used in colposcopic procedures.

Histologic Findings

The histologic patterns of the 4 different papilloma types proved to be similar and as a result inadequate for use in diagnostic differentiation (Table II). There were, however, 6 distinct cytoplasmatic vacuolization types (koilocytosis types 0–5) of squamous and granular cells. In some biopsies a com-

TABLE II. *Histologic patterns of anogenital warts*

	Condyloma acuminatum	Flat condyloma-like lesion	Pigmented papular lesion	Condyloma planum
Acanthosis	++	(+)	+	(+)
Granulosis	+	+/−	+/−	+/−
Papillomatosis	++	(+)	+/(+)	(+)
Orthokeratosis	++	(+)	++	(+)
Parakeratosis	+	+	+	+
Koilocytosis	++/−	(+)/−	(+)/−	++/−

TABLE III. *Correlation between the clinical picture, koilocytosis type, and HPV DNA present in anogenital warts*

Koilocytosis type	HPV-6	HPV-11	HPV DNA Type [a] 6 or 11[b]	HPV-16	HPV-6/-11/-16 neg
1	11 CAC	6 CAC 1 FCL	2 CAC		
2	4 CAC		1 CAC		
3	11 CAC	1 CAC	1 CAC		
4	8 FCL	1 FCL			
5	2 CAC	2 PPL	1 FCL		3 CAC 1 PPL
0	9 CAC	6 CAC	1 FCL	6 FCL[c] 2 PPL[c]	2 CAC 2 PPL
Total: 84	45	17	6	8	8

Key: CAC = condyloma acuminatum
  FCL = flat condyloma-like lesion
  PPL = pigmented papular lesion
[a] Hybridization under stringent condition.
[b] Not differentiated between HPV-6 or -11.
[c] Determined as bowenoid papulosis (histologically carcinoma in situ).

bination of 2 vacuolization types appeared. In these cases the predominant feature was taken as representative (Table III).

Koilocytosis type 1: This type was characterized by squamous cells with clearing of the cytoplasm, a centrally located nucleus of normal size depicting a "spoke-like" pattern, and often possessing a marked vesiculation of the nuclear plasma. The cytoplasmic vacuoles were of differing size and appeared to be separated by cytoplasmic filaments (Fig 1A).

Koilocytosis type 2: The squamous and granular cells were of varying size and clusters of them showed a prominent perinuclear cytoplasmic vacuolization which could be compared to "Swiss cheese" (Fig 1B). The nuclei of these cells appeared pyknotic and were pushed to the perimeter of the cells. The heterochromatin was dense and marginated (Fig 1B).

Koilocytosis type 3: This type featured equally sized cells with regularly marginated sickle-shaped nuclei of normal or reduced size and a more or less prominent clearing of the cytoplasm—so-called sickle-shape pattern (Fig 1C).

Koilocytosis type 4: The characteristic cell was a koilocyte depicting a so-called honeycomb pattern of the epidermis and possessing a marked perinuclear halo (Fig 1D). The nucleus appeared hyperchromatic and the chromatin was often marginated. Bi- and multinucleation was seen occasionally. The cytoplasm was located toward the outer surface of the cell and was hardly detectable. Vacuolization types 1, 3, and 4 presented a diffuse arrangement of the koilocytes whereas type 2 featured clustering of the vacuolized keratinocytes (Fig 1B).

Koilocytosis type 5: In a number of lesions investigated (Tables III–V) some vacuolization forms were present that could not classified within types 1–4 (Fig 2). Similarities between this heterogenous group and the clear cell types described earlier in common or flat warts occurred frequently [23].

Koilocytosis type O (non-koilocytotic lesions): No vacuolization at all was detected in biopsies of this type. Nuclei appeared to be hyperchromatic and upon occasion intranuclear vesiculation was found. Histologic markers indicating a productive
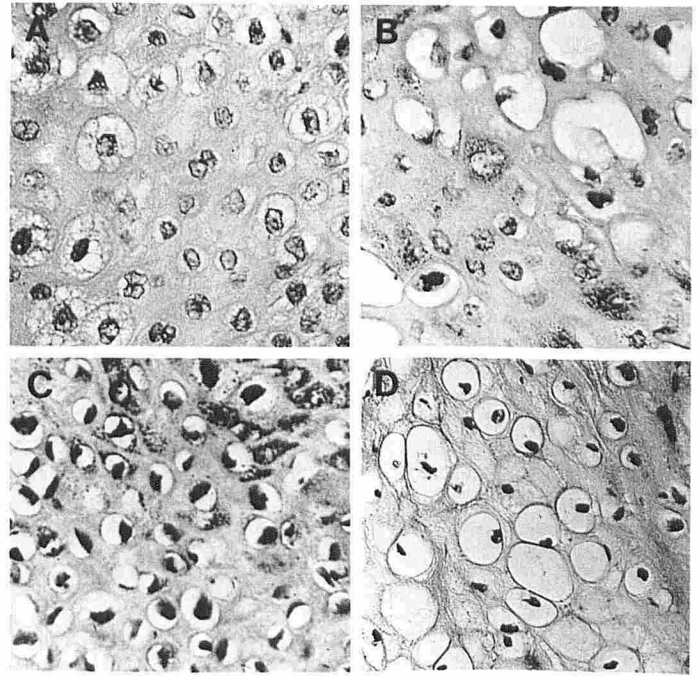

FIG 1. Cytologic features of the anogenital HPV infection. *A*, Section of a HPV-11-induced condyloma acuminatum. Koilocytosis type 1. *B*, Section of a HPV-6-induced condyloma acuminatum. Koilocytosis type 2. *C*, Section of a HPV-6-induced condyloma acuminatum. Koilocytosis type 3. *D*, Section of a flat condyloma-like lesion induced by HPV-11. Koilocytosis type 4. *A–D* H & E, × 460.

TABLE IV. *Distribution of the different koilocytosis types determined in 84 virologically distinct genital warts*

Koilocytosis type	Condylomata acuminata	Flat condyloma-like lesions	Pigmented papules
1	19	1	—
2	5	—	—
3	13	—	—
4	—	9	—
5	5	1	3
0	17	7[a]	4[b]

[a] Six of seven were bowenoid papulosis.
[b] Two of four were bowenoid papulosis.

TABLE V. *Immunocytochemical detection of papillomavirus capsid antigens in koilocytotic and non-koilocytotic anogenital warts*

Koilocytosis type	Number of specimens tested	Papillomavirus capsid antigen-positive anogenital warts
1	19	16
2	5	5
3	13	3
4	10	8
5	9	4
0	28	0
Total	84	36 (43%)

HPV infection such as koilocytosis were regularly absent (Fig 3A).

Type of atypia: The results of the histologic grading are summarized in Table VI. Koilocytotic condylomatous lesions showed either no atypia or a mild to moderate atypia (atypia I or II). Severe atypia (atypia III), in comparison, was found exclusively in non-koilocytic lesions which appeared clinically as flat condyloma-like papules or as pigmented lesions. The

histologic picture, however, classified them as bowenoid papulosis (Fig 3*B*).

Detection of PV Capsid Antigens Using the Immunoperoxidase-PAP Technique

In order to identify PV capsid antigens in virologically typed biopsies of anogenital warts, 84 specimens were investigated by means of the PAP staining technique. The presence of PV antigens was disclosed by an intranuclear, dark brown precipitate. Only a few epidermal nuclei in superficial and granular cells of genital warts were stained with regularity (Fig 4*A*). In contrast, common warts used as positive controls were characterized by an intense staining of a greater amount of nuclei in the deep squamous layer and superficial cells (Fig 4*B*).

As shown in Table V, PV capsid antigens were present in only 36/84 (43%) of the anogenital warts. On a more or less consistent basis biopsies of koilocytosis types 1–5 were antigen positive (64.3%) whereas PV antigens were uniformly absent in non-koilocytotic (type 0) lesions. It could be concluded, therefore, that koilocytes are pathognomonic for virus maturation.

Virus Classification

^{32}P-Labeled molecularly cloned DNAs of HPV-6, HPV-11, and HPV-16 were used as specimens to analyze the DNAs of 84 genital wart biopsies. The Southern blot hybridization technique was used (Fig 5) and results are presented in Table III.
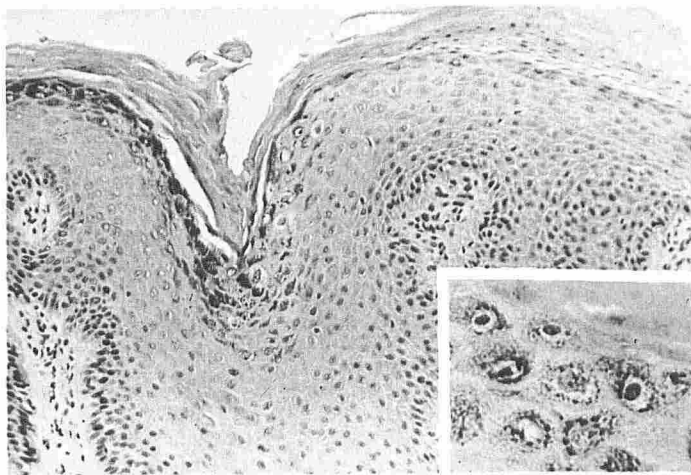

FIG 2. Section of a pigmented papular lesion associated with HPV-11. Koilocytosis type 5 (H & E, × 150). *Inset,* Marked granular layer with discrete cytoplasmic vacuolization and condensed keratohyaline granules as described in HPV-2-induced common warts (H & E, × 460).

In 54 of 59 condylomata acuminata, HPV-6 or HPV-11 DNA was detected. HPV-16 DNA was not found in any of the biopsies. Six of 18 flat condyloma-like lesions harbored HPV-16 DNA and were histologically classified as bowenoid dysplasia. The remainder of the flat condyloma-like lesions represented both clinically and histologically benign anogenital warts which were associated with HPV-6 (8 of 18), HPV-11 (2 of 18), or remained unclassified (HPV-6 or HPV-11) (2 of 18).

In pigmented papules (7 cases) HPV-6 was not detected; however, HPV-16 and HPV-11 DNA were present in 2 of 8 biopsies, respectively. In 3 cases the phenol-extracted cellular DNA did not hybridize either with HPV-6, HPV-11, or HPV-16 DNA (Table III). The HPV-16 positive lesions were classified as bowenoid papulosis, since histologic features of intraepithelial neoplasia were present. In contrast, the 2 HPV-11 positive lesions showed only mild epithelial atypia.

DISCUSSION

Four distinct HPV-associated anogenital epithelial lesions could be differentiated using the clinical picture. On a pathologic-anatomic level, however, a clear-cut classification was not possible. In line with the findings in skin warts [23], HPV-associated anogenital lesions showed characteristic patterns of cytoplasmatic vacuolization. Six different patterns were discernible: namely, 1 without koilocytosis and 5 with distinct koilocytotic features. One of these, koilocytosis type 5, however, included heterogenous vacuolization types, sometimes similar to flat or common warts [23]. A significant correlation between the clinical picture and the histologic typing could not be established. Nevertheless, some trends were observed as demonstrated in Table IV. It is, however, of particular significance to realize that these herein newly described flat condyloma-like lesions and pigmented papules, in parallel to the classic condylomata acuminata, are also HPV associated. It is likely that pigmented papules have, to date, not been recognized as a HPV-related disease, since their clinical appearance resembles that of seborrheic warts. Furthermore, their content of mature papillomavirus particles is rather minimal if not at times entirely lacking, with the result that the existence of PV structure antigens cannot be verified through use of the PAP assay.

The distribution of this study's HPV types into distinct genital warts is comparable to other reports [1] (Table III). No stringent correlation was established between the virus types

TABLE VI. *Histologic grading*

Koilocytosis type	Total number	Degree of epithelial atypia			
		0	I	II	III
1–5	130	17	95	18	0
0	59	0	17	20	22^a

^{a} Twenty-two cases with bowenoid papulosis from the anogenital and perineal skin.
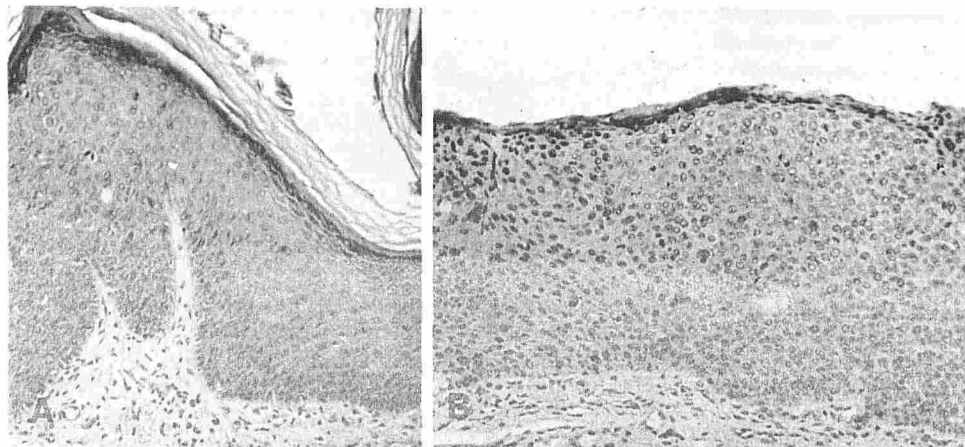

FIG 3. Sections of non-koilocytotic lesions (koilocytosis type 0). *A,* Section of a lesion from the glans penis appearing clinically as a flat condyloma-like lesion. Loss of polarity in the lower third of the epidermis, plumping of rete ridges. Hyperchromatic nuclei of the squamous layer with, occasionally, vesicular plasma. Mild atypia with individually keratinized cells in the basal layer (H & E, × 120). (HPV type not definitely available: HPV-6 or HPV-11 DNA.) *B,* Section of a HPV-16-induced flat condyloma-like papule from the penis with severe atypia. Pathologically-anatomically a bowenoid papulosis should be diagnosed (H & E, × 120.)
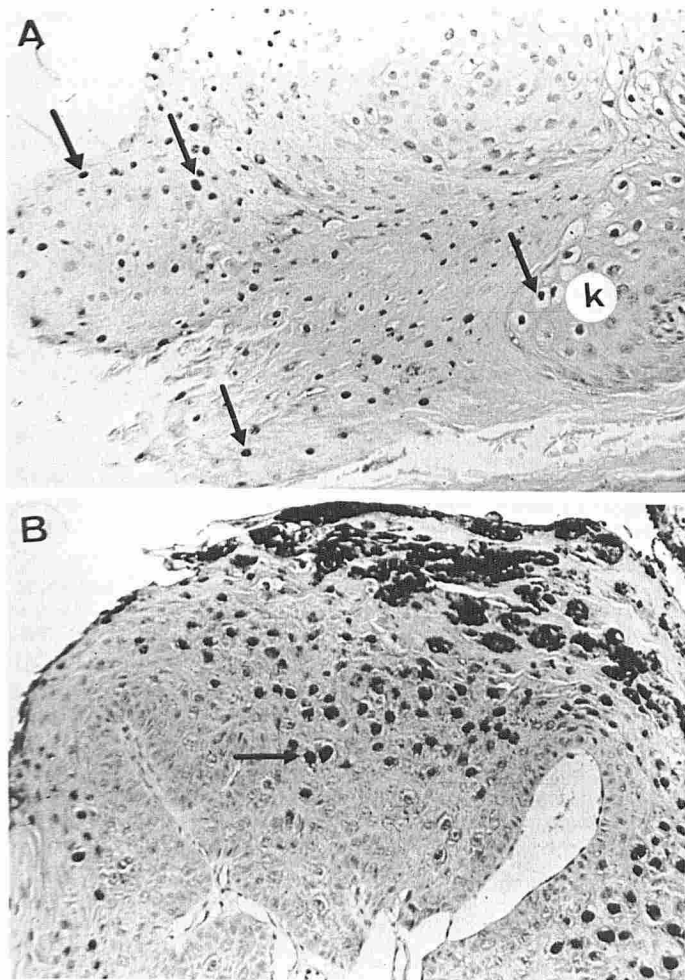
FIG 4. Demonstration of PV structural antigens using the immunoperoxidase-PAP technique. *A,* HPV-6-induced condyloma acuminatum. Positive reaction within nuclei of parakeratotic corneal and squamous cells (*arrows*). *k* = Koilocytes. H & E, × 120. *B,* HPV-2-induced common wart. *Arrow* points to positive cells in the deep squamous layer (H & E, × 120).

FIG 5. Blot hybridization of cellular DNA with ^{32}P-labeled HPV-11 DNA under stringent (*a–d*) and with ^{32}P-labeled HPV-16 DNA under nonstringent (*e–g*) conditions. DNAs extracted from 4 different condylomata acuminata (*a–d*) were cleaved with the Pst 1 restriction endonuclease and processed as described in *Materials and Methods.* Different HPV-6 subtypes were identified by their typical fragment pattern. DNA derived from a flat condyloma of the vulva (*e*) and from 2 pigmented papules (*f* and *g*) were cleaved with Bam HI. By washing at the nonstringent temperature, HPV DNA was identified in all 3 materials. Washing of the same filter at a higher temperature resulted in a loss of the label in lanes *e* and *g* (not shown), indicating the presence of a type of PV different from HPV-16.

and both the clinical picture and histology. It was discovered, however, that exophytic condylomatous lesions such as condylomata acuminata and the giant condylomata, show a preference for HPV-6 DNA, which was also found in flat condyloma-like lesions of the anogenital skin and anal mucosa. HPV-16 was detected exclusively in non-koilocytotic, flat, condyloma-like lesions and in those pigmented papules which were characterized histologically as bowenoid papules through the presence of intraepithelial neoplasia features. HPV-16 DNA, which has rarely been detected in benign genital lesions, has been verified in 24 of 54 of the cervical and 4 of 17 of the vulvar and penile carcinomas so far investigated and in a number of dysplasias and carcinomas in situ of the cervix, the vulva, and of the anogenital skin and mucosa of both sexes [1,4,8–11].

As a rule, koilocytosis in lesions with severe atypia was absent. The conclusion drawn was the existence of an inverse relationship between the extent of koilocytosis and the degree of epidermal atypia (Table VI), as described earlier by other authors [24,25]. In none of the non-koilocytotic lesions were HPV structural antigens detectable through PAP staining, perhaps due to poor reproduction of HPV-16 within these lesions. In contrast, a particle production was demonstrated immunocytochemically with regularity in biopsies of the koilocytosis types 1 through 5 (Table V, Fig 4). As verified through electron microscopy in a previous study [26], condylomata with koilocytosis type 2 appeared to contain more mature viral
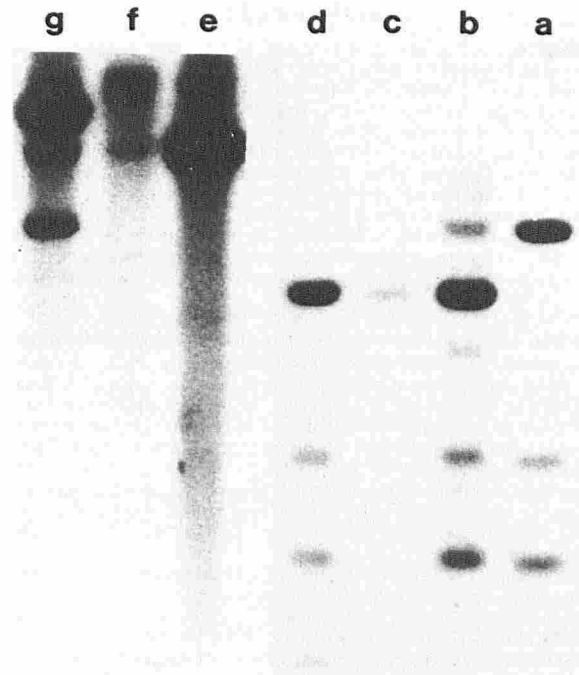
particles than did lesions of other types [1,12]. This is consistent with the repeated failure in detecting HPV particles in malignant squamous cell tumors using electron microscopy or the indirect immunoperoxidase-technique [27,28].

This together with the findings of other groups [24,25,28,29] indicates a correlation between koilocytosis and the expression of virus particles associated in anogenital HPV infections. The form of koilocytosis, however, does not allow the definition of a specific virus type.

Whereas Grusendorf-Conen et al conclude that with respect to viral warts a direct correlation between cytoplasmatic vacuolization and the differing amounts of virus particle production exists [30], we were not able to corroborate this interpretation in the case of genital warts where koilocytosis is mostly prominent and, in addition, virus particles are present only in minimal number or are lacking entirely.

The newly described classification of flat condyloma-like lesions and of pigmented papular lesions may be used to detect high-risk cancer patients, including their sexual partners. Recent observations employing these classifications implicate the transmission not only of HPV-6 and HPV-11 but also of HPV-16 between sexual partners (G. Gross et al, in preparation).

From the clinical point of view, however, routine histology, even with determination of koilocytosis type, is not sufficient in predicting the type of PV. In conclusion, therefore, a rapid and sensitive assay is required in order to detect condylomatous and condyloma-like lesions harboring possible oncogenic PV DNAs such as HPV-16 among others.

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