



Fig. 2. The same nails 3 months later, now typical cases of white nail.

were located to the nail bed. This is also the case in white nails and in the so-called bands of Muehrcke (2), where two white bands run parallel to the lunula. From the number of bands and lack of hypoalbuminaemia, which is found in patients with Muehrcke's bands, our patient is clearly distinguished. Multiple transverse white bands were not noted in Terry's patients (3), and to our knowledge no similar case has been reported. The cause, which leads to the formation of white bands and later to white nails, remains uncertain, but it could be a progressive alteration of the vascular system in the nail bed.

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## Is Sebosuppression by Cimetidine an Antiandrogenic Effect?

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**Abstract.** By using the Syrian hamster ear model it is shown that cimetidine inhibits cell proliferation in the sebaceous gland. Furthermore, the S phase of sebaceous gland cells is lengthened and the number of labelled cells still in contact with the basal lamina of the sebaceous gland 6 days after isotope application related to the total number of labelled sebaceous gland cells is reduced. The effect of cimetidine is absolutely identical with that of cyproterone acetate, but is quite different from that of the nonhormonal sebosuppressive agent benzoyl peroxide.

**Key words:** Cimetidine; Antiandrogenic effect; Sebaceous gland

Lyons et al. (3) have demonstrated that cimetidine significantly reduces sebaceous gland secretion in man. The authors pose the question of whether this phenomenon is an antiandrogenic effect or is caused by blockade of the H<sub>2</sub> receptors. Several investigations using the nonhormonal sebosuppressive agent benzoyl peroxide and the antiandrogen cyproterone acetate on the Syrian hamster ear model have clearly shown that hormonal and nonhormonal sebosuppression differ in their effect upon various parameters of cell kinetics in the sebaceous gland (2, 8). It therefore seemed appropriate to investigate the mechanism of sebosuppression with cimetidine by using the Syrian hamster ear model.

#### MATERIALS AND METHODS

Sixty male Syrian hamsters were investigated (weight at start of experiments 90–110 g; breeder: Babin, Alzey, FRG). Thirty animals were injected i.p. three times daily for 2 weeks with 22.9 mg cimetidine-HCl (corresponding to 20 mg cimetidine; Tagamet® injection solution of Smith Kline Dauelsberg GmbH, Göttingen, FRG) diluted to 0.5 ml with normal saline solution. The other animals were left untreated.

After 2 weeks of treatment, an *in vivo* double labelling autoradiography with [<sup>3</sup>H] and [<sup>14</sup>C]thymidine was carried out on 15 treated and 15 untreated animals. The investigations were performed at the same time of day to avoid fluctuations due to circadian rhythms. Injections of 30 μCi

[<sup>3</sup>H]thymidine (spec. act. 20 Ci/mmol; NEN Chemicals, Dreieich, FRG) diluted to 0.5 ml with normal saline solution were given i.p. four times at 30 min intervals. The last two injections also contained 5  $\mu$ Ci [<sup>14</sup>C]thymidine (spec. act. 40–60 mCi/mmol; NEN Chemicals).

Thirty minutes after the last injection, the animals were killed with a blow to the neck. Tissue was excised immediately from the inner side of the left ear and prepared for double-labelling autoradiography in the usual manner with G5 Photoemulsion (Ilford Ltd., Basildon, England). This method allows differentiation of the single-labelled [<sup>3</sup>H]thymidine cells and double-labelled [<sup>3</sup>H] and [<sup>14</sup>C]thymidine cells. The number of single-labelled [<sup>3</sup>H]thymidine cells corresponds to the number of cells that leave the S phase during one hour and is therefore a measure of cell proliferation. The quotient "double-labelled cells/single-labelled [<sup>3</sup>H]thymidine cells" provides an approximation of the length of the S phase in hours (5). In each case 1000 basal cells in the sebaceous glands were analysed. The plate integration method of SAUTER and LOUD (4) was applied to determine the percentage surface area occupied by sebaceous glands, excluding cartilage and epidermis (Integration plate II 100/25; Carl Zeiss C., Oberkochen, FRG).

The remaining 15 cimetidine-treated hamsters and 15 control animals were injected i.p. with 100  $\mu$ Ci [<sup>3</sup>H]thymidine (spec. act. 20 Ci/mmol; NEN Chemicals) diluted to 1 ml with normal saline solution, 2 days before the last application of cimetidine. Six days later (i.e. 4 days after the last treatment with cimetidine), the animals were killed at the same time of day with a blow to the neck. Autoradiographic preparation of the immediately excised tissue from the left ear was performed in the usual manner with K2 Photoemulsion (Ilford Ltd.). The percentage of labelled cells still in contact with the basal lamina of the sebaceous gland was determined, related to the total number of labelled sebaceous gland cells. In each case 1000 sebaceous gland cells were analysed altogether.

The statistical evaluation of the two groups was made with the U-test at a required significance level of  $\alpha=0.01$ .

## RESULTS

The results are presented in Table I. The following conclusions can be drawn:

1. Cimetidine significantly reduces the size of the sebaceous gland ( $\alpha=0.01$ ).
2. Cimetidine significantly decreases the number of [<sup>3</sup>H]thymidine-labelled cells in the sebaceous gland ( $\alpha=0.01$ ). This implies reduced cell proliferation in the sebaceous gland.
3. Cimetidine significantly increases the quotient "double-labelled cells/single-labelled [<sup>3</sup>H]thymidine cells" in the sebaceous gland ( $\alpha=0.01$ ). This indicates that cimetidine medication lengthens the S phase in sebaceous gland cells.
4. The percentage of labelled sebaceous gland cells still in contact with the basal lamina 6 days

Table I. Average values of the above parameters in the animals treated with cimetidine and in the untreated animals

Standard deviations in parentheses

	Cimetidine-treated animals	Controls
Proportion of sebaceous glands in the entire surface (%)	34.50 (5.74)	47.47 (4.40)
Single-labelled cells with [ <sup>3</sup> H] thymidine (double labelling autoradiography) (%)	6.6 (1.0)	15.1 (2.0)
Double-labelled cells with [ <sup>3</sup> H] and [ <sup>14</sup> C] thymidine (double labelling autoradiography) (%)	90.2 (13.8)	147.1 (17.9)
Quotient "double-labelled cells/single-labelled cells" which runs parallel to the duration of S phase (hrs)	13.5 (1.1)	9.7 (0.9)
Proportion of labelled cells which remain in contact with the basal lamina of the sebaceous gland after 6 days (%)	20.7 (3.5)	33.7 (4.3)

after labelling related to the total number of labelled sebaceous gland cells is significantly reduced ( $\alpha=0.01$ ).

## DISCUSSION

Cimetidine is widely used in the therapy of stomach and duodenal peptic ulcers. Side effects of male impotence and gynecomastia have been described. Experimental endocrinologic investigations have repeatedly demonstrated an antiandrogenic effect of cimetidine, which is most likely related to competitive inhibition of the dihydrotestosterone receptor (1, 6, 7).

Lyons et al. (3) have demonstrated that treatment with cimetidine reduces surface lipids of the skin. The present investigations using the Syrian hamster ear model support these observations by showing that cell proliferation in the sebaceous gland is inhibited by cimetidine. They further demonstrate that the S phase of sebaceous gland cells is lengthened and the percentage of labelled sebaceous gland cells still in contact with the basal lamina 6 days after application of isotopes related to the total number of labelled sebaceous gland cells is reduced.

Previous investigations have shown that the antiandrogen cyproterone acetate produces identical results in the same experimental procedure, while the non-hormonal sebosuppressive agent benzoyl peroxide influences the parameters mentioned partly in a different manner (2, 8). This allows the assumption that cimetidine exerts its sebosuppressive effect through an antiandrogenic mechanism.

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## Vitamin A Transport Complex during Treatment with an Oral Aromatic Retinoid (RO 10-9359)

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*Abstract.* No significant changes were noted in the serum levels or molar ratios of vitamin A, retinol-binding protein (RBP) and prealbumin even during long-term (up to 15 months) treatment with RO 10-9359 in 19 patients with normal renal function. Nor did any significant alteration occur in the highly significant correlations between vitamin A and RBP, and between RBP and prealbumin. In 3 patients with slightly elevated serum creatinine, some tendency towards an elevation of vitamin A and RBP levels was seen.

*Key words:* Aromatic retinoid; Vitamin A transport complex; Retinol-binding protein; Prealbumin

Vitamin A is known to control the growth and differentiation of epithelial tissues (4). New synthetic retinoids (analogs of vitamin A), especially an aromatic retinoid (RO 10-9359), have proved to be effective in the treatment of psoriasis and keratinization disorders (3, 4).

Studies with radioactive RO 10-9359 have shown that, after oral administration, 75% of the dose can be detected in faeces (most of it excreted by bile) and 12% in the urine within 8 days (2). In view of the slow excretion, some accumulation obviously occurs. This is supported by the clinical experience of prolonged action (3).

Many side effects of the aromatic retinoid, such as dryness of the mucous membranes, desquamation of the skin and loss of hair, are also seen after prolonged overdosing with vitamin A. They are obviously general side effects of retinoids which may be produced without interference with vitamin A metabolism. In order to test this theory the serum levels of vitamin A, retinol-binding protein (RBP) and prealbumin, which are known to form the transport complex of vitamin A (9, 10, 11), were monitored during treatment with the aromatic retinoid.