of view, it should be so (11–13). An escape from this impasse might be direct interference of dithranol in the dermis. Indeed, such an involvement, resulting in the release of mediators of inflammation which result in inflammation, seems unlikely (14, 15). As melanin is localized exclusively in the epidermis, the pigmentary system might not be in a position to scavenge dithranol-induced free radicals at the site of action in the dermis.

In conclusion, the present study does not support the hypothesis that the pigmentary system is of relevance to dithranol-induced irritancy.

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Melanocytic Proliferation in Condylomata Acuminata

A Report of Two Cases and Investigation by In situ Hybridisation

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Two cases of melanocytic lesions occurring in condylomata acuminata are described. In situ hybridization with human papillomavirus (HPV) DNA probes specific for 6 b, 11, 16, 18 revealed positivity with HPV 6 and 11, in the non-dysplastic condylomata, and HPV 18 positivity in the case showing severe dysplasia. The HPV localization was confined to the superficial parakeratotic zones, remote from the melanocytic proliferation. The relationship between human papillomavirus and the melanocytic lesions is discussed. ***Key words: Melanoma; Human papillomavirus.***

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The incidence of clinically obvious genital warts (condylomata acuminata) has more than doubled in the past 10 years, and this has paralleled the increase in cases of cervical intraepithelial neoplasia (CIN) in women under 35 years old (1). Evidence from various sources indicates that the human papillomavirus

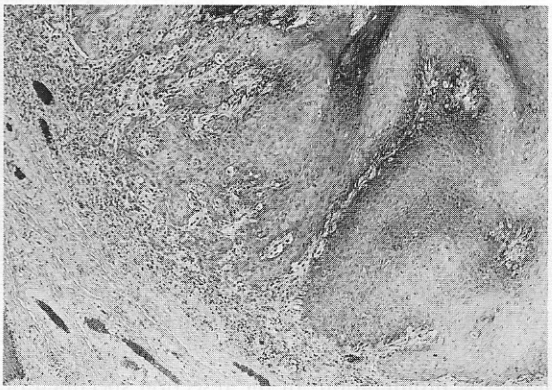

Fig. 1. Case 1. Diffuse melanocytic proliferation is present in the condyloma (left). There is continuous involvement of the basal layer with disruption of the dermo-epidermal junction. (*Right*) Typical acanthotic hyperplasia and hypergranulosis of the condyloma. H&E, ×32.

(HPV) plays a role in the development of condylomata, CIN and squamous carcinoma. HPV types 6 and 11 are associated with condylomata acuminata and low grade CIN, whereas HPV types 16 and 18 are found in higher grades of CIN and invasive carcinomas of the cervix (2–5). There have been no reports indicating a melanocytic component in such viral lesions; however, Scheurlen et al. have identified wart virus DNA in a malignant melanoma of superficial spreading type (6).

We report here 2 cases of melanocytic lesions, occurring within condylomata acuminata, one a superficial spreading malignant melanoma the other localized atypical melanocytic hyperplasia. While these may represent chance findings, they raise the question of a viral role in the aetiology of melanoma. The lesions also presented problems of clinical management.

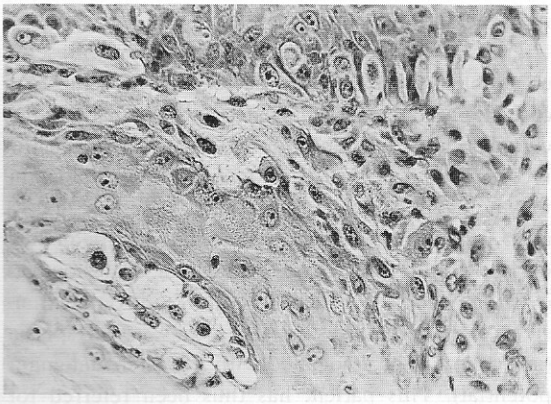

Fig. 2. Case 1. Continuous junctional proliferation of spindle-shaped melanocytes. They show nuclear variation, prominent nucleoli and occasional mitoses. Melanocytes have invaded the epidermis (though not reaching the surface layer of the thickened fronds) and the papillary dermis. H&E, ×218.

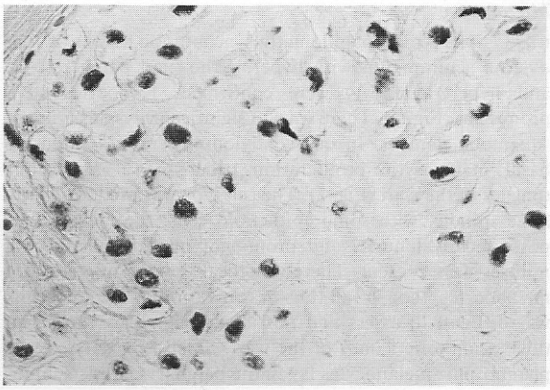

Fig. 3. Case 2. Strong positivity from the HPV 18 probe, confined to the superficial layers, and not seen in association with the melanocytic component. ×268.

CASE REPORTS

Case 1

A 17-year-old female presented with multiple perianal and perineal warts of 2 months' duration, and was found on examination to have approximately fifteen typical condylomata acuminata around the vulvar and anal margins. Relevant medical history was of a termination of pregnancy and administration of the oral contraceptive pill. She smoked 20–30 cigarettes per day.

The genital warts were initially treated with 2% eosin, following which she was referred for surgery. Under a general anaesthetic, the warts were removed by curettage and she was discharged.

Case 2

A 20-year-old woman presented with vulvar warts of 6 months' duration. On examination, she was found to have multiple vulvar warts and a pigmented papule on her left vulva. Initially the pigmented lesion was excised locally but following the pathology report a wider margin of skin was removed around the wound.

Pathology

Biopsy samples were processed and paraffin sections produced in the routine manner. Additionally, representative blocks were selected for in situ hybridization, performed by the method described by Lewis et al. (7), using HPV DNA probes specific for 6b, 11, 16 and 18.

Microscopy

Case 1: The typical papillomatous, acanthotic lesions of condyloma acuminatum with hyper, ortho- and parakeratosis, and hypergranularity, were confirmed. Koilocytes were prominent (Fig. 1). There was no significant dysplasia in the squamous element. In one condyloma there was extensive basal melanocytic proliferation occupying at least four tongues of the wart (Fig. 2). The cell type was predominantly large spindle, with some epithelioid cells; the melanocytes possessed oval nuclei and prominent nucleoli. Occasional mitoses were present. There was focal upward migration of melanocytes, though full thickness invasion of the epidermis was difficult to assess and possibly obscured by the broad thick acanthotic fronds of the wart. Small aggregates of the pleomorphic melanocytes lay in the papillary dermis/submucosa where there was associated rich vascularization and a moderate lymphocytic infiltrate. The appearance was of a superficially invasive malignant melanoma which was closely excised on lateral and deep aspects.

In-situ hybridization revealed the presence of HPV 6 and 11, focally and strongly in the more superficial layers of the condyloma, but not in the melanocytic component. Neither HPV 16 nor 18 were identified.

Case 2. The initial biopsy showed typical papilliferous, hyper- and parakeratotic lesions. Additionally, there was atypical melanocytic hyperplasia within the basal layers but without upward invasion into the epithelium. There was no dysplasia within this condyloma. However, wider excision showed coexistent condylomatous and dysplastic changes amounting focally to severe dysplasia (VIN III); no residual melanocytic component was identified.

In-situ hybridization of the initial biopsy showed focal positivity with HPV 6, again in the superficial layers of the lesions. The melanocytic component was negative. In the wider excision, HPV 6 and 11 were found in the wart areas now showing dysplastic changes. However, HPV 18 was present in the area showing severe dysplasia (Fig. 3).

DISCUSSION

The incidence of malignant melanoma varies from one country to another, but several studies indicate a generally rising trend (8, 9). However, melanomas occurring in the perineal area are uncommon and usually affect the over-60 age group (10). In the second case the lesion could represent a pre-existing naevus that had been present in the vulvar skin, having been drawn into the developing wart, but in case 1 the pattern of melanocytic proliferation, atypia and invasion were unacceptable as a junctional naevus. In neither case were there specific features within the lesion or at its margin to suggest histological criteria for a pre-existing dysplastic naevus.

The possibility of a virally provoked proliferation is speculative. A possible association between koilocytic and dysplastic lesions of cervix and malignant melanoma has recently been suggested (11), these being an over-representation of malignant melanoma in a group of women with cervical dysplasia and a similar higher incidence of CIN in women with malignant melanoma. In situ hybridization using the HPV DNA probes specific for the types normally associated with the genital tract, i.e. 6, 11, 16, 18, showed strong, focal 6 and 11 positivity in the parakeratotic zones of the warts containing the melanocytic lesions. The melanocytic population failed to stain for any of the four HPV types sought. No 16 or 18 staining was seen in the non-dysplastic condylomata containing the melanocytic proliferation. In the resection specimen of case 2, HPV 18 was found in the epithelium showing severe dysplasia. One might predict that the melanocyte with its slow cell turnover would be less susceptible to viral entry and replication than is the labile population of basal cells. Of course an unexpected HPV type may be involved in the melanocytic proliferative lesions. In this respect the HPV types found in the superficial spreading melanoma by Scheurlen's group were HPV 17a and a new type called HPV 37. The latter is closely related to HPV 9, 15, 17, 22 and 23 (6). These HPV types were not sought in the present study.

In the absence of other evidence one may propose an unrelated coincidental development of viral and melanocytic lesions. However, with the increasing incidence of genital warts, their more frequent removal and histological assessment, their more detailed evaluation for dysplasia and with more sophisticated methods of viral localization, we may see changes in other resident skin and mucosal cells, the melanocyte in particular.

The clinical management of these patients presented problems. Genital warts often recur; in the first case there were residual warts and the patient declined follow-up appointments. However, since the recommended lateral excision margin of malignant melanoma is 1 cm for each 1mm (Breslow depth) (12), in this respect the melanoma was adequately excised. In the second case the melanocytic lesion was eventually excised widely, revealing not only extensive wart virus changes but also focal severe dysplasia (and a viral type associated with a greater malignant potential). This patient has thus been referred for colposcopic investigation and careful gynaecological follow-up. It is important that any pigmented lesions in the genital region, discovered during gynaecological examination, be carefully evaluated and subjected to histological examination.

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Serum Aminoterminal Propeptide of Type III Procollagen

A Non-invasive Test for Liver Fibrogenesis in Methotrexate-treated Psoriatics

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Serum aminoterminal propeptide of type III procollagen (PIIINP) was studied in 73 psoriatics receiving methotrexate and in 11 selected for trial with methotrexate or etretinate. 72 of the patients on methotrexate were also investigated with liver biopsies. The highest PIIINP value was found in a patient with ascites and her PIIINP decreased after medication was discontinued. Psoriatics with fibrosis or cirrhosis in their liver biopsies had a significantly higher mean PIIINP than patients without fibrosis, who had the same mean value as psoriatics prior to treatment. Based upon the individual data together with data from serial PIIINP investigations of 11 patients studied during treatment, it is concluded that PIIINP can be utilized as a valuable non-invasive test for liver fibrogenesis in methotrexate-treated psoriatics. PIIINP is not specific for the liver, but the study indicates that the number of liver biopsies can be reduced in psoriatics on methotrexate who have normal levels of PIIINP.

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The recent accumulation of new knowledge concerning the structure and immunochemistry of connective tissue constituents has led to the development of non-invasive assays of connective tissue metabolism. Radio-immunoassays of the aminoterminal propeptide of type III procollagen (PIIINP) have been proposed as means of clinical chemical diagnosis and follow-up of fibrotic liver disease (1, 2). In collaboration with the researchers who developed a new rapid equilibrium type of radio-immunoassay for this purpose (3), we have recently published preliminary results of investigations on methotrexate-induced liver fibrosis and cirrhosis (4). This study indicated that analyses of PIIINP in serum could be utilized as a valuable non-