ABSTRACT

Fourteen patients with epidermodysplasia verruciformis were studied to correlate the type of human papillomavirus (HPV) found in benign lesions to their clinical aspects and to the course of the disease; nine patients were familial cases, and six had carcinomas. The type of the virus was determined by the RNA-DNA filter hybridization technique, using complementary RNA’s transcribed from the DNA’s of the four types of HPV’s previously identified, and by immuno-fluorescence studies, using antisera specific for the four types of viruses. HPV type 3 was found in seven patients presenting lesions of only the verruca plana type. These cases were mostly stationary or abortive and showed no malignant conversion. HPV type 4 was detected in four patients with lesions of different types: very flat, often reddish warts; reddish plaques; and pityriasis versicolor-like pigmented or achromic plaques. All these patients showed cancers. Both types of viruses were found in two patients: HPV type 3 in flat wart-like lesions and, for one patient, in large confluent pigmented plaques and HPV type 4 in reddish or pityriasis versicolor-like plaques. One of these patients had early malignant lesions (Bowen’s disease), and the other had multiple carcinomas. For one patient, the type of virus could not be identified because of an insufficient amount of material.

These results point to the role of virus in the pathogenesis of epidermodysplasia verruciformis, together with genetic and immunological factors. They suggest, in addition, different oncogenic potentials for viruses involved in the disease.

INTRODUCTION

EV2 (13) is a rare, lifelong disease characterized by disseminated skin lesions which usually resemble flat warts but may appear also as reddish plaques or pityriasis versicolor-like pigmented or achronic lesions (for review, see Refs. 9, 11, 15, and 25). Malignant transformation of some of the lesions has been observed in 25 to 30% of the cases; cancers are usually of the Bowen’s type (Bowen’s disease or Bowen’s carcinomas), but squamous or basal cell carcinomas are also found (9, 11, 15, 25). Many cases occur in families, and EV has been considered as a genodermatosis, probably transmitted by an autosomal recessive gene (11, 15, 23). Most of the patients thus far investigated showed abnormal cell-mediated immunity (5, 22).

Flat wart-like EV lesions were shown to be transmittable by auto- or heteroinoculation (10, 11, 14). Typical papillomavirus particles were regularly found by electron microscopy in benign lesions (1, 6, 7, 23, 25, 26, 29). They were also observed by some authors in situ carcinomas (3, 25, 29) but were never detected in advanced malignant lesions (1, 3, 8, 9, 25, 27, 29). It was long thought that the virus found in EV lesions was responsible for all viral skin warts (19, 24). It is only recently that different types of HPV showing distinct antigenic properties and only little DNA sequence homology were characterized in skin lesions (4, 17–21) and that the association of EV with particular types of HPV was demonstrated (20, 21). Of the 4 HPV types characterized in our studies, 2 of them, HPV-3 and HPV-4, were found in EV lesions (20). Furthermore, our previous study involving 11 patients (5 of them with cancers) had suggested that the aspect of EV lesions and the probability of malignant transformation could depend on the virus type (20). The aim of the present studies is to extend these results to 3 additional patients (one with cancers) and to analyze the correlation between the type of the virus, the clinical aspect of the lesions, and the course of the disease.

MATERIALS AND METHODS

Sample Collection. Scrapings and biopsies of lesions were collected from patients with EV who were attending the Department of Dermatology, Warsaw School of Medicine (Table 1). For virus purification and viral DNA extraction, repeated samples from some patients and, for some of them, from various types of lesions were collected in Eagle’s minimum essential medium containing antibiotics and were stored until use at −70 °C. For immunofluorescence studies, biopsies were either processed immediately or frozen in liquid nitrogen 12 to 24 hr after collection in culture medium.

Virus Purification and Viral DNA Preparation. EV HPV’s were purified from the pooled scrapings of each of the patients, T. G., J. K., E. D., J. D., and S. M., and HPV-1 and HPV-2 were purified from deep plantar warts and hand common warts, respectively, as previously described (18, 20). Viral DNA’s were obtained either by extraction from the
virions (20) or by selective extraction from the lesions (18), and DNA concentration was determined by electron micros-
copy as previously described (18).

Molecular Hybridization Experiments. DNA's from HPV-
1, HPV-2, J. D. HPV, and J. K. HPV (taken as prototypical
HPV-3 and HPV-4, respectively), as well as from T. G. HPV,
were transcribed in vitro into cRNA's, using Escherichia
coli RNA polymerase containing α-factor (a gift from S.
Saragosti, Institut Pasteur, Paris, France) (18). cRNA-DNA
filter hybridization under paraffin (12) was performed as
previously reported (18, 20).

Immunofluorescence Studies. Direct and indirect immu-
nofluorescence tests were performed mainly as described
by Beutner et al. (2). Specific guinea pig antiseras were
raised against full particles of HPV-1 (G 121, G 122), HPV-2
(G 206), HPV-3 [using J. D. HPV (G 280) or E. D. HPV (G
281)], and HPV-4 [using S. M. HPV (G 271)] or against empty
particles of HPV-4 [using J. K. HPV (G 251) or S. M. HPV (G
264)]. These sera had been used in previous studies (18,
20), except G 271, which was obtained under the conditions
described for other EV HPV's (20). Fluorescein-labeled IgG
fractions with a fluorescein to protein molar ratio of 2 or 5
were prepared from anti-HPV-1 antiserum as previously
described (16) and were used in direct immunofluorescence
tests at a concentration of 0.5 mg/ml. Anti-HPV-2, anti-HPV-
3, and anti-HPV-4 antiseras were used in indirect immuno-
fluorescence tests at a dilution of 1/80 to 1/320. Tissues
embedded in Tissue-Tek II O.C.T. compound medium (Lab-
Tek Products) were cut in a cryostat (SLEE, London, Eng-
land) at −20°. Seven-μm-thick sections were set on gelatin-
coated slides, fixed for 10 min at −20° in acetone, and
washed for 20 min in 0.05 M sodium phosphate/0.1 M NaCl
(pH 7.2). For direct immunofluorescence tests, sections
were incubated for 30 min at 37° with fluorescein-labeled
anti-HPV-1 IgG. For indirect immunofluorescence tests,
sections were incubated for 30 min at 37° with diluted
antiseras or preimmune sera and then, after washing, with
fluorescein-labeled anti-guinea pig IgG rabbit IgG at a
concentration of 0.5 mg/ml (fluorescein to protein molar
ratio ranging from 1 to 2.5) (16, 20). Sections were mounted
in buffered glycerol (pH 8.0), examined, and photographed
with an American Optical Company microscope or a Zeiss
Photomicroscope II.

RESULTS

Morphology of EV Lesions as Related to the Virus Type

Characteristics of EV Lesions. The 14 patients studied
are presented in Tables 1 and 2. Nine were familial cases,
and 6 had cancers. All patients had lesions on the dora
of the hands and on the face, and most of them had lesions
on the extremities and the trunk. Patients showed various
types of lesions: (a) flat wart-like lesions, somewhat more
elevated on the dorsa of the hands (Fig. 1) but in some
patients almost at the skin level and often reddish (Fig. 2);
(b) reddish plaques, usually on the trunk (Fig. 3); (c) scaling
brownish or achromatic lesions resembling pityriasis versi-
color (Fig. 4); (d) large, pigmented, irregularly shaped
confluent plaques (Fig. 5); and (d) common warts intermin-
gled with verruca plana-type lesions (Fig. 6).

Molecular Hybridization Data. In our previous studies
(20), characterization of the virus present in lesions of
patients with EV was performed by molecular hybridization
without taking into account the clinical types of the lesions.
However, results indicated the occurrence of HPV-3 in

Table 1

Patients with EV

<table>
<thead>
<tr>
<th>Patients</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Age at onset of disease (yr)</th>
<th>Carcinomas</th>
<th>Cell-mediated immunity</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. T. G.</td>
<td>M</td>
<td>52</td>
<td>5</td>
<td>++</td>
<td>–</td>
<td>Brother of J. K. and H. D.</td>
</tr>
<tr>
<td>2. J. K.</td>
<td>F</td>
<td>38</td>
<td>5</td>
<td>++</td>
<td>–</td>
<td>Mother of E. D., D. D., and W. D.</td>
</tr>
<tr>
<td>3. H. D.</td>
<td>F</td>
<td>46</td>
<td>11</td>
<td>+</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>4. E. D.</td>
<td>F</td>
<td>22</td>
<td>7</td>
<td>+</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>5. D. D.</td>
<td>F</td>
<td>21</td>
<td>7</td>
<td>+</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>6. W. D.</td>
<td>M</td>
<td>9</td>
<td>5.5</td>
<td>+</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>7. R. P.</td>
<td>M</td>
<td>47 Early childhood</td>
<td>37</td>
<td>+</td>
<td>–</td>
<td>Warts disappeared after biopsies</td>
</tr>
<tr>
<td>8. A. P.</td>
<td>F</td>
<td>25</td>
<td>10</td>
<td>+</td>
<td>–</td>
<td>Father of A. P.</td>
</tr>
<tr>
<td>9. E. I.</td>
<td>F</td>
<td>18</td>
<td>4</td>
<td>+</td>
<td>–</td>
<td>Father with long-standing, flat warts on hands</td>
</tr>
<tr>
<td>10. J. D.</td>
<td>M</td>
<td>43 Early childhood</td>
<td>37</td>
<td>+</td>
<td>–</td>
<td>Nonfamilial case</td>
</tr>
<tr>
<td>11. J. G.</td>
<td>M</td>
<td>24</td>
<td>7</td>
<td>+</td>
<td>–</td>
<td>Nonfamilial case</td>
</tr>
<tr>
<td>12. M. G.</td>
<td>M</td>
<td>21</td>
<td>7</td>
<td>+</td>
<td>–</td>
<td>Nonfamilial case</td>
</tr>
<tr>
<td>13. S. M.</td>
<td>M</td>
<td>22</td>
<td>8</td>
<td>+</td>
<td>–</td>
<td>Nonfamilial case</td>
</tr>
<tr>
<td>14. R. M.</td>
<td>M</td>
<td>36</td>
<td>2</td>
<td>+</td>
<td>–</td>
<td>Nonfamilial case</td>
</tr>
</tbody>
</table>

* Characteristics of benign lesions are described in Table 2.
* +, premalignant lesions of Bowen's type (carcinoma in situ) and single carcinoma; ++, multiple Bowen's carcinomas; ++++, invasive carcinomas, at various sites.
* Depressed (−), lowered (±), or preserved (+) nonspecific cell-mediated immunity, as checked by in vitro methods and cutaneous tests (5).³
* ND, not done.
Characteristics of the benign lesions of patients with EV

Table 2
Morphology and distribution of skin lesions

<table>
<thead>
<tr>
<th>Patients</th>
<th>Extension</th>
<th>Flat wart type</th>
<th>Reddish plaques</th>
<th>Pityriasis versicolor type</th>
<th>Pigmented plaques</th>
<th>Common warts</th>
<th>Activity</th>
<th>HPV type</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Elevated</td>
<td>Very flat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. T. G.</td>
<td>++</td>
<td>Hands, face</td>
<td>Trunk</td>
<td>Trunk, arms, thighs</td>
<td>++</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. J. K.</td>
<td>+++++</td>
<td>Hands, feet,</td>
<td>Face, extremities</td>
<td>Whole skin</td>
<td>Trunk, arms</td>
<td>++++</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>forearms, legs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>arms, thighs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. E. D.</td>
<td>++</td>
<td>As H. D.</td>
<td>Trunk</td>
<td>Trunk, arms, thighs</td>
<td>++++</td>
<td>3, 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. D. D.</td>
<td>+++</td>
<td>As H. D.</td>
<td>Whole skin</td>
<td>Trunk, arms, legs</td>
<td>+</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. W. D.</td>
<td>+</td>
<td>Face, hands</td>
<td>Hands, leg, foot</td>
<td>Trunk</td>
<td>++</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. R. P.</td>
<td>+</td>
<td>Hands</td>
<td></td>
<td></td>
<td></td>
<td>Inconclusive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. A. P.</td>
<td>+</td>
<td>Hands</td>
<td>Face</td>
<td></td>
<td>++</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. E. I.</td>
<td>+</td>
<td>Hands</td>
<td>Face</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. J. D.</td>
<td>+++</td>
<td>Face, extremities</td>
<td>Trunk</td>
<td>Trunk, arms, legs</td>
<td>++++</td>
<td>3, 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. J. G.</td>
<td>+</td>
<td>Hands</td>
<td>Face</td>
<td></td>
<td>++</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>12. M. G.</td>
<td>++</td>
<td>Hands</td>
<td>Face, thighs,</td>
<td></td>
<td>++</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>legs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. S. M.</td>
<td>+++</td>
<td>Face, extremities</td>
<td>Trunk</td>
<td>Trunk</td>
<td>++++</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. R. M.</td>
<td>+++++</td>
<td>Face, extremities</td>
<td>Trunk</td>
<td>Trunk</td>
<td>++</td>
<td>4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a +, hands and face; ++, hands, face, and some at other locations; ++++, widespread; +++++, generalized.
b Flat wart-type lesions are either somewhat elevated or very flat, almost at the skin level. Reddish plaques are flat macular lesions (up to 2 cm). Pityriasis versicolor-type lesions are brownish scaling or achromic plaques. Pigmented plaques are dark brown, large, confluent, and irregularly shaped lesions. Common warts are elevated hyperkeratotic papules.
c –, no new lesions for many years; + to +++++, from a few new lesions to extensive spreading at the time of studies.
d As determined in a previous study (20) and in this study.

The typical elevated flat wart-like lesions observed at first gradually flattened throughout the years. Although still slightly raised, the lesions are clearly distinct from those of the patient's relatives (Cases 3 to 6).

patients showing only flat wart-type lesions and, for Patient J. D., in confluent pigmented plaques, while HPV-4 was found in patients showing reddish plaques and/or pityriasis versicolor-like lesions together with somewhat flatter and reddish verruca plana-type lesions (Table 2).

Molecular hybridization data reported in Table 3 were obtained on 3 new patients and on different types of lesions of several patients, using cRNA's specific for the 4 types of HPV's, with J. D. and J. K. HPV's as prototypical HPV-3 and HPV-4, respectively. With the conditions used, 50 to 60% of the radioactivity binds to filters when homologous DNA's and cRNA's are hybridized, while almost no annealing is observed between heterologous prototypical cRNA's and DNA's. Of the 3 new patients, Patient T. G., showing reddish plaques and pityriasis versicolor-like lesions, was found to be infected by HPV-4, while Patient M. G., showing only wart-like lesions, was infected by HPV-3. The limited amount of material from Patient R. P. did not allow conclusions. A lesser extent of annealing was observed when T. G. and J. K. HPV cRNA's were hybridized with J. K. and T. G. DNA's, as compared to homologous hybridizations, confirming the genetic heterogeneity already reported for viruses belonging to type 4 (20). Data further reported in Table 3 show that viral DNA obtained from the reddish and pityriasis versicolor-like brownish plaques present on the back of Patient J. D. for some years (which have been spreading lately) annealed only with HPV-4 cRNA. These lesions had not been tested previously. Two viral DNA preparations obtained from lesions collected from the legs of this patient (Fig. 5) at a 1-year interval were both of HPV-3 type, but the most recent showed also some annealing with HPV-4 cRNA, coinciding with the eruption of a few reddish and brownish plaques at this location. Clear evidence for infection by HPV-3 and HPV-4 was also found for Patient D. D., whose wart-like lesions [analogous to those of her mother, H. D., and sister, E. D. (Fig. 1)] are clearly due to HPV-3 and whose reddish plaques [similar to those of her aunt, J. K. (Fig. 3), and uncle, T. G.] are due to HPV-4. HPV-2 was detected in the typical common warts of Patient J. G. (Fig. 6), while the viral DNA found in his flat wart-like lesions hybridized only with HPV-3 cRNA. The lesser extent of hybridization observed, as compared to HPV-3 prototypical DNA, confirms previous results obtained for this patient, which showed the genetic heterogeneity of viruses belonging to type 3 (20). However, HPV-4 was found both in flat verruca plana-type lesions and in reddish and pityriasis versicolor-like plaques (Fig. 4) of Patient R. M., as previously found for the different lesions of Patients J. K.
types of HPV with particular cutaneous lesions has been typical flat wart-like lesions gave a positive reaction only to confirm the data obtained by molecular hybridization. Axial studies have shown that viral capsid antigens are detected in the nuclei of the upper keratinizing cells and in keratinized cells of the lesions. Previous studies by the immunofluorescence technique, using specific antisera against each of the 4 HPV types. Previous studies have shown that viral capsid antigens are detected in the nuclei of the upper keratinizing cells and in keratinized cells of the lesions (18, 20). Results reported in Table 4 confirm the data obtained by molecular hybridization experiments. This is best illustrated for Patient D. D., whose typical flat wart-like lesions gave a positive reaction only with anti-HPV-3 antiserum (Fig. 7, a and b), while her reddish plaques gave a positive reaction only with anti-HPV-4 antiserum (Fig. 7, c and d). In addition, results show that, for most patients, no antigen could be detected with the 4 types of antisera in some of the samples tested. Widely variable amounts of viral antigens were also observed in a previous study of numerous common warts of a patient infected with HPV-2 (18).

**Malignant Conversion as Related to the Virus Type Found in EV Lesions**

Malignant conversion of lesions was observed only in the 6 patients infected with HPV-4, 2 of them being infected also with HPV-3 (Tables 1, 2, and 5). In Patient D. D., infected with both viruses, lesions were of early Bowen's disease type (carcinoma in situ) (Fig. 8) and were controlled by topical 5-fluorouracil. In other patients, malignant lesions were of Bowen's carcinoma type; they were usually multiple, mostly on light-exposed parts of the body, and sometimes invasive (Fig. 9); metastases were never observed.

**DISCUSSION**

Our studies indicate that the clinical aspect of the lesions, the course of the disease, and the malignant conversion in EV are related to the type of HPV responsible for the infection. Patients infected with HPV-3 alone show flat wart-like lesions, a more protracted course of the disease, and no malignant conversion (Tables 1 and 2). This includes abortive and/or stationary familial cases; in one of them, the lesions did not reappear after removal. HPV-4 infection results in flatter verruca plana-like lesions, often reddish, only slightly elevated on the dorsa of the hands, associated with redness plaques and pityriasis versicolor-like lesions mostly on the trunk. It was always associated with carcinomas.

Two patients were found to be infected by both viruses. One of them showed all the different types of lesions and had multiple premalignant or early malignant lesions of Bowen's disease type. It is worth stressing that her mother, sister, and brother were infected with HPV-3 and showed no malignant lesions, whereas her aunt and uncle were infected with HPV-4 and had multiple cancers. The second patient showed, in addition, large, pigmented, confluent plaques on the legs due to HPV-3 and had cancers, including an invasive carcinoma of the forehead. He was first considered to be infected only by HPV-3 (20) on the basis of molecular hybridization data obtained with 6 DNA preparations from limb lesions including large pigmented plaques until the plaques on his back were tested. Finally, HPV-2 was detected in typical common warts intermingled with elevated verruca plana-like lesions due to HPV-3 in one patient. This virus has been shown to be preferentially associated with common warts (18, 19), so its possible role in the few cases described as EV and showing hypertrophic typical common warts (15, 28) should be considered.

In conclusion, this study shows that the morphological aspects of lesions and the type of HPV associated with them may be of prognostic significance. It further reinforces our...
Table 4
Characterization of the virus present in different EV lesions by immunofluorescence techniques

<table>
<thead>
<tr>
<th>Patients</th>
<th>Elevated wart-type lesions</th>
<th>Very flat wart-type lesions</th>
<th>Reddish plaques</th>
<th>Pityriasis versicolor-type lesions</th>
<th>Other types of lesions tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. T. G.</td>
<td>HPV-4 (1/2)</td>
<td>HPV-4 (2/3)</td>
<td>HPV-4 (3/5)</td>
<td>HPV-4 (4/5)</td>
<td>HPV-4 (1/5)</td>
</tr>
<tr>
<td>2. J. K.</td>
<td>HPV-4 (1/4)</td>
<td>HPV-4 (2/3)</td>
<td>HPV-4 (3/5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. H. D.</td>
<td>HPV-3 (2/2)</td>
<td>HPV-3 (1/2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. E. D.</td>
<td>HPV-3 (4/5)</td>
<td>HPV-3 (1/1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. D. D.</td>
<td>HPV-3 (7/10)</td>
<td>HPV-3 (2/3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. W. D.</td>
<td>(0/2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. A. P.</td>
<td>HPV-3 (1/2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. E. I.</td>
<td>HPV-3 (1/3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. M. G.</td>
<td>HPV-3 (5/6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. S. M.</td>
<td>HPV-4 (4/4)</td>
<td>HPV-4 (1/1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. R. M.</td>
<td>HPV-4 (2/2)</td>
<td>HPV-4 (1/3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. M.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Numbers in parentheses, number of positive lesions versus number of lesions tested.

Table 5
Carcinomas in patients with EV as related to the virus type

<table>
<thead>
<tr>
<th>Virus type</th>
<th>Malignant conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV-3</td>
<td>0/7</td>
</tr>
<tr>
<td>HPV-4</td>
<td>4/4</td>
</tr>
<tr>
<td>HPV-3, HPV-4</td>
<td>2/2</td>
</tr>
</tbody>
</table>

Note Added in Proof
Since this manuscript was submitted, a classification of human papillomaviruses based on the chronological order of their identification was proposed. While the designation of HPV-1, HPV-2, and HPV-3 remains unmodified, HPV-4 should now be designated HPV-5 (Coggins, J. H., Jr., and zur Hausen, H. Meeting report: workshop on papillomaviruses and cancer. Cancer Res. 39: 545-546, 1979).

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REFERENCES
6. Grupper, C., Prunieras, M., Delescluse, C., Arouete, J., and Garely, E. Epidermodysplasia verruciforme: etude ultrastructurale et autoradiographique operational or through interaction with environmental factors, such as actinic radiations. Nevertheless, although molecular hybridization and immunofluorescence evidence for the persistence and the expression of the viral genome in EV carcinomas must be obtained, our data strongly suggest that HPV-4 is associated somehow with malignant progression and, thus, that one HPV, at least, has an oncogenic potential.

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Gérard Orth, Stefania Jablonska, Maria Jarzabek-Chorzelska, et al.


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