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10 LT-ST strains and 2 of the 9 LT strains that did not belong to the selected O serogroups were also in O group O 153.

Discussion

We found that antisera prepared against ETEC strains belonging to selected O serogroups identified 64% of ETEC isolated from diarrhoea cases that had been detected by enterotoxin testing of *E. coli* isolates. The antisera were more effective in identifying LT-ST strains than in identifying ST strains. This is not surprising given the greater restriction in the range of O serogroups of LT-ST strains observed previously⁶ and confirmed in this study. As there were 9 ST strains belonging to O group 128, the number of ST strains detected would have been greater if O128 antisera had been included in the screening procedure. Some strains of *E. coli* O128 are known to be enterotoxigenic,⁹ and appropriate antiserum could be included in future studies. The number of LT cases was too small to draw conclusions about the usefulness of the antisera in their detection.

Compared with enterotoxin testing the polyvalent antisera had an overall specificity of 96% and predictive value of 89%. These results suggest that such antisera may be of value in the identification of ETEC, especially in laboratories unable to do toxin testing.

Further studies must be carried out in other geographical areas to determine both the value of the antisera in the diagnosis of ETEC diarrhoea and whether any alterations in the constituent O groups might improve their sensitivity. These studies should include less severe cases of ETEC diarrhoea which were not included in this study as well as more cases infected with LT strains. Routine use of these ETEC antisera should not be recommended until the results of such studies are known.

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TOPICAL VITAMIN-A-ACID THERAPY FOR CUTANEOUS METASTATIC MELANOMA

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Summary Two patients with cutaneous metastatic melanoma were treated with a topical retinoid, β -all-trans-retinoic acid. Complete regression of the treated lesions was noted in one patient and a partial response was seen in the other patient. The mechanism of anti-tumour action of the retinoids is not completely known but binding to intracytoplasmic receptors with promotion of cellular differentiation, alteration of membranes, and immunological adjuvant effects may be involved.

Introduction

RETINOIDS are chemically related to vitamin A and have diverse biological activities including antineoplastic effects against skin tumours.^{1–3} Retinoids inhibit murine melanoma growth in vitro.^{4–6} We demonstrated that these compounds inhibit the growth of clonogenic cells⁷ in a system used to predict in-vivo response of chemotherapeutic agents.⁸ In this study topical β -all-trans-retinoic acid was used to treat multiple cutaneous metastases in two patients with malignant melanoma.

Methods

After informed consent had been obtained in accordance with established hospital procedures a 4 mm biopsy specimen was taken from a representative lesion before treatment. The patients were instructed to apply one drop of β -all-trans-retinoic acid, 0.05% solution ('Retin A'), to each lesion once a day and then cover the lesion with occlusive tape ('Blenderm'). The patients were seen every 4 weeks to assess the progress of therapy and after 12 weeks 4 mm skin biopsy specimens were again taken from treated lesions.

Results

Case 1

A 54-year-old man noted a mole on his right upper back in February, 1978. An excisional biopsy was performed and histological examination showed a melanoma (Clark's level 4, 1.0 mm thickness). The lesion was widely excised and the right axilla was dissected. 1 of the 25 nodes was positive for tumour. BCG was given by scarification in May, 1978, after a pre-therapy screen had revealed no evidence of metastatic disease. In October, 1978, numerous pigmented nodules were noted in the right axilla without evidence of visceral metastases. BCG was discontinued and he was treated with carmustine, dacarbazine, hydroxyurea, and levamisole. A mixed response was noted, with all the older lesions regressing to some extent but new nodules continuing to appear. In May, 1979, while on chemotherapy the disease was progressing with little regression of older nodules. The patient had 21 skin lesions at this time. Physical examination and laboratory and radiological studies revealed no evidence of extracutaneous metastasis. Chemotherapy was discontinued and 3 weeks later he was started on topical β -all-trans-retinoic acid, 0.05%, under occlusive tape. Mild perilesional erythema was

noted, and after 1 month all the lesions had flattened leaving nonpalpable blue-purple macules of the same diameter as the original papules. Four additional lesions were added to the treatment protocol and these lesions also became flattened over the next 2 months.

In October, 1979, biopsy specimens were taken of two of the treated lesions. Both showed dermal extracellular and intracellular melanosis without evidence of tumour cells. Although the treated lesions were clinically identified as metastases, no pre-treatment biopsy specimens had been obtained, thus we could not be certain that tumour was present before the start of retinoid therapy. Therefore we performed a superficial shave biopsy of a portion of a previously untreated $2 \times 2 \times 1$ cm lesion in the right axilla. Topical retinoic acid therapy was started and over 4 weeks, the tumour became completely flattened, while remaining deep blue. A 4 mm punch biopsy was performed through the centre of the lesion. We then applied topical vitamin-A acid to all of the previously untreated lesions. In all instances the lesions regressed. Treatment was discontinued in January, 1980, and in the ensuing 5 months, no new lesions have appeared and no old tumours have become reactivated.

Case 2

In a 59-year-old woman with a history of right breast carcinoma in 1965 a melanoma of the right fourth digit developed in 1977 for which a wide excision was performed. Cutaneous metastases developed over the right biceps without evidence of nodal metastasis and in 1978 the patient was treated with local BCG by scarification without a response. In March, 1979, intra-arterial regional melphalan infusion was given without effect. In July, 1979, a trial of lomustine was given but no response was noted and numerous new cutaneous lesions

developed in the right arm. Chemotherapy was discontinued in November, 1979. At no time was there evidence of systemic metastatic disease.

In December, 1979, after a pre-treatment skin biopsy was performed, the patient was started on topical vitamin-A acid, 0.05%, under an occlusive dressing. Twenty-two lesions were treated over the course of 3 months and three of the nodules became slightly hypopigmented and flattened. Other lesions showed no clinical change. In February, 1980, skin biopsy specimens were taken from two regressing lesions and one stable lesion. In March, 1980, the patient discontinued therapy to start on another experimental protocol.

Both patients were able to complete the 12-week study without interruption. Patient 1 noted pronounced lesional and perilesional erythema with mild accompanying pruritus. Patient 2 noted little change in all but two lesions, which developed a grey, soft, slightly fluctuant roofs suggestive of epithelial necrosis.

Pathology

In both patients pre-treatment biopsy specimens showed a dense dermal infiltration of atypical melanocytes with nuclear pleomorphism, chromatin clumping, and extensive pigmentation (fig. 1).

Fig. 1—Pre-treatment biopsy specimen of tumour showing masses of atypical melanocytes and extensive pigmentation in upper dermis.

Hæmatoxylin-eosin. ($\times 100$).

Fig. 2—Post-treatment skin biopsy specimen (case 1) which reveals dermal melanosis without evidence of neoplastic cells.

Hæmatoxylin-eosin. ($\times 40$).

In case 1 the post-therapy biopsy specimen demonstrated that the cells in the dermis had a uniform cytological appearance, with no nuclear atypia or mitotic activity. There were many collections of brown pigment, mostly within mononuclear cells in the dermis (fig. 2). Multiple step sections did not reveal evidence of tumour cells. The histological diagnosis was dermal melanosis.

In case 2, biopsy specimens of two clinically regressing lesions showed epidermal necrosis with the epithelium replaced by fibrin and an acute inflammatory infiltrate. The upper dermis demonstrated pronounced acute inflammation with scattered seemingly malignant cells. The mid and lower dermis had a tumour infiltrate composed of nests of pleomorphic cells, many of which contained pigment. The histological diagnosis was metastatic melanoma, with a suggestion of resolution of the neoplastic process in the upper dermal layer.

Biopsy findings in a clinically unchanged tumour were essentially the same as those in the pre-therapy histological sections.

Discussion

Two patients with cutaneous metastatic melanoma were treated with a topical retinoid, β -all-trans-retinoic acid. In case 1 there was a complete regression of the lesions. In case 2 there was histological and clinical evidence of a partial response. The histological evidence of response in the upper corium suggests that the vitamin-A acid may be capable of penetrating only to a certain depth in the dermis and that this distance corresponds to the depth of anti-tumour action. Schaefer et al.⁹ demonstrated that vitamin-A acid does penetrate into at least the mid dermis but this agent was not detected at the dermal-subcutaneous border. Perhaps the compound is avidly resorbed by the dermal blood-vessels and thus is not available in sufficient concentration to have an effect.

In-vitro experiments indicate that the retinoids may be effective anti-tumour agents.^{4,5,7,10} Lotan et al. noted a direct inhibition of growth of numerous transformed animal and human cell lines by retinoic acid. The cell lines included murine⁴ and human melanoma cells.⁵ We have also noted inhibition of growth of clonogenic human melanoma cells⁷ and cells of human melanoma lines.¹⁰

The mechanisms of inhibition are probably complex. Retinoids bind to specific intracellular receptors,¹¹ modify membrane integrity,¹² alter glycolipid synthesis,¹³ and promote cellular differentiation.¹¹ Alternatively, retinoids may work through immunological mechanisms in vivo. Felix et al.¹⁴ demonstrated that vitamin A was more effective against allogeneic tumours than against syngeneic neoplasms and proposed that vitamin A acts as an immunological adjuvant. Dennert et al.¹⁵ demonstrated that a low dose of retinoic acid acts as a specific adjuvant for the induction of cytotoxic T cells rather than as a general T-cell mitogen or adjuvant. The pronounced inflammatory response in case 2 suggests that immunological mechanisms may have been operating.

The positive responses that these two patients with cutaneous metastatic melanoma demonstrated when a topical retinoid was applied, together with the known in-vitro inhibition of malignant growth, the potent in-vivo immunological effects as well as the considerable

activity⁷ in a system used to predict clinical response⁸ suggest that retinoids should be further examined for anti-tumour activity. The recent interest in these compounds¹⁶ may well stimulate the search for safe and effective retinoids for use in cutaneous and systemic cancers of diverse histological types.

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RENAL CLEARANCE OF PENTAVALENT ANTIMONY (SODIUM STIBOGLUCONATE)*

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Summary Kenyan kala azar is sometimes unresponsive to a standard course of sodium stibogluconate. The renal excretion of sodium stibogluconate was therefore studied in patients with kala azar and in volunteers; both urine and serum levels of sodium stibogluconate were measured. After intravenous injection sodium stibogluconate seemed to be distributed throughout the extracellular fluid and to have a renal clearance similar to that of inulin. At 6 h blood levels had fallen to less than 1% of peak values. After intramuscular injection, peak blood levels were lower and

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