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ULTRASTRUCTURAL CHANGES OF MITOCHONDRIA IN DITHRANOL-TREATED PSORIATIC EPIDERMIS

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Abstract. The morphology of the mitochondria of dithranol-treated psoriatic epidermis has been studied with electron microscopy. Changes in the inner membrane of a large number of mitochondria are observed. The changes correspond closely to those seen in chemically induced respiration-deficient (RD) strains of yeast. The RD-induction is believed to be mediated by changes in the mitochondrial deoxyribonucleic acid (DNA). The findings support the theory that the anti-psoriatic effect of dithranol is due to an interaction between dithranol and mitochondrial DNA giving rise to a certain number of respiration-deficient mitochondria.

In 1965 Swanbeck & Thyresson (10) showed that dithranol interacts with deoxyribonucleic acid (DNA) in vitro. It was then assumed that this interaction was of importance for the healing effect of dithranol on psoriasis. Later it could be shown that dithranol is a potent inducer of respiration-deficient mutants in yeast (4, 13). These mutations probably take place in the mitochondrial DNA (13). In spite of great efforts it has not been possible to induce chromosomal mutations with dithranol (13). On this basis Zetterberg & Swanbeck (13) suggested the possibility that an important step in the pharmacodynamics of the effect of dithranol on psoriasis is the induction of a certain number of respiration-deficient mitochondria in the psoriatic epidermis.

The possibilities of testing this hypothesis on epidermal cells in vivo are rather limited. However, the induction of respiration-deficient yeast cells is accompanied by certain ultrastructural changes in the mitochondria (3, 12). The most prominent morphological alteration is the loss of the cristae mitochondriales.

An electron microscopic study of dithranol-treated psoriatic epidermis may therefore provide evidence for or against an induction of respiration-deficient mitochondria by dithranol in psoriatic epidermis. To our knowledge no electron microscopic study has been published of dithranol-treated psoriatic skin.

MATERIAL AND METHODS

Four patients with psoriasis vulgaris have taken part in the investigation. One patient has served as a control and had only used white petrolatum with 2% salicylic acid on his lesions for a few weeks. Three patients had been treated for 2–3 weeks with a dithranol paste containing 0.05–0.25% dithranol and 2% salicylic acid applied once daily and on occasions had had white petrolatum with salicylic acid to moisten the skin.

No X-ray, UV- or systemic treatment had been given to the patients during the last month before biopsies were taken. For the dithranol-treated patients the lesions were nearly healed while for the control patient no significant healing was noticed when biopsies were taken.

For light microscopy as well as for electron microscopy biopsies were taken and immediately fixed with 1% osmium tetroxide and embedded in Epon according to standard procedures. For light microscopy thick sections were cut on an ultrotome, stained with toluidine blue and studied with normal as well as phase contrast microscopy. From these areas electron microscopy was performed with a Siemens Elmiskop I.

RESULTS

The lower part of the spinous layer or possibly the basal cell layer has been studied. With light microscopy the well defined stages of normal and non-treated psoriatic epidermis were well recognized (Fig. 1 A and C). The dithranol-treated lesions showed an intermediate, light microscopical morphology between normal epidermis and untreated

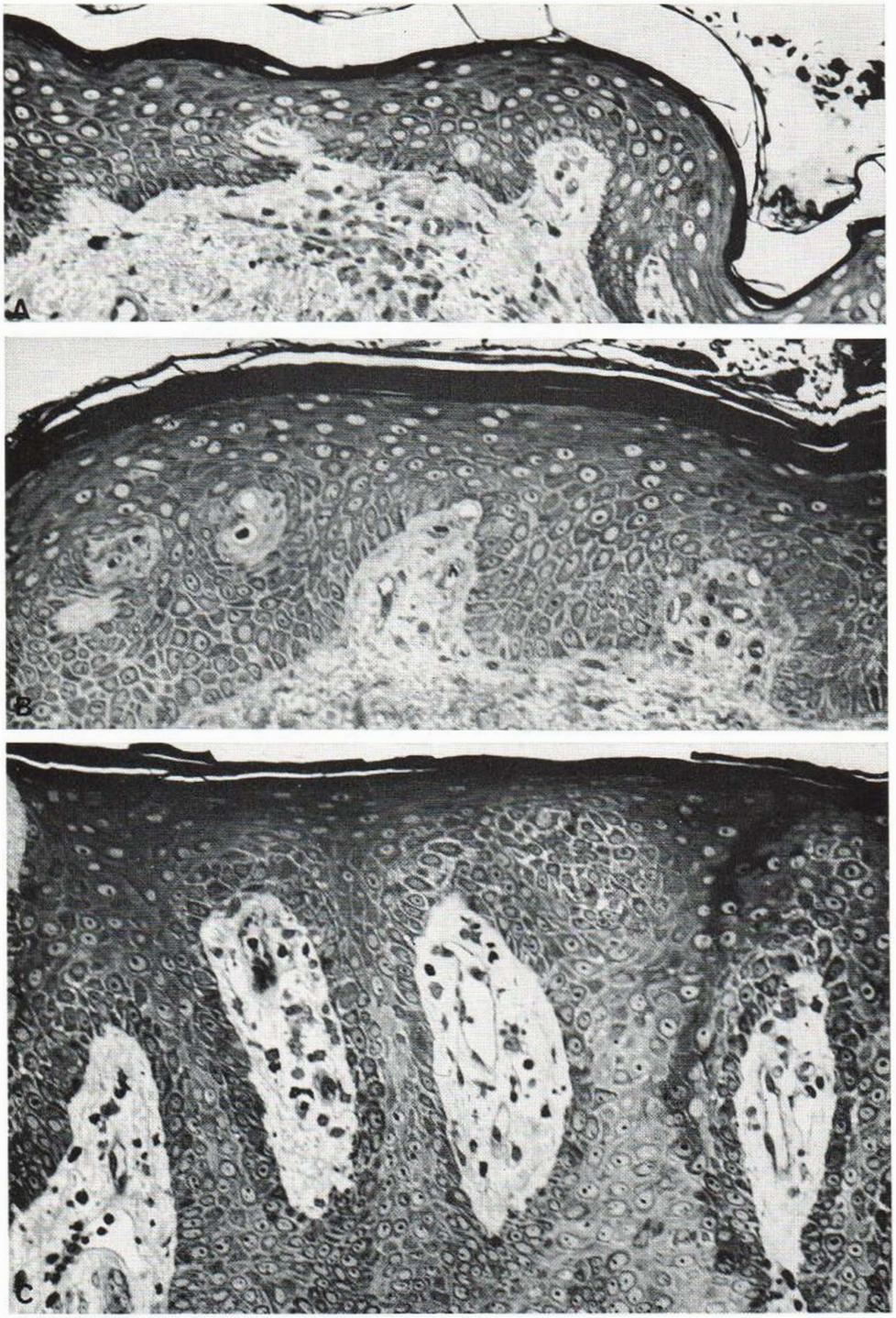

Fig. 1. Light microscopical surveys of the typical specimens studied. (A) Normal epidermis; (B) dithranol-treated psoriatic epidermis; (C) untreated psoriatic epidermis. × 250.

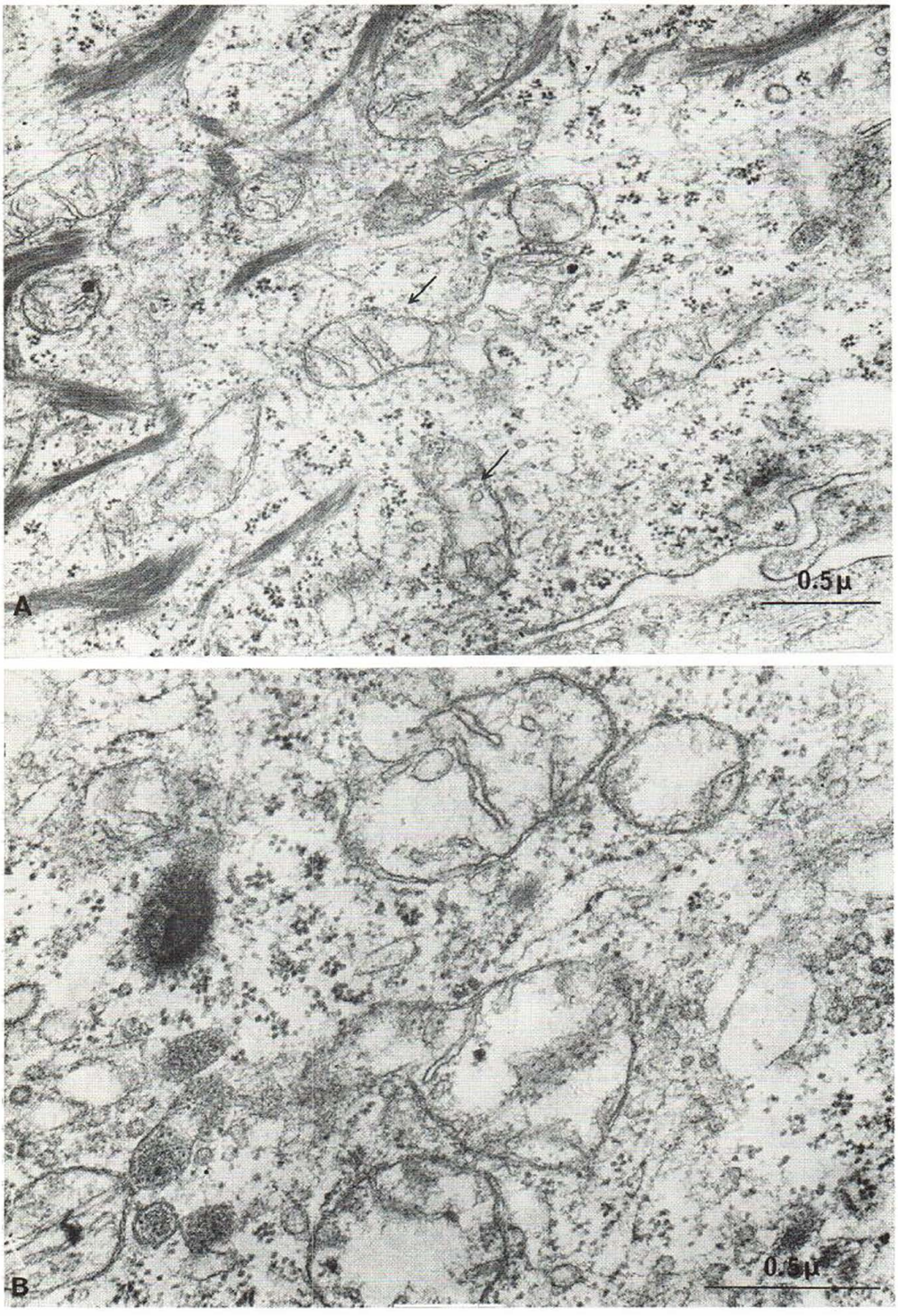

Fig. 2. (A) Detail of spinous cell of dithranol-treated lesion with normal appearing cytoplasmic ground substance and ribosomes as well as tonofilaments, though also with some disturbed mitochondria. Arrows indicate clear zones formed in mitochondria with disappearance of the crista mitochondriales. (B) Detail of dithranol-treated mitochondria of a spinous cell with mitochondria exhibiting almost completely vanished cristae and clearing of the matrix. The outer mitochondrial membrane still seems to be intact and there is no marked swelling of the mitochondria.

psoriatic epidermis (Fig. 1 B). However, at this level of magnification analysis of the cytological changes is not possible. In the control patient, who received no dithranol-treatment (Fig. 1 C) light microscopy as well as electron microscopy revealed the regular features of well preserved cells and intracytoplasmic organelles.

In the dithranol-treated lesion (Fig. 2), changes in the mitochondria were regularly found and some of these exhibited changes of the cristae mitochondriales. Some mitochondria were normal, but it was a regular finding that the mitochondrial cristae seemed to be dissolved and clear zones were seen in many mitochondria. No other conspicuous cytoplasmic changes were found. The appearance of ribosomes as well as tonofilament bundles was similar to that of the normal cell.

DISCUSSION

In the psoriatic epidermis the mitochondria are more numerous than in the normal epidermis. Any significant morphological changes of the mitochondria have, however, not been reported (2, 5, 7). The mitochondria in the dithranol-treated psoriatic epidermis appear according to the present investigation to have a disturbed cristae formation and may also be somewhat swollen. We are therefore inclined to conclude that the dithranol treatment gives rise to mitochondrial changes that mainly are characterized by a disturbance of the cristae formation. In the material studied in the present investigation not all, although many, mitochondria show these changes.

The changes in the mitochondria described here are similar to those found in respiration-deficient yeast (3, 12) and in acriflavine-treated trypanosomes (6).

Acriflavine is a potent inducer of respiration-deficient mutants in yeast.

It has been known for some time that mitochondria contain DNA. The role of the mitochondrial DNA is not clear in every detail but it seems to be responsible for the coding of proteins of the inner membrane and cristae of the mitochondria (see refs. 9 and 11).

It has been shown in yeast that certain chemicals, for instance acridines, induce mutations in the mitochondrial DNA, giving rise to respiration-deficient strains (see ref. 9). As has been pointed out above the ultrastructural changes in the mitochondria of the dithranol-treated epidermis are similar to those of the respiration-deficient yeast cells. We know that dithranol forms complexes with DNA (10) and induces respiration-deficient mutants in yeast (4, 13). These facts together with the findings presented in this paper make it likely that two important steps in the pharmacodynamics of the antipsoriatic effect of dithranol are: (*a*) an interaction between dithranol and mitochondrial DNA, and (*b*) the formation of a certain number of respiration-deficient mitochondriae caused by the altered mitochondrial DNA.

In two recent reports Braun-Falco et al. (1) and Rassner (8) show that dithranol has an inhibitory effect on the energy-donating metabolism of the psoriatic epidermis. Braun-Falco et al. (1) point out that the healing begins in the higher strata of epidermis and not in the basal layer. These findings seem to be in accordance with the data and interpretations of the present paper.

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