Efficacy of Interferons on Bowenoid Papulosis and Other Precancerous Lesions

Gerd Gross, Angelika Roussaki, and Uwe Papendick
Department of Dermatology (GG, AR), University School of Medicine, Hamburg-Eppendorf, and Thomae, Branch of Boehringer Ingelheim (UP), F.R.G.

Preliminary results of an open randomized trial of recombinant interferon gamma in patients suffering from bowenoid papulosis are described.

Recombinant interferon gamma was given subcutaneously to 12 patients at a daily dose of 4×10^6 I.U. by injection. Four patients each were assigned to one of three treatment groups consisting of continuous therapy (group A) with three subcutaneous injections per week for 13 weeks; intermittent block therapy (group B) with four six-week cycles consisting of five injections on days 1, 3, 5, 7, and 9 of each cycle; and intermittent single-dose therapy (group C) with six four-week cycles consisting of only one subcutaneous injection on day one of each cycle. At the twenty-sixth week after onset of therapy, complete responses were seen in three of four patients of treatment group A, whereas in the treatment groups B and C only one patient, respectively, responded partially.

These results suggest that in contrast to condylomata acuminata bowenoid papulosis lesions respond better to continuous than to intermittent interferon gamma injections. *J. Invest Dermatol 95:152S–157S, 1990*

Genital infections with human papilloma viruses (HPV) have long been recognized in the form of condylomata acuminata [1]. During the past decade a number of reports have described a disorder characterized by benign-appearing partially pigmented maculopapular lesions in the anogenital region of both sexes, exhibiting histologic features of a squamous cell carcinoma in situ (CIS) of Bowen's type. Due to the histologic similarity to true Bowen's disease, these lesions were described in 1970 as multicentric pigmented Bowen's disease (MPBD) [2], before they have received the term bowenoid papulosis in 1978 by Wade and coworkers [3,4]. In the meantime the same disorder has been reported in the medical literature under a large variety of different titles (Table I).

Abbreviations:
BPV: bovine papillomavirus
CIN: cervical intraepithelial neoplasia
Cis: carcinoma in situ
CO_2-laser: carbondioxide-laser
Gg: part of the NIH code for the interferon gamma standard
HBS-antigen: hepatitis B-virus surface-antigen
HPV: human papillomavirus
I.U.: international unit
MPBD: multicentric pigmented Bowen's disease
PIN: penile intraepithelial neoplasia
SGOT: serum-glutamat-oxalacetat-transaminase
  (aspertat-oxalacetat-transaminase)
VAIN: vaginal intraepithelial neoplasia
VIN: vulvar intraepithelial neoplasia

Although histologically difficult to differentiate from Bowen's disease, clinical and prognostic distinctions can be drawn between the two conditions (Table II). Bowenoid papulosis lesions are usually multiple and have a multicentric origin. The clinical appearance includes a spectrum of inconspicuous, non-condylomatous lesions with mostly smooth and only slight papillomatous surfaces. Lesions in the male are mainly located on the glans penis and the penile shaft, on the perianal skin, and also in the groins. In women, the whole external genital area including the perianal skin may be involved. The disorder affects predominantly young adults (mean age about 30 years) thus following the age distribution of sexually transmitted diseases such as genital herpes and condylomata acuminata, with which bowenoid papulosis may be associated [3,19–24]. There is a tendency to spontaneous regression after several months or years of duration, especially after delivery [8,9]. This is in contrast to Bowen's disease, where after a long duration invasive carcinoma develops. Bowenoid papulosis, the etiology of which was unknown until 1983 [25], is now regarded as a sexually transmitted HPV disease, mostly linked with HPV type 16 [21,24]. Recently, additional HPV types have been identified in these lesions in rare instances such as HPV 39 [26], HPV 40 (De Villiers EM, unpublished), and HPV 55 (Favre M, unpublished). DNA sequences of HPV 31, HPV 33, and HPV 34 have been detected in cervical intraepithelial neoplasia and in Bowen's disease of the skin, respectively [27–29]. Bowenoid papulosis is fundamentally identical with vulvar intraepithelial neoplasia (VIN) III and penile intraepithelial neoplasia (PIN) III, which exhibit the same histologic features as cervical intraepithelial neoplasia (CIN) III. Bowenoid papulosis is regarded as a "high-risk" disorder in cervical carcinogenesis, because the concurrent presence of HPV 16 DNA in genital CIS in both sexual partners was reported [18,21,22,24,30–33].

Although bowenoid papulosis lesions may regress spontaneously, the possibility exists that this disease, harboring HPV 16, is also a risk factor with respect to the etiology of genitoanal carcinoma. The risk of malignant change, however, is far higher in the cervix uteri than in the vulva, vagina, penis, and anus [1,21,22,34–37].

Factors that play the most important role for either the benign or malignant course of anogenital infections with potentially onco-

Table I. Synonyms for Bowenoid Papulosis

Name	Author(s)	Reference
Intraepithelial and infiltrative carcinoma of the vulva: Bowen's type	Abell and Gosling, 1961	[5]
Multicentric pigmented Bowen's disease (MPBD)	Lloyd, 1970 Kimura et al, 1978	[2] [6]
Reversible vulvar atypia	Friedrich, 1972	[7]
Bowenoid atypia of the vulva	Skinner et al, 1973	[8]
Multicentric Bowen's disease of the genitalia	Berger and Hori, 1978	[9]
Pigmented penile papules with carcinoma in situ changes	Katz et al, 1978	[10]
Early vulvar carcinoma	Kunschner et al, 1978	[11]
Bowenoid papulosis of the penis	Wade et al, 1978	[3]
Vulvar neoplasia in the young	Hilliard et al, 1979	[12]
Bowenoid papulosis of the genitalia	Wade et al, 1979	[4]
Carcinoma in situ of the vulva	Buscema et al, 1980	[13]
Intraepithelial carcinoma of the vulva	Kaplan et al, 1981	[14]
Multicentric vulvar carcinoma in situ	Wilkinson et al, 1981	[15]
Bowenoid dysplasia of the vulva	Ulbright et al, 1982	[16]
Vulvar intraepithelial neoplasia (VIN)	Crum et al, 1984	[17]
Penile intraepithelial neoplasia (PIN)	Levine et al, 1984	[18]

genic HPV types are deficient intracellular surveillance mechanisms [36] and an immunosurveillance mechanism directed against the virus-induced tumors. This last hypothesis is supported by the approximately 100-times increased incidence of anogenital malignant tumors in immunosuppressed patients [38–43]. Mainly the natural cell-mediated cytotoxicity seems to be responsible for the intact immunosurveillance in patients suffering from genital HPV disease and bowenoid papulosis [44]. Definitely less clear is the role of circulating antibodies in the regression of HPV-associated lesions. In this context it is noteworthy that there are endogenic factors such as hormones and exogenic factors such as cigarette smoking and drug addiction that may also modulate the outcomes of genital HPV disease and bowenoid papulosis [8–10,21,23].

THERAPEUTIC MODALITIES

There is a large number of therapeutic modalities in HPV associated precancerous lesions of the genital tract [22–24,45]. Radical surgical methods should be avoided in bowenoid papulosis because the course of this disease is often benign. Nevertheless, due to ignorance of this peculiar entity there are still young women with scars and psychologic disorders as a consequence of such therapies.

In analogy with CIN, superficial surgery such as vaporization with CO_2 laser, cryotherapy, or electrocautery is recommended. In addition, topical 5-fluorouracil or ointments containing vitamin A acid, are proposed [11–13]. In circumscribed disease, local surgical excision is generally indicated [6,45]. Similar to condylomata acuminata, bowenoid papulosis lesions tend to recur after ablative therapy or after initially successful topical treatment.

There are increasing data from clinical studies that support the hypothesis that interferon therapy is useful in HPV diseases such as viral warts, laryngeal papillomatosis, and condylomata acuminata [46]. Furthermore, clinical improvement was reported in flat condylomata of the uterine cervix, in VIN and CIN (Table III). In general, interferon-alpha, -beta, and -gamma have therapeutic effects in HPV-associated disease. Interferons can be given topically, intralesionally, or systemically both as monotherapy and as adjuvant together with the above-mentioned conventional procedures (Table III). In most of the early studies reported, interferon therapy consisted of various intra- or perilesional injections of human fibroblast interferon (interferon beta) or interferon alpha [46,61]. A cautionary note on the intralesional use of interferon in genital warts came from the description of a patient with HPV 16–induced

Table II. Differential Diagnosis

Characteristics	Bowenoid Papulosis	Bowen's Disease
Age of onset (years)	About 30	Over 50
Number of lesions	Multiple	Single
Distribution of lesions	Skin and mucous membranes	Skin
Spontaneous regression	+	−
Symptoms	None (slight pruritus)	Pruritus in about 50% of cases
Clinical appearance of disease	Lichenoid papules Pigmented papules (MPBD) Erythematous macules Leukoplakia-like lesions	Slightly raised erythematous plaque
Color of lesions	Pink/reddish Greyish/white Brown/black	Red White

Table III. Clinical Response of CIN, VIN, VAIN, and PIN to Interferon

Disease	Interferon	Administration	Number of Evaluated Patients	Complete Regression	Partial Regression	No Change	Author	Reference
CIN II–III	Alpha	Gel	15	3	—	12	Ikic et al, 1981	[47]
CIN II–III	Alpha	Gel	6	3	3	—	Möller et al, 1983	[48]
CIN II–III	Beta	Intralesional + gel	11	6	2	5	de Palo et al, 1984	[49]
VIN III	Beta	Intralesional + gel	2	1	—	1	de Palo et al, 1984	[49]
VAIN I–II	Alpha	Gel	8	3	2	3	Vesterinen et al, 1984	[50]
PIN I[a]	Beta	Intralesional	1	1	—	—	Gross et al, 1984	[51]
CIN II–III	Beta	Perilesional	16	8	2	6	de Palo et al, 1985	[52]
CIN II–III	Beta	Gel	7	2	4	1	Choo et al, 1985	[53]
CIN II–III	Alpha and Beta	Intralesional	12	9	—	3	Choo et al, 1986	[54]
CIN II–III	Alpha	Gel	13	3	—	10	Byrne et al, 1986	[55]
PIN III[b]	Alpha	Subcutaneous	3	1	2	—	Gross et al, 1986	[56]
CIN I–III	Alpha	Subcutaneous + gel	6	3	2	1	Schneider et al, 1987	[57]
VIN III	Alpha	Subcutaneous + gel	3	—	3	—	Schneider et al, 1987	[57]
VIN II[b]	Alpha	Subcutaneous	1	1	—	—	Slotman et al, 1988	[58]
CIN II–III	Gamma	Gel	24	10	9	5	Schneider et al, 1989	[59]
CIN II–III	Beta	Perilesional + gel	24	14	3	7	Neis et al, 1989	[60]

[a] Initially complete regressive, then relapse of a flat penile lesion histologically PIN III (Bowenoid papulosis).
[b] Low-dose cyclic therapy.

penile flat lesions (PIN I) which initially improved but then underwent neoplastic change (PIN III) [51].

As early as 1984, a placebo-controlled study showed that intramuscular injections of interferon-beta were effective in curing genital warts in 80% of the patients treated [62]. In contrast, clinical responses in 36–53% reported from controlled intralesional interferon-alpha studies [63,64] refer always to one to five selected warts and not to the total number of visible lesions. As untreated warts do not respond, and local pain and systemic toxicity are not conducive to further therapy, this approach has a rather low practical value.

In a smaller number of uncontrolled studies, interferons were also given to precancerous lesions such as CIN, VIN, vaginal intraepithelial neoplasia (VAIN), and also bowenoid papulosis–PIN (Table III).

In view of favorable results in condylomata acuminata with systemic (subcutaneous) cyclic therapy of low doses of recombinant interferon-alpha or recombinant interferon-gamma [65], bowenoid papulosis was treated using the same regimen of daily subcutaneous injections during seven consecutive days followed by a 4-week therapy-free interval. Such a cycle was repeated in the case of no or partial response. Both interferon-alpha$_2$ (daily dose 5×10^6 I.U.) and interferon-gamma (daily dose, 4×10^6 I.U.) lead to complete remission of bowenoid papulosis in one of three [56] and in three of six patients treated (Gross G, personal communication). This effect was seen, however, only after a very long treatment duration of about 7 to 10 months.

In order to improve efficacy and shorten duration of therapy, we have begun an open randomized trial in bowenoid papulosis patients with injections of recombinant interferon-gamma given subcutaneously to the healthy-appearing lateral aspect of the abdominal skin.

MATERIALS AND METHODS

Between October 1988 and November 1989, 12 patients of both sexes, 16 to 50 years of age, with constant or progressive bowenoid papulosis (duration of disease more than 6 months) histologically confirmed as CIS, entered the randomized open pilot study after giving written informed consent.

Recombinant Interferon-Gamma Interferon-gamma was provided by Dr. K. Thomae GmbH (Boehringer Ingelheim, FRG).

Natural human interferon-gamma is a glycoprotein with a molecular weight of 20,000–25,000 Daltons depending on the degree of glycosylation. The molecule has been shown to be active as an antiviral, antitumour, and immunomodulatory agent. The biologically active form is a dimer.

The gene for human interferon-gamma has been cloned and expressed in *Escherichia coli*. Recombinant human interferon gamma is a non-glycosylated molecule with a molecular weight of 17,500 Daltons. The material used had a specific activity of 2×10^7 IU/ 1 mg protein according to the NIH standard Gg 23-901-530 and a degree of purity more than 98%.

Vials containing 0.2 mg interferon gamma as lyophilized powder were reconstituted with 1 ml 0.9% NaCl solution.

Patients and Medication At the initial visit a standard medical history was taken and the patient was examined to exclude other severe sexually transmitted diseases. Further exclusion criteria were congenital or acquired immunodeficiency, positive HIV-1 and -2 serology, pregnancy, HBS-antigen seropositivity, decreased levels of leukocytes ($< 1.500/mm^3$) and platelets ($< 70.000/mm^3$), or elevated levels of both serum creatinin (> 1 mg %) and SGOT.

The patients were randomly assigned to one of three interferon-gamma treatment groups (dose per injection 0.2 mg, i.e., 4×10^6 I.U.) (Fig 1).

Group A: Continuous therapy with three subcutaneous injections of interferon-gamma per week for 13 weeks, i.e., a total of 39 injections.

Group B: Intermittent therapy consisting of five injections on days 1, 3, 5, 7, and 9 of each therapy cycle. Four 6-week cycles were planned, i.e., a total of 20 injections.

Group C: Intermittent therapy with only one subcutaneous injection given on the first day of the 4-week cycle. Duration of therapy is 24 weeks, with a total number of 6 subcutaneous injections.

Follow-Up Assessment of Response and Response Criteria After the initial visit, evaluation was performed in group A at the beginning of week 2 and then every two weeks until week 14, at weeks 20 and 26. Patients of group B were seen before every intermittent therapy regimen and at week 26. Patients of group C were evaluated before the administration of interferon-gamma, and at week 26. The response was assessed on the basis of clinical examination and colposcopy.

The results were allocated into four categories: complete regression, partial regression, no change, and progression of the disease.
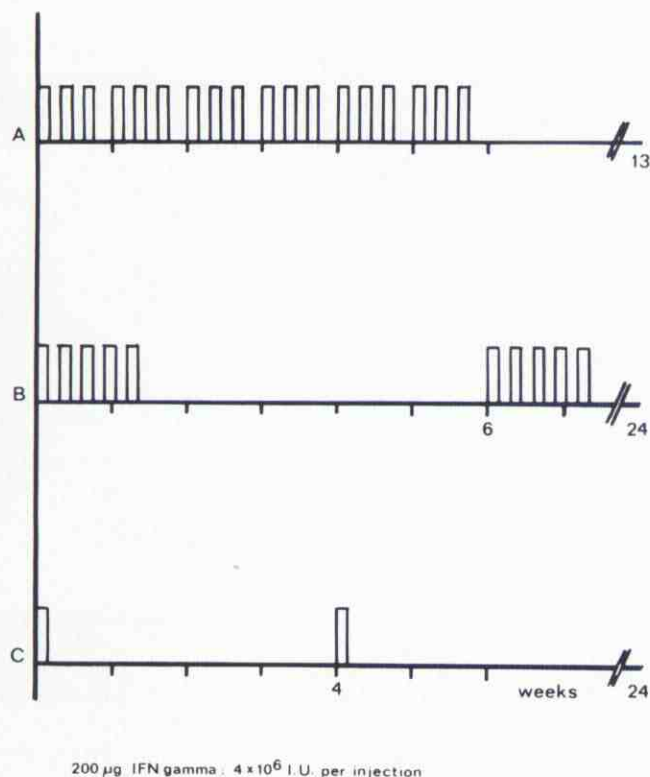
200 μg IFN gamma ; 4 x 10⁶ I.U. per injection

Figure 1. IFN gamma in Bowenoid papulosis. Three dosage regimens.

Complete regression was defined as the complete disappearance of the lesions by clinical investigation and colposcopy without any lesion being left. Partial regression was defined as a reduction of at least 50% of the lesions as determined by colposcopy. No change was defined as being a disease without clinical improvement at all and progression of the disease was defined as eruption of new lesions and/or an increase of more than 25% in size of existing bowenoid papulosis lesions.

Patients were strongly advised to use condoms during the treatment period and for 6 months after clearance of the lesions. Follow-up was carried out for 12 months after the lesions had been cured. All partners were also examined for the presence of bowenoid papulosis, CIN, and condylomata acuminata and treated if necessary.

RESULTS

We treated 12 patients with bowenoid papulosis with subcutaneous injections of 4×10^6 I.U. interferon-gamma. Four of the patients were allocated to three different treatment groups (Fig 1). There were no significant differences in clinical or other characteristics between the three groups (Table IV). In all cases at the beginning of the treatment the lesions had persisted for more than half a year. On average more than two other therapies had preceded therapy with interferon-gamma. At the twenty-sixth week after onset of therapy, the rates of complete clearance of bowenoid papulosis were higher

among the continuously treated group A. No patient in groups B and C receiving interferon-gamma intermittently, however, showed complete response (Table V). One patient in each of these groups had a partial response. There was a total of seven treatment failures. Side effects were seen in 7 of the twelve patients. Toxicity consisted mainly in influenza-like symptoms. Further complaints were burning eyes and dizziness. One patient suffering from both bowenoid papulosis and atopic dermatitis showed a refractory facial dermatitis. In total, severity and duration of side effects depended on the dosage regimen and were prominent in continuously treated patients.

DISCUSSION

There are many methods of treating bowenoid papulosis [23,24,45], but few of them have been assessed by controlled randomized trials. The present study was intended to obtain information on conservative therapy with interferon-gamma in patients suffering from recalcitrant bowenoid papulosis. The data indicate that low-dose systemic interferon therapy is effective in this disease. In contrast to previous trials in condylomata acuminata [65], however, bowenoid papulosis lesions respond better to continuous than to intermittent therapy. The main disadvantage of this therapy is the long duration.

Alternatively, interferon can be given as an adjuvant to superficial surgery especially to colposcopy-guided CO_2 laser, possibly also to 5-fluorouracil pretreated lesions [66,67]. The adjuvant gel therapy may also be effective in bowenoid papulosis and in Bowen's disease of immunocompromised patients such as HIV-positive individuals as was shown in genital wart patients with immunodefects [68]. The mechanism of this strategy is unclear. Probably the effect is independent of the "general" immune system, protecting uninfected basal epithelial cells against (re)infection with papilloma viruses or activating local immunogenicity [69]. So far it could not be demonstrated that interferon treatment inhibits HPV, as is known for bovine papilloma virus (BPV) type 1 [70]. In these anecdotal experiments it could be shown that interferon inhibits BPV 1 transformation of mouse C 127 cells, reduces the amount of extrachromosomal BPV-1 DNA in transformed cells, and cures the treated cells of the viral DNA.

Compared to destructive therapeutic methods, the systemic interferon approach is a conservative one, preventing side effects such as scarring. Furthermore, this treatment has the advantage of being active in all multiple and multifocal lesions, characteristic for bowenoid papulosis, CIN, and other precancerous HPV–associated diseases of the genital tract. Additionally, the injections can be given by the patients themselves. Thus, this treatment is very suitable for outpatients.

Experimental and clinical work is now necessary in order to answer questions regarding the influence of interferon on the HPV genome, especially on HPV 16 DNA, on the outcome of bowenoid papulosis, and on the other HPV–associated dysplasias such as VIN, CIN, and VAIN. Furthermore, close follow-up is required to obtain more information on long-term safety and on efficacy of interferon in HPV-related disorders.

Whether the systemic approach or the adjuvant approach will be followed in the future for the treatment of HPV-associated precancerous lesions will primarily depend on the grade of safety and efficacy in preventing invasive genital carcinoma in the long term.

Table IV. Characteristics of Treatment Groups

	Therapy Group A (n = 4)	Therapy Group B (n = 4)	Therapy Group C (n = 4)
Male/female	3/1	1/3	2/2
Age of patients in years [median (range)]	31.5 (29–35)	30.25 (23–35)	31 (24–41)
Duration of lesions in years [median (range)]	6.5 (2–16)	7.25 (3–15)	6.375 (0.5–14)
Number of lesions [median (range)]	7.5 (5–10)	3.75 (1–10)	6.5 (2–5)
Number of pretreatments [median (range)]	2.5 (1–4)	2.0 (1–3)	3.5 (1–6)

Table V. Recombinant Interferon Gamma in Bowenoid Papulosis — Results of the Study[a]

		Number of Patients Evaluated	Number of Interferon Administrations	Duration of Treatment (weeks)	Clinical Response			
					Complete Regression	Partial Regression	No Change	Progressive Disease
Group A	Continuous therapy	4	39	13	3		1	
Group B	Intermittent therapy	4	20	24		1	3	
Group C	Intermittent therapy	4	6	24		1	3	

[a] 200 μg recombinant interferon gamma, i.e., 4×10^6 I.U. by injection.

REFERENCES

1. Zur Hausen H: Human papillomaviruses and their role in squamous cell carcinomas. Curr Top Microbiol Immunol 78:1–30, 1977
2. Lloyd KM: Multicentric pigmented Bowen's disease of the groins. Arch Dermatol 101:48–51, 1970
3. Wade TR, Kopf AW, Ackermann AB: Bowenoid papulosis of the penis. Cancer 42:1890–1903, 1978
4. Wade TR, Kopf AW, Ackermann AB: Bowenoid papulosis of the genitalia. Arch Dermatol 115:306–308, 1979
5. Abell MR, Gosling JR: Intraepithelial and infiltrative carcinoma of the vulva: Bowen's type. Cancer 14:318–329, 1961
6. Kimura S, Hirai R, Harada R, Nagashima M: So-called multicentric Bowen's disease. Report of a case and a possible etiologic role of human papillomavirus. Dermatologica 157:229–237, 1978
7. Friedrich EG: Reversible vulvar atypia. A case report. Obstet Gynecol 39:137–141, 1972
8. Skinner MS, Sternberg WH, Ichinose H: Spontaneous regression of bowenoid atypia of the vulva. Obstet Gynecol 39:173–181, 1973
9. Berger BW, Hori Y: Multicentric Bowen's disease of the genitalia. Spontaneous regression of lesions. Arch Dermatol 114:1698–1699, 1978
10. Katz H, Posalaky Z, McGinley D: Pigmented penile papules with carcinoma in situ changes. Br J Dermatol 99:155–162, 1978
11. Kunschner A, Kenbour A, David B: Early vulvar carcinoma. Am J Obstet Gynecol 132:599–602, 1978
12. Hilliard GD, Massey FM, O'Toole RV: Vulvar neoplasia in the young. Am J Obstet Gynecol 135:185–188, 1979
13. Buscema J, Woodruff JD, Petros P: Carcinoma in situ of the vulva. Obstet Gynecol 64:16–20, 1980
14. Kaplan AL, Kaufmann RH, Birken RA: Intraepithelial carcinoma of the vulva with extension to the anal canal. Obstet Gynecol 58:368–371, 1981
15. Wilkinson EJ, Friedrich EG, Fu YS: Multicentric nature of vulvar carcinoma in situ. Obstet Gynecol 58:69–74, 1981
16. Ulbright TM, Stehmann FB, Roth IM: Bowenoid dysplasia of the vulva. Cancer 50:2910–2919, 1982
17. Crum CP, Liskow A, Petros P: Vulvar intraepithelial neoplasia (severe atypia and carcinoma in situ): a clinicopathologic analysis of 41 cases. Cancer 54:1429–1434, 1984
18. Levine RM, Crum CP, Herma F: Cervical papillomavirus infection and intraepithelial neoplasia: a study of male sexual partners. Obstet Gynecol 64:16–20, 1984
19. Gross G, Hagedorn M, Ikenberg H, Rufli T, Dahlet C, Grosshans E, Gissmann L: Bowenoid papulosis. Presence of human papillomavirus (HPV) structural antigens and of HPV 16-related DNA sequences. Arch Dermatol 121:858–863, 1985
20. Gross G, Ikenberg H, Gissmann L, Hagedorn M: Papillomavirus infection of the anogenital region: correlation between histology, clinical picture and virus type. Proposal of a new nomenclature. J Invest Dermatol 85:147–152, 1985
21. Gross G, Ikenberg H, de Villiers EM, Schneider A, Wagner D, Gissmann L: Bowenoid papulosis: a venereally transmissible disease as reservoir for HPV 16. In: Zur Hausen H, Peto P (eds.). Origin of
22. Gross G: Lesions of the male and female external genitalia associated with human papillomaviruses. In: Syrjänen K, Gissmann L, Koss LG (eds.). Papillomaviruses and Human Disease. Springer-Verlag, Berlin, 1987, pp 197–234
23. Obalek S, Jablonska S, Orth G: HPV associated intraepithelial neoplasia of external genitalia. Clin Dermatol 3:104–113, 1985
24. Obalek S, Jablonska S, Beaudenon MB, Walczak L, Orth G: Bowenoid papulosis of the male and female genitalia: risk of cervical neoplasia. J Am Acad Dermatol 14:433–444, 1986
25. Ikenberg H, Gissmann L, Gross G, Grussendorf-Conen EI, Zur Hausen H: Human papillomavirus type-16-related DNA in genital Bowen's disease and in bowenoid papulosis. Int J Cancer 32:563–565, 1983
26. Beaudenon S, Kremsdorf D, Obalek S, Jablonska S, Pehau-Arnandet M, Croissant O, Orth G: Plurality of genital human papillomaviruses: characterization of two new types with distinct biological properties. Virology 161:374–384, 1987
27. Beaudenon S, Kremsdorf D, Croissant O, Jablonska S, Wain-Hobson S, Orth G: A novel type of human papillomavirus associated with genital neoplasia. Nature 321:246–249, 1986
28. Kawashima M, Jablonska S, Favre M, Obalek S, Croissant O, Orth G: Characterization of a new type of human papillomavirus found in a lesion of Bowen's disease of the skin. J Virol 57:688–692, 1986
29. Lorincz AT, Lancaster WD, Temple GF: Cloning and characterization of the DNA of a new human papillomavirus from a woman with dysplasia of the uteri cervix. J Virol 58:225–229, 1986
30. Gross G, Wagner D, Hauser-Brauner B, Ikenberg H, Gissmann L: Bowenoide Papulose und Carcinoma in situ der Cervix uteri bei Sexualpartnern. Hautarzt 36:465–469, 1985
31. Barrasso R, de Brux J, Croissant O, Orth G: High prevalence of papillomavirus-associated penile intraepithelial neoplasia in sexual partners of women with cervical intraepithelial neoplasia. N Engl J Med 317:916–920, 1987
32. Gross G, Schneider A, Hauser-Brauner B, Wagner D, Ikenberg H, Gissmann L: Transmission of genital papillomavirus infections: a study of sexual partners. J Cell Biochem (suppl) 96:71, 1985
33. Hauser B, Gross G, Schneider A, de Villiers EM, Gissmann L, Wagner D: HPV 16 related bowenoid papulosis. Lancet II:106, 1985
34. Planner RS, Andersen HE, Hobbs JB, Williams RA, Fogarty LF, Hudson PJ: Multifocal invasive carcinoma of the vulva in a 25-year-old woman with bowenoid papulosis. Aust NZ J Obstet Gynecol 27:291–295, 1987
35. Bergeron C, Naghashfar Z, Canoan C, Shah K, Fu YS, Ferency A: Human papillomavirus type 16 in intraepithelial neoplasia (bowenoid papulosis) and coexistent invasive carcinoma of the vulva. J Gynecol Pathol 6:1–11, 1987
36. Zur Hausen H: Intracellular surveillance of persisting viral infections. Human genital cancer results from deficient cellular control of papillomavirus gene expression. Lancet II:1370–1372, 1986
37. Bracken RB: Genitourinary cancer. Cancer Chemother 2:199–242, 1981
38. Porecco R, Penn I, Droegmueller W, Greer B, Makowski E: Gyneco-

logic malignancies in immunosuppressed organ homograft recipients. Obstet Gynecol 45:359–364, 1975

39. Pelissier CI, Yaneva M, Joubert E: Cancers genitaux et lesions precancereuses chez les femmes transplantees renales. A propos de l'etude de 90 femmes greffees. Gynecologie 32:359–365, 1981

40. Penn I: Cancers of the anogenital region in renal transplant recipients. Analysis of 65 cases. Cancer 58:611–616, 1986

41. Schneider V, Kay S, Lee HM: Immunosuppression as a high-risk factor in the development of condyloma acuminatum and squamous neoplasia of the cervix. Acta Cytol 27:220–224, 1983

42. Sillmann FH, Stanek A, Sedlis A, Rosenthal J, Lauks KW, Buchhagen D, Nicastri A, Boyce G: The relationship between human papillomavirus and lower genital intraepithelial neoplasia in immunosuppressed women. Am J Obstet Gynecol 150:300–308, 1984

43. Sillmann FH, Sedlis A: Anogenital papillomavirus infections and neoplasia in immunodeficient women. Obstet Gynecol Clin North Am 14:537–558, 1987

44. Malejczyk J, Majewski S, Jablonska S, Orth G: Natural cell-mediated cytotoxicity in patients with anogenital lesions induced by potentially oncogenic human papillomaviruses. In: Steinberg BM, Brandsma JC, Taichman LB (eds.). Cancer cells 5, Papillomaviruses. Cold Spring Harbor, New York, 1987, pp 381–385

45. Schwartz RA: Bowen's disease. In: Schwartz RA (ed.). Skin Cancer: Recognition and Management. Springer Verlag, New York, 1988, pp 26–35.

46. Androphy EJ: Papillomaviruses and interferon. In: Ciba Foundation Symposium 120: Papillomaviruses. Wiley and Sons, New York, 1986, pp 221–228

47. Ikic D, Kirchmajer V, Maricic Z, Jasic D, Krusic J, Knezevic M, Rode B, Soos E: Application of human leukocytic interferon in patients with carcinoma of the uterine cervix. Lancet I:1027–1030, 1981

48. Möller BR, Johannesen E, Osther K, Ulmsteen U, Hastrup J, Berg K: Treatment of dysplasia of the cervical epithelium with an interferon gel. Obstet Gynecol 62:625–629, 1983

49. de Palo G, Stefanon B, Rilke F, Ghione M: Human fibroblast interferon in cervical and vulvar intraepithelial neoplasia associated with papilloma virus infection. Int J Tissue Reac VI (6):523–526, 1984

50. Vesterinen E, Meyer B, Cantell K, Purola E: Topical treatment of flat vaginal condyloma with human leukocyte interferon. Obstet Gynecol 64:535–538, 1984

51. Gross G, Ikenberg H, Gissmann L: Bowenoid dysplasia in human papillomavirus 16 DNA positive flat condyloma during interferon beta treatment. Lancet I:1467–1468, 1984

52. de Palo G, Stefanon B, Rilke F, Pilotti S, Ghione M: Human fibroblast interferon in cervical and vulvar intraepithelial neoplasia associated with viral cytopathic effects. J Reprod Med 30:404–408, 1985

53. Choo YC, Hsu C, Seto WH, Miller DG, Merigan TC, Ng NH, Ma HK: Intravaginal application of leukocyte interferon gel in the treatment of cervical intraepithelial neoplasia (CIN). Arch Gynecol 237:51–54, 1985

54. Choo YC, Seto WH, Hsu C, Merigan TC, Tan YH, Ma HK, Ng NH: Cervical intraepithelial neoplasia treated by perilesional injection of interferon. Br J Obstet Gynecol 93:372–379, 1986

55. Byrne MA, Möller BR, Taylor-Robinson D, Harris JRW, Wickenden C, Malcolm ADB, Anderson MC, Coleman DV: The effect of interferon on human papillomavirus associated with cervical intraepithelial neoplasia. Br J Obstet Gynecol 93:1156–1174, 1986

56. Gross G, de Villiers EM, Roussaki A, Papendick U, Schöpf E: Successful treatment of condylomata acuminata and bowenoid papulosis with subcutaneous injections of low-dose recombinant interferon alpha. Arch Dermatol 122:749–750, 1986

57. Schneider A, Papendick U, Gissmann L, de Villiers EM: Interferon treatment of human genital papillomavirus infection: importance of viral type. Int J Cancer 40:610–614, 1987

58. Slotman BJ, Helmerhorst TJM, Wijermans PW, Calame JJ: Interferon-alpha in treatment of intraepithelial neoplasia of the lower genital tract: a case report. Eur J Obstet Gynecol Reprod Biol 27:327–333, 1988

59. Schneider A, Kirchmayr R, Wagner D, Schlunck G, Papendick U: Efficacy trial of topically applied gamma interferon in cervical intraepithelial neoplasia. In: Gross G (ed.). Genital Papillomavirus Infections. Advances in Modern Diagnostic and Therapy, abstract 57, Hamburg, 1989

60. Neis KJ, Tesseraux M, Claußen C, Hündgen M, Bastert G: Lokale Therapie cervikaler intraepithelialer Neoplasien mit natürlichem beta-Interferon. Arch Gynecol 245:550, 1989

61. Weck T, Debra A, Buddin MSN, Whisnant JK: Interferons in the treatment of genital human papillomavirus infections. Am J Med 855(2A):159–164, 1988

62. Schonfeld A, Schattner A, Crespi M, Levari H, Shoham J, Nitke S, Wallach D, Hahn T, Yarden O, Revel M: Intramuscular human interferon-beta injections in treatment of condylomata acuminata. Lancet I:1038–1041, 1984

63. Eron LJ, Judson FN, Tucker S, Prawer S, Mills J, Murphy K, Hickey M, Rogers M, Flannigan S, Hien N, Katz H, Goldman S, Gottlieb A, Adams K, Barton P, Tanner D, Taylor E, Peets E: Interferon therapy of condylomata acuminata. N Engl J Med 315:1059–1069, 1986

64. Vance JC, Bart BJ, Hansen RC, Reichman RC, McEwen C, Hatch KD, Berman B, Tanner DJ: Intralesional recombinant alpha-2 interferon for the treatment of patients with condyloma acuminatum or verruca plantaris. Arch Dermatol 122:272–277, 1986

65. Gross G, Ikenberg H, Roussaki A, Drees N, Schöpf E: Systemic treatment of condylomata acuminata with recombinant interferon alpha-2a: low-dose superior to the high-dose regimen. Chemotherapy 32:537–541, 1986

66. Hohenleuthner U, Landthaler M, Braun-Falco O, Schmöckel C, Haina D: Condylomata gigantea (Buschke-Löwenstein Tumor). Behandlung mit dem CO_2-Laser und Interferon. Dtsch Med Wochenschr 113:985–987, 1988

67. Tiedemann KH, Ernst TM: Kombinationstherapie von rezidivierenden Condylomata acuminata mit Elektrokaustik und alpha-2 interferon. Akt Dermatol 14:200–204, 1988

68. Gross G, Roussaki A, Pfister H: Recurrent vulvar Buschke-Löwenstein's tumor-like condyloma acuminata and Hodgkin's disease effectively treated with recombinant interferon alpha 2c gel as adjuvant to electrosurgery. In: Fritsch P, Schuler G, Hintner H (eds.). Immunodeficiency and skin. Current Problems In Dermatology, Vol. 18. Karger, Basel, 1989, pp 178–184

69. Edelson RL, Fink JM: The immunologic function of skin. Sci Am 252:34–41, 1985

70. Turek L, Byrne JC, Lowy DR, Dvoretzky I, Friedmann RM, Howley PM: Interferon induces morphological reversion with elimination of extrachromosomal viral genomes in bovine papillomavirus-transformed mouse cells. Proc Natl Acad Sci USA 79:7914–7918, 1982