United States
Environmental Protection
Agency

Pesticides And
Toxic Substances
(TS-796)

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PREFACE

This atlas was developed after broad consultation with experts in pathology and toxicology from academe, industry and various government agencies. Readers seeking more background information can go to the references cited on page 2. EPA scientists who contributed to the preparation of this atlas included Drs. Mary Argus, Karl Baetcke, Diane Beal, James Murphy, Stephen Nesnow, Vanessa Vu, and Mrs. Vivian Turner Williams.

EPA was assisted in this effort by the Dynamac Corporation, under contract number 68–01–7266, and by Clement International, Inc., under contract number 68–01–7290.

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INTRODUCTION

In April 1987, the Health and Environmental Review Division (HERD), Office of Toxic Substances, conducted an EPA Workshop to discuss issues involved in (a) the design of a bioassay protocol for chemicals by the dermal route, and (b) the feasibility of a screening assay for the potential oncogenicity of acrylates/methacrylates (EPA 1989a). As a result of that workshop, the issue of using histopathologic evidence of irritation to help determine the level at which the integrity of the skin is destroyed [possible indicator of the maximum tolerated dose (MTD)] was identified as an area requiring further analysis prior to the development of a dermal bioassay protocol. A second workshop was held in Research Triangle Park, NC in May 1988 to address the feasibility of formulating a system which would serve as a guideline to aid pathologists in arriving at consistent diagnosis/grading of skin lesions to be used in establishing an MTD for chronic studies (EPA 1989b). A set of proposed guidelines was sent out for review by both pathologists and toxicologists. As a result of the responses received and the discussions at the RTP Workshop, there was agreement on the gross and histologic conditions which constitute criteria for having reached or having exceeded the MTD.

In conjunction with the grading guidelines, a set of photomicrographs of dermal lesions considered to be representative of the spectrum of dermal irritation/toxicity reactions seen in dermal studies was reviewed by a group of pathologists at the RTP Workshop. The photomicrographs were selected from prechronic "skin paint" studies conducted by the National Toxicology Program (NTP).

HERD requested the Experimental Pathology Branch of the NTP to provide information regarding "skin paint" studies performed under the direction of the NTP. The NTP was selected because of its well–recognized international stature in the field of experimental pathology and expertise in "state–of–the–art" toxicology/pathology studies in rodents. The wealth of archival material maintained by the NTP from approximately 23 subchronic and/or chronic "skin painting" on rats and/or mice was also considered to be an important source of data available for review.

The NTP recommended review of recent prechronic "skin paint" studies which were available at the NTP Archives. A site visit was made to the archives on September 24th and 25th, 1987, for the purpose of examining tissue sections from rodent "skin paint" studies. Random microscopic evaluation of skin sections from high does groups was carried out in rats and mice from benzethonium chloride, triethanolamine and vinylcyclohexene diepoxide prechronic studies. Review was limited to high dose groups because these groups appeared to manifest the greatest variety of changes ranging from thickening to frank ulceration. The microscopic review was

conducted to detect the presence of certain lesions characteristic of skin toxicity reactions. A spectrum of lesions typical of changes frequently found in skin irritation studies was present in this archival material. It was from this material that the study set of representative lesions was selected.

The object of the pathology segment of the RTP Workshop was to generate a working guideline for use by pathologists in establishing an MTD for conducting chemical exposure studies by the cutaneous route. This was to be accomplished by demonstration of lesions that occur commonly during the performance of "skin paint" studies and by achieving a consensus regarding the diagnostic terminology used to describe the lesions.

As futher background to the development of guidelines for a dermal bioassay protocol, the pathology panel was also charged with defining what lesions constitute a compromise in the integrity of the skin, arriving at a consensus regarding lesions that should and should not be permitted for the MTD, discussing the feasibility of lesions grading/scoring, and recommending the appropriate method(s) for handling skin lesions at necropsy to promote uniform and consistent sampling.

SUMMARY

A consensus was reached by the panel of pathologists at the RTP Workshop regarding the diagnostic terminology to be used for the microscopic lesions that were presented. It was agreed that the lesions presented represent the most common changes that would be encountered in a dermal toxicity study. The panel stressed that a thorough description of all lesions present in the photomicrographs, as well as the major lesions, should be included in the guidelines. It was recommended that the anatomical extent of the reaction should be indicated as well as whether it is focal or diffuse in distribution (e.g., perifollicular, epidermal, dermal, subcutaneous, etc.).

The panel of pathologists emphasized that the magnitude of the gross lesions should be correlated with the microscopic changes and that microscopy should be used as confirmatory evidence for the grossly observed changes.

REFERENCES

EPA 1989a. Environmental Protection Agency: "Summary of the EPA Workshop on Carcinogenesis Bioassay via the Dermal Route, April 28–29, 1987, Washington, DC". (EPA 560/6–89–002); available from NTIS, 5284 Port Royal Road, Springfield, VA 22161 (703 487–4650).

EPA 1989b. Environmental Protection Agency: "Summary of the Second EPA Workshop on Carcinogenesis Bioassay via the Dermal Route, May 18–19, 1988, Research Triangle Park, NC". (EPA 560/6–89–003); available from NTIS, 5284 Port Royal Road, Springfield, VA 22161 (703 487–4650).

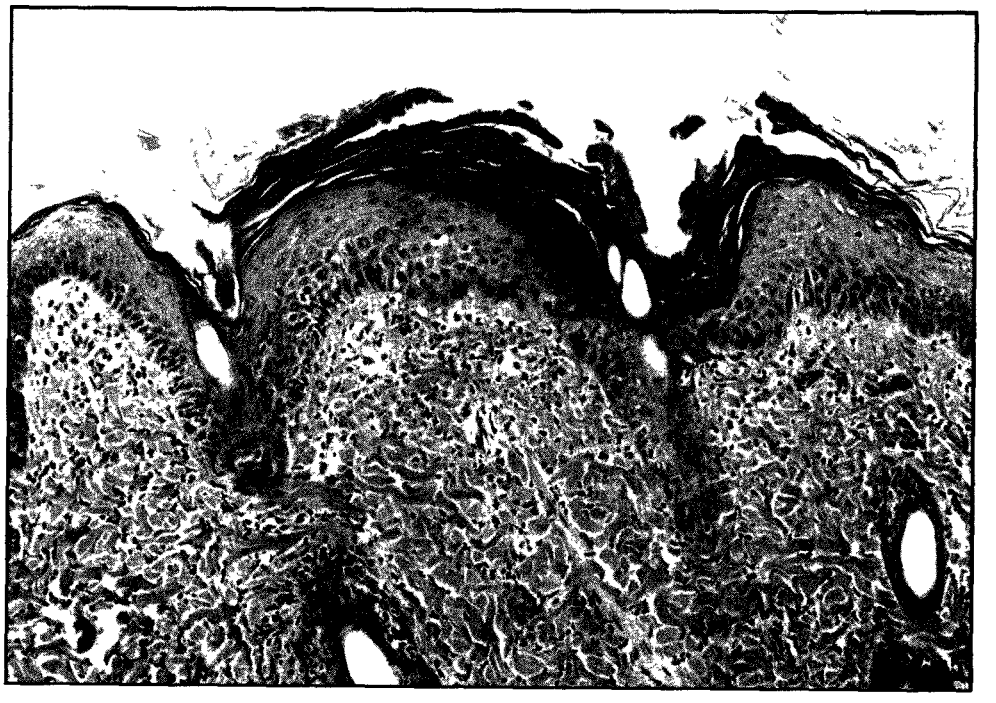

Fig. 1. Acanthosis, parakeratosis, and hyperkeratosis. A mild inflammatory cellular infiltrate is present in the dermis. benzethonium chloride. 25 mg/kg, ethanol vehicle. Rat. x33

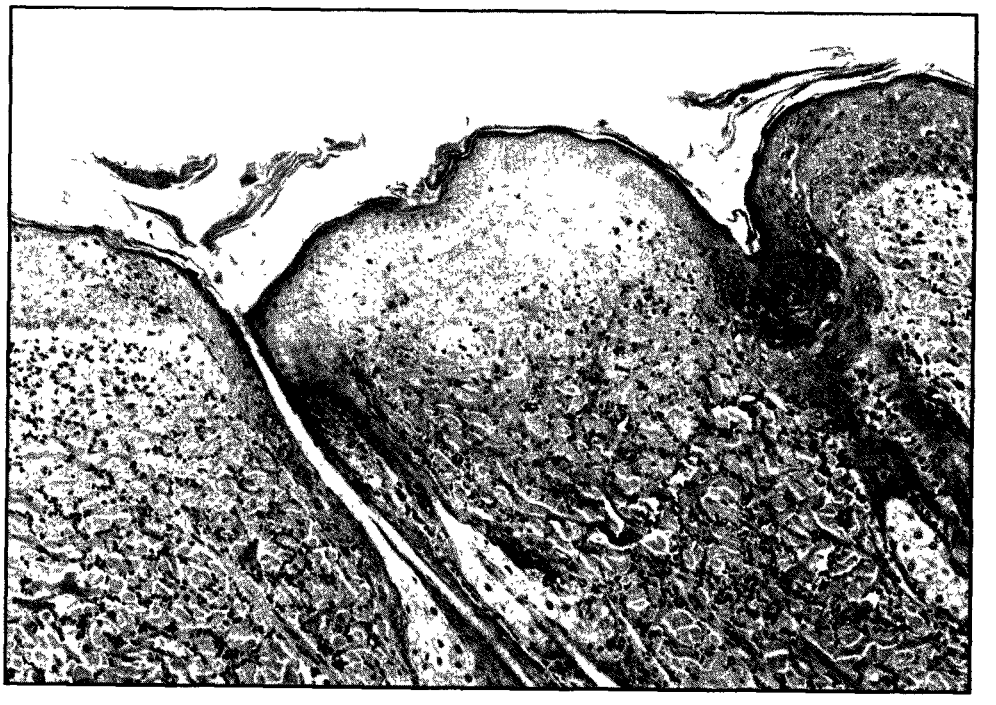

Fig. 2. Minimal focal epidermal necrosis. Acanthosis and hyperkeratosis are present at the junction of the necrotic and viable epidermis. A diffuse moderate, suppurative inflammatory infiltrate is present in the dermis. benzethonium chloride. 25 mg/kg, ethanol vehicle. Rat. x33

Fig. 3. Minimal focal epidermal necrosis. The viable epidermis is acanthotic and hyperkeratosis is evident. Focal epidermal ulceration is noted at the left. The dermis is mildly and diffusely infiltrated with inflammatory cells. benzethonium chloride. 25 mg/kg, ethanol vehicle. Rat. x50

Fig. 4. Focal epidermal necrosis, hyperkeratosis, parakeratosis, and acute dermal inflammation. The adjacent viable epidermis is mildly acantotic and hyperkeratotic. benzethonium chloride. 25 mg/kg, ethanol vehicle. Rat. x50

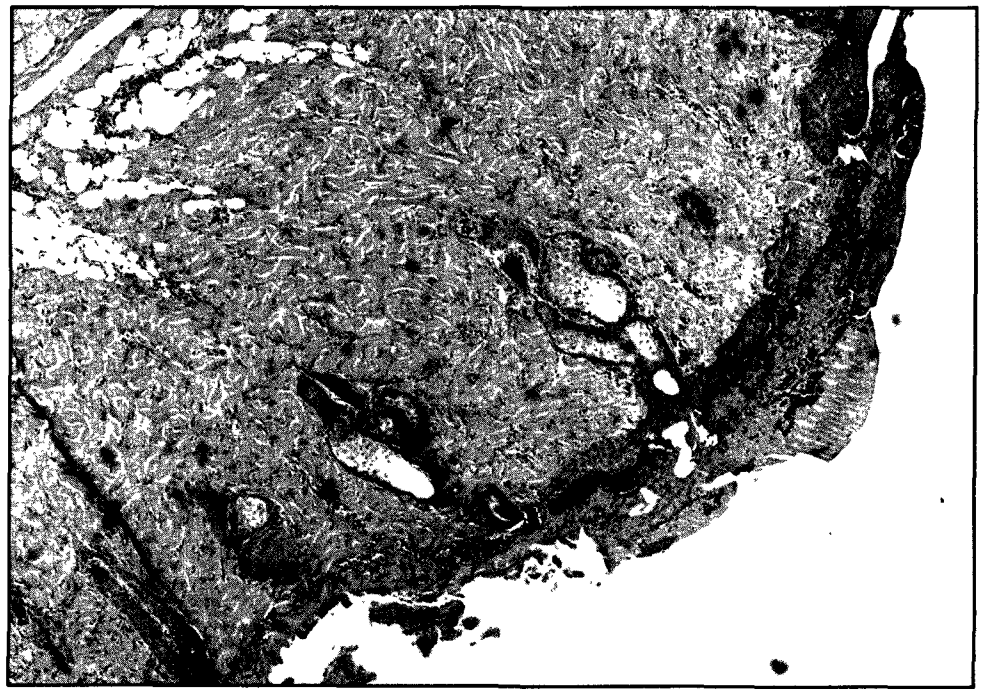

Fig. 5. Multifocal epidermal necrosis and ulceration. A thick crust is present over the affected epidermis. benzethonium chloride. 25 mg/kg, ethanol vehicle. Rat. x13.2

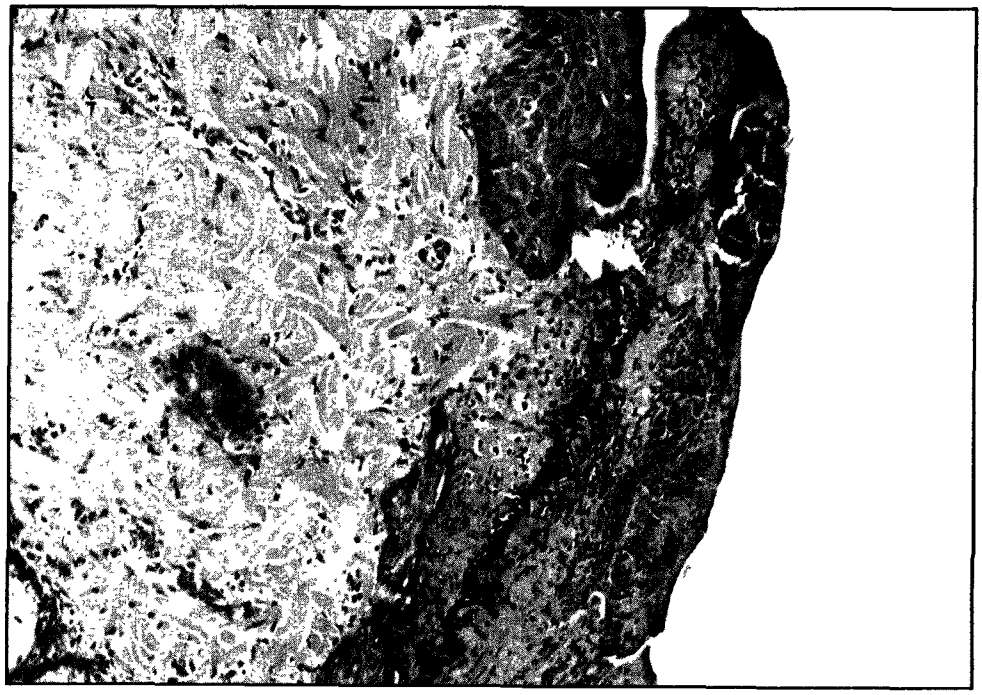

Fig. 6. Focal epidermal necrosis and ulceration. A crust of necrotic epithelium, erythrocytes, serum, and inflammatory cells covers the focal ulcer. The epidermis at the left is acanthotic. benzethonium chloride. 25 mg/kg, ethanol vehicle. Rat. 50

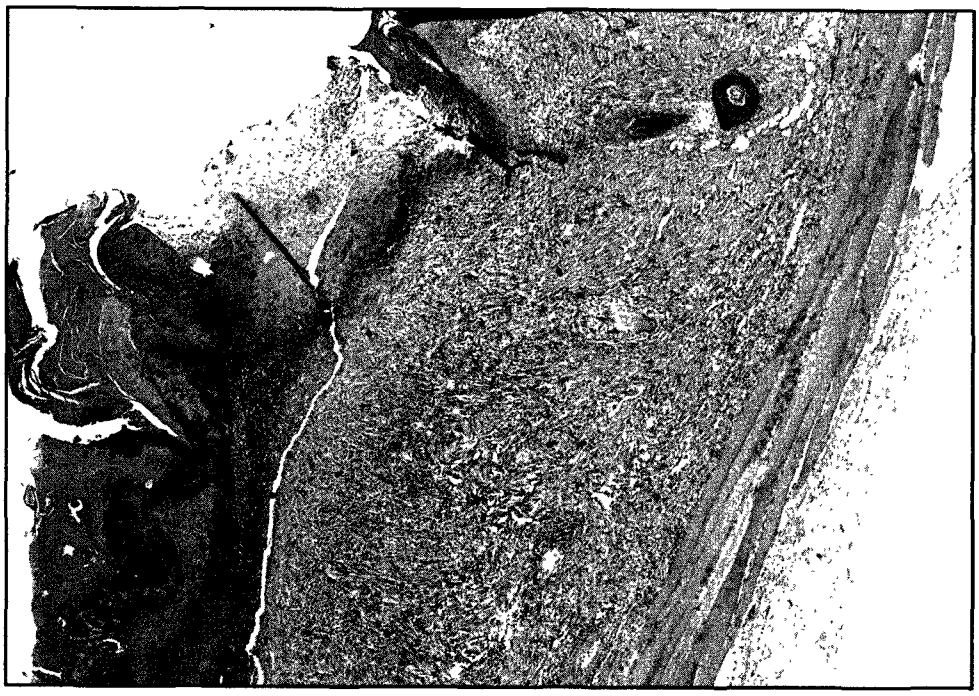

Fig. 7. Extensive necrosis, ulceration and crust formation. The dermis and subcutis are markedly infiltrated with inflammatory cells to the level of the panniculus. The epidermis at the edge of the ulcer (at the right) is acanthotic and hyperkeratotic. benzethonium chloride. 25 mg/kg, ethanol vehicle. Rat. x13.2

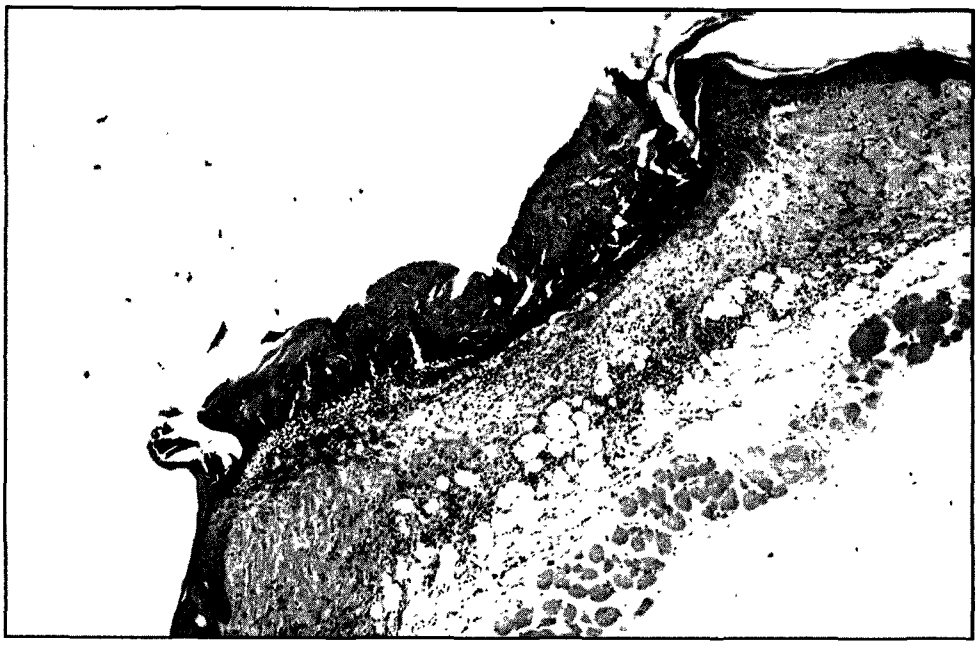

Fig. 8. Focal crateriform epidermal ulceration. The ulcer is covered by a crust and the underlying dermal collagen shows basophilic degenerative change. Acanthosis is evident at the edges of the ulcer. Moderate inflammation extends from the base of the ulcer into the subcutis. benzethonium chloride. 25 mg/kg, ethanol vehicle. Rat. x16

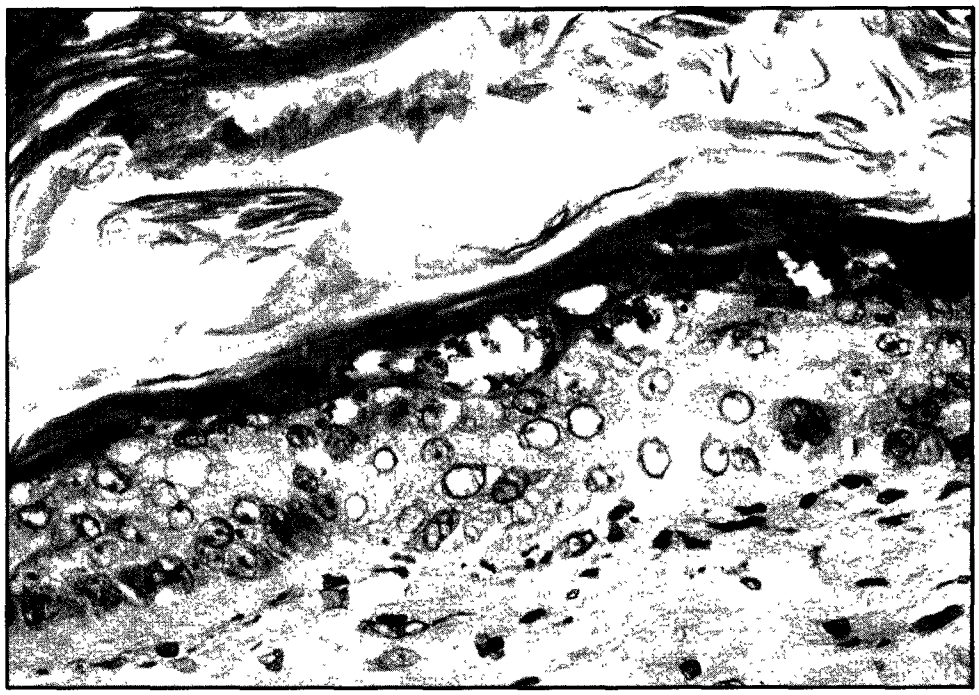

Fig. 9. Subcorneal microvesicles. Hydropic degenerative change is noted in the epithelium beneath the microvesicles. The epidermis is acanthotic and hyperkeratotic. vinylcyclohexene diepoxide. 100 mg/ml, acetone vehicle. Rat. x100

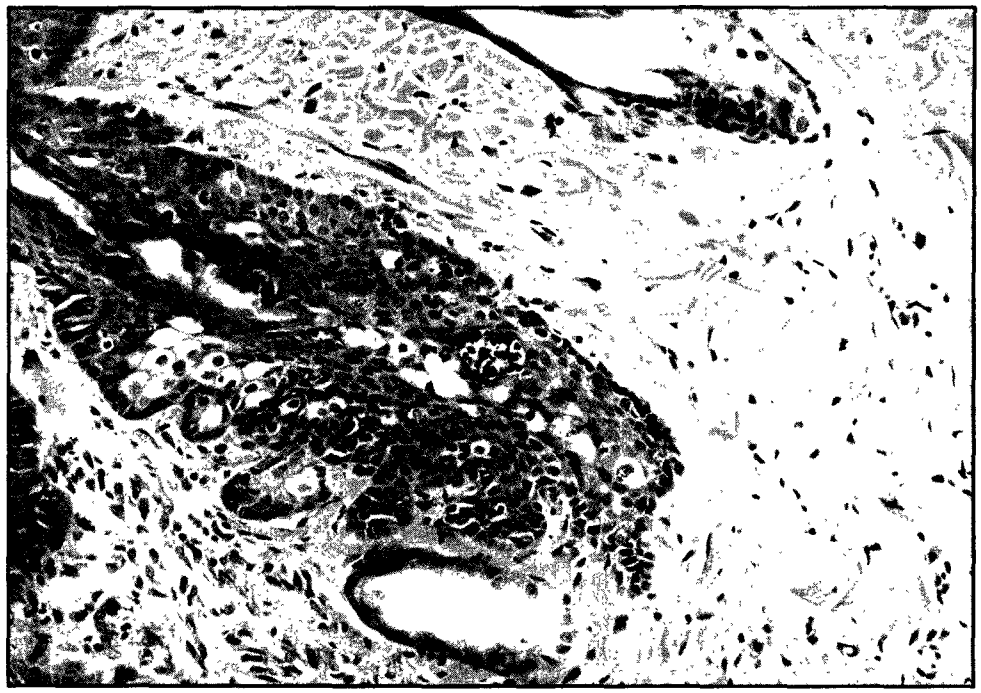

Fig. 10. Intraepithelial pustule (microabscess) of perifollicular epithelium. Mild exocytosis of acute inflammatory cells is present in the surrounding epithelium. vinylcyclohexene diepoxide. 100 mg/ml, acetone vehicle. Rat. x40

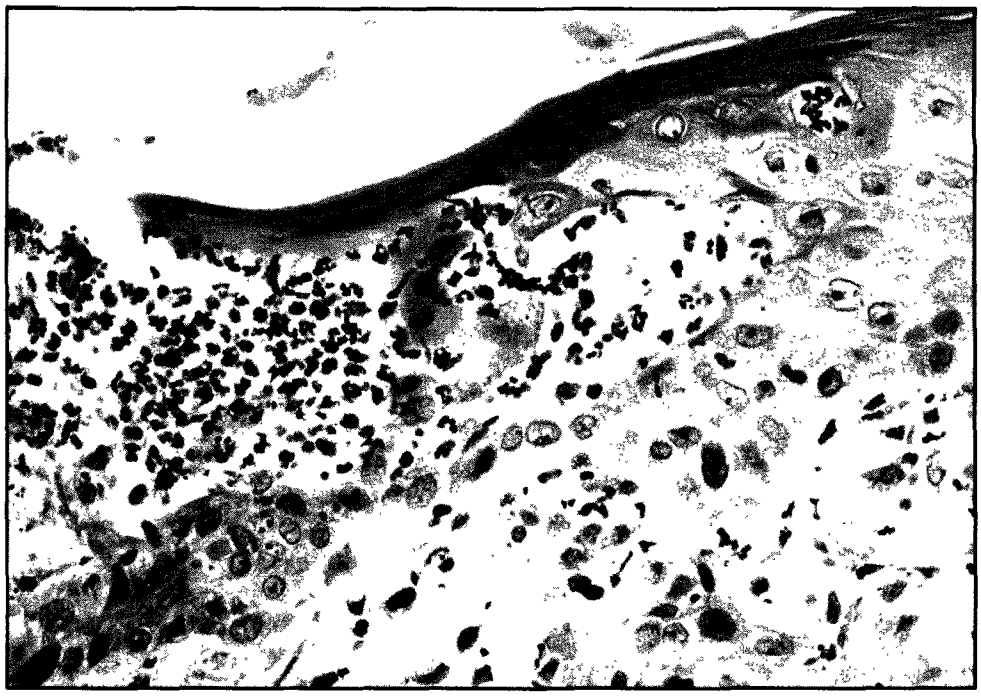

Fig. 11. Intraepithelial pustule. The pustule contains serous fluid, erythrocytes and numerous polymorphonuclear leukocytes. The "roof" of the pustule to the left appears ruptured. The viable epidermis to the right is acanthotic, the superficial dermis is edematous and has a mild inflammatory cellular infiltrate. vinylcyclohexene diepoxide. 100 mg/ml, acetone vehicle. Rat. x100

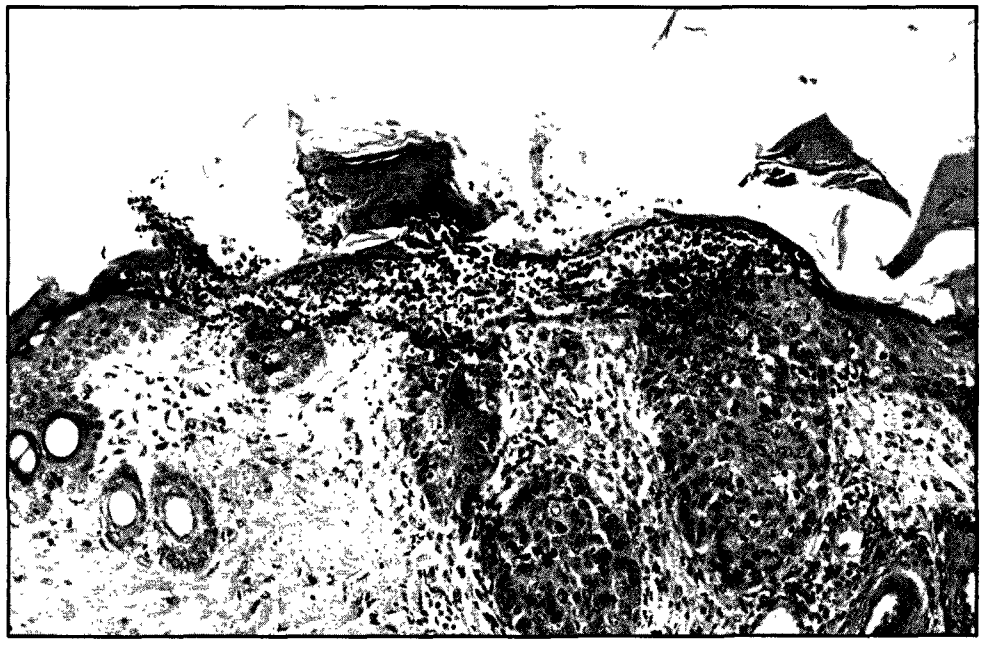

Fig. 12. Intraepithelial pustule filled with neutrophils and serous fluid. The epidermis is acanthotic with prominent exocytosis. Superficial dermal inflammation is evident. vinylcyclohexene diepoxide. 100 mg/ml, acetone vehicle. Rat. x50

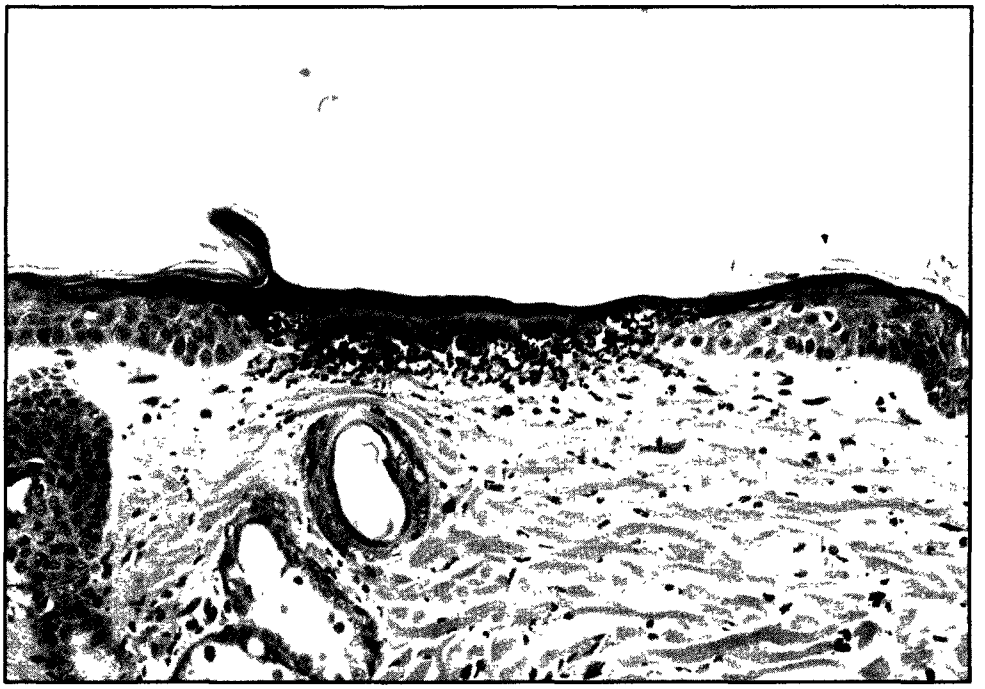

Fig. 13. Subepidermal pustule. The inflammatory cells are located at the dermoepidermal junction and the covering epidermis is necrotic. vinylcyclohexene diepoxide. 100 mg/ml, acetone vehicle. Rat. x50

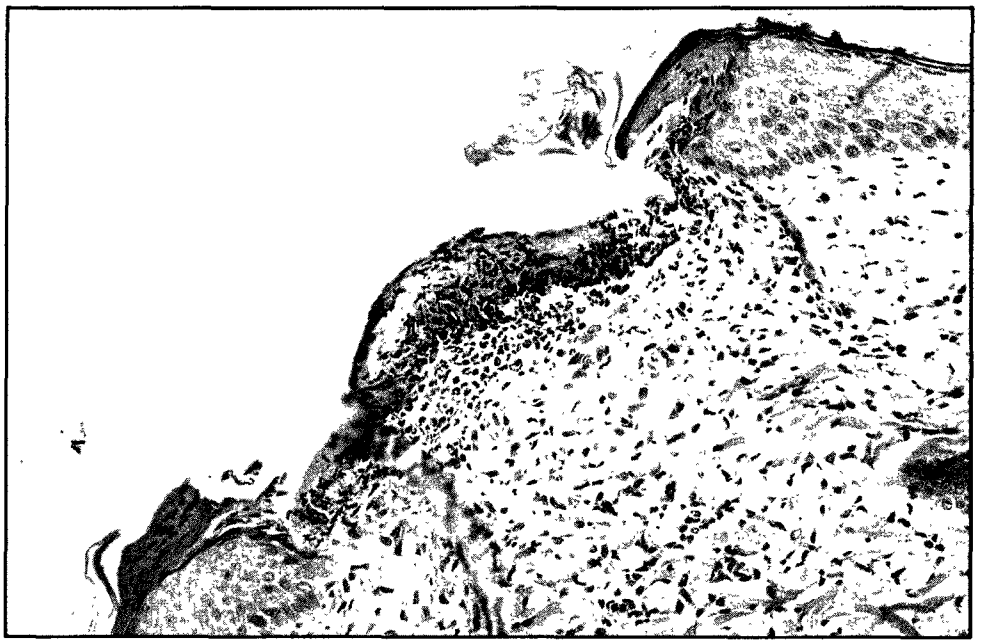

Fig. 14. Subepidermal pustule (dermoepidermal junction). The pustule is covered by necrotic epidermis and suppurative inflammation is evident in the dermis beneath the pustule. Acanthosis, hyperkeratosis, and parakeratosis are present in the adjacent epidermis. vinylcyclohexene diepoxide. 100 mg/ml, acetone vehicle. Rat. x50

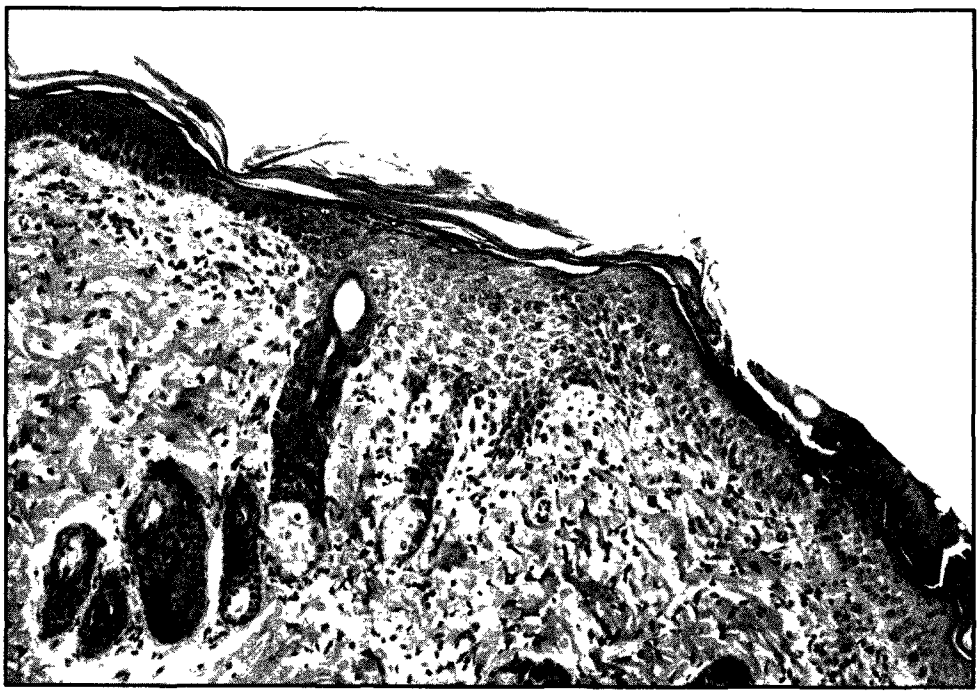

Fig. 15. Focal epidermal spongiosis. Note the widening of the intercellular spaces in the stratum spinosum and edema of the superficial dermis beneath the spongiotic area. Acanthosis and hyperkeratosis are evident in the epithelium and crust formation is noted at the right. A mild dermal inflammatory response is evident. benzethonium chloride. 25 mg/kg, ethanol vehicle. Rat. x33

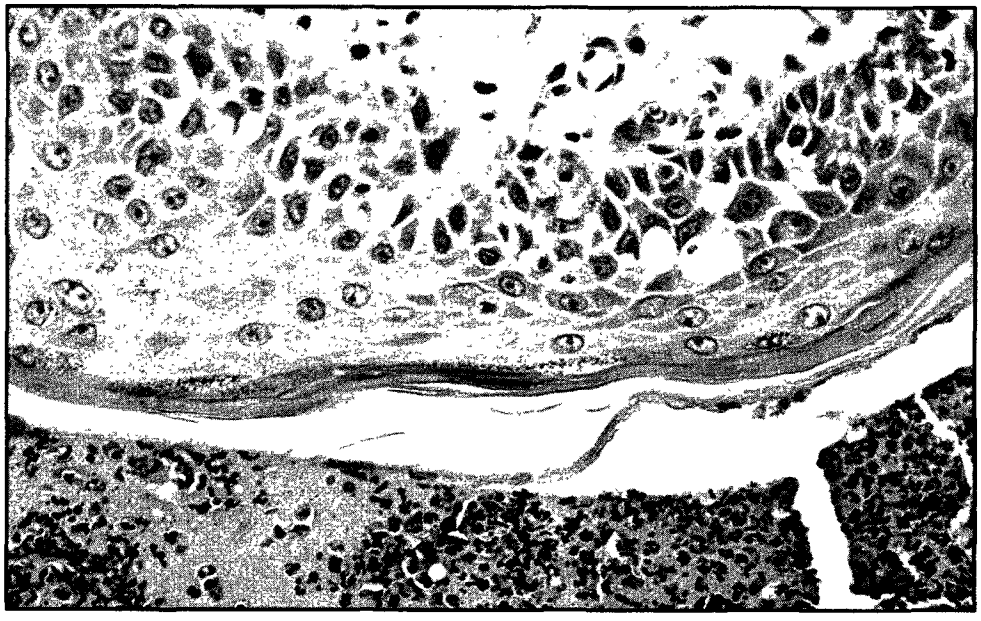

Fig. 16. Epidermal spongiosis. Widening of intercellular spaces is present in the basal layer as well as the stratum spinosum. Coalescence of areas of intercellular edema suggest early microvesicle formation. The underlying dermis is edematous and shows dilatation of capillaries and small lymphatic vessels. A single eosinophilic dyskeratotic cell is observed at the mid–level of the stratum spinosum. triethanolamine. 2 gm/kg, acetone vehicle. Rat. x80

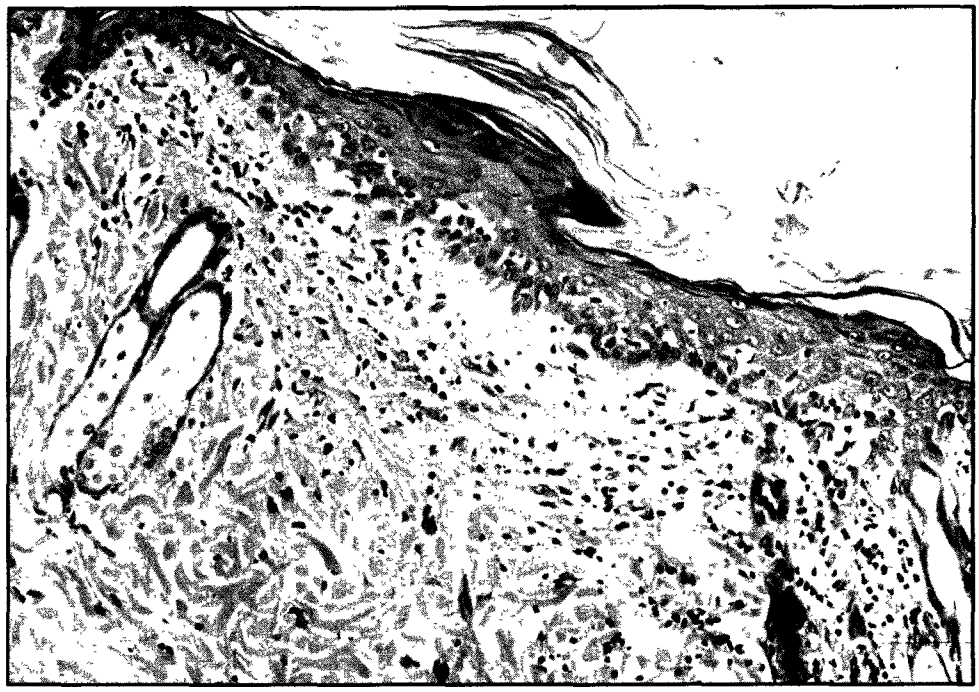

Fig. 17. Hydropic degenerative change in the basal layer and lower stratum spinosum of the epidermis. Mild hyperkeratosis is present. Mild superficial dermal inflammation is evident. vinylcyclohexene diepoxide. 100 mg/ml, acetone vehicle. Rat. x50

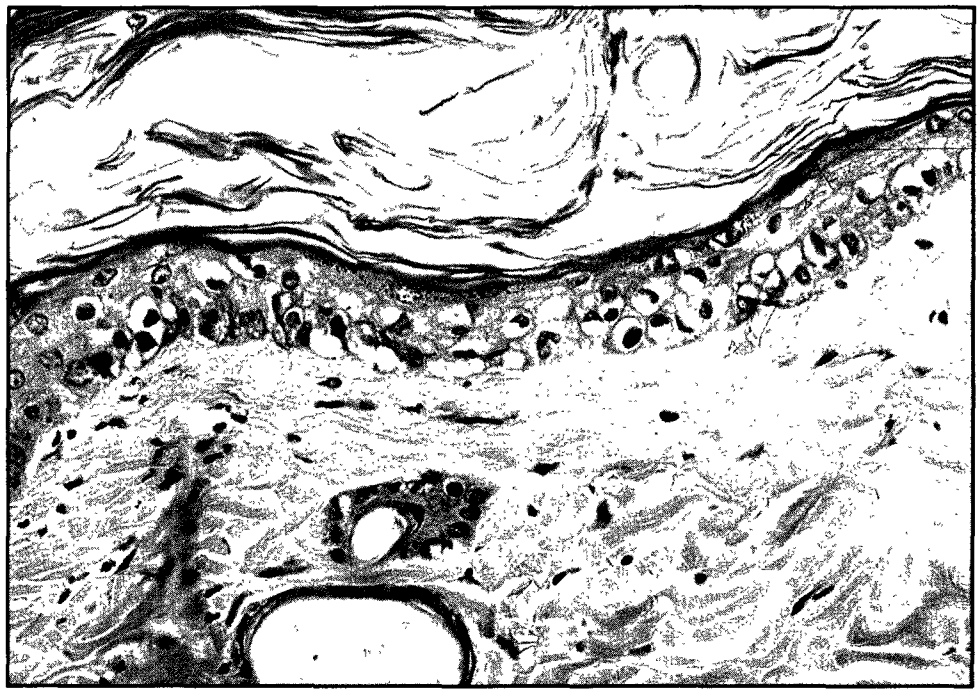

Fig. 18. Intracellular edema. Epithelial cells of the basal and stratum spinosum layers have swollen pale water–clear cytoplasm with eccentric pyknotic nuclei. Single necrotic cells (eosinophilic and shrunken) are noted at the left. Hyperkeratosis is present. vinylcyclohexene diepoxide. 100 mg/ml, acetone vehicle. Rat. x80

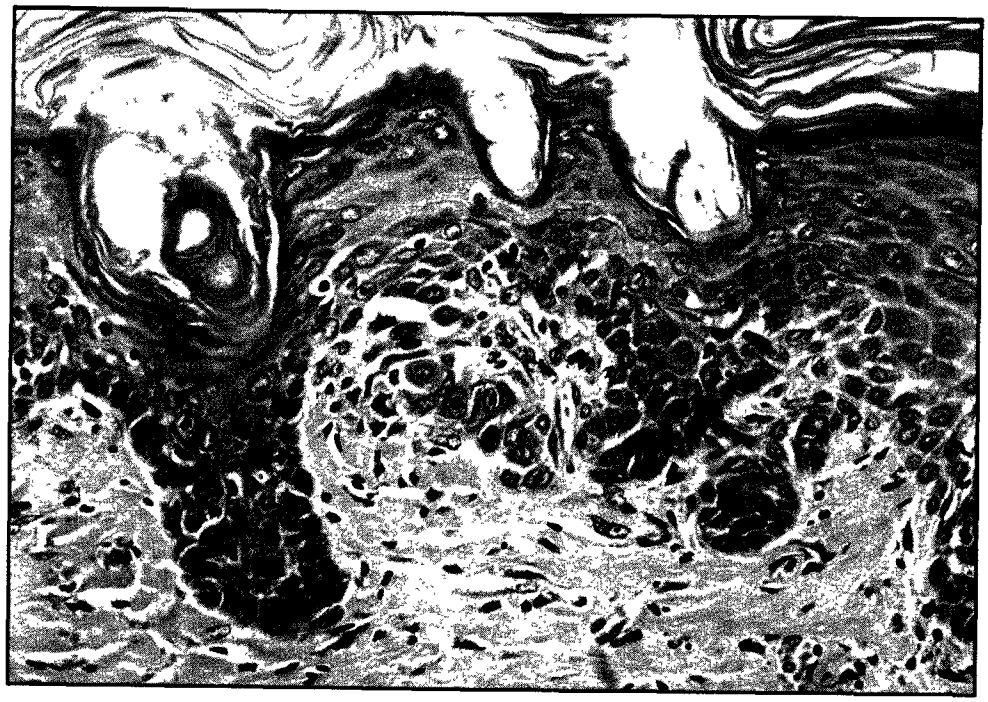

Fig. 19. Dyskeratotic cells are noted from basal layer to the mid–stratum spinosum. The cytoplasm is eosinophilic and abundant and is occurring in the non–keratinizing area of the epidermis. The epidermis is acanthotic and hyperkeratotic. vinylcyclohexene diepoxide. 100 mg/ml, acetone vehicle. Rat. x80

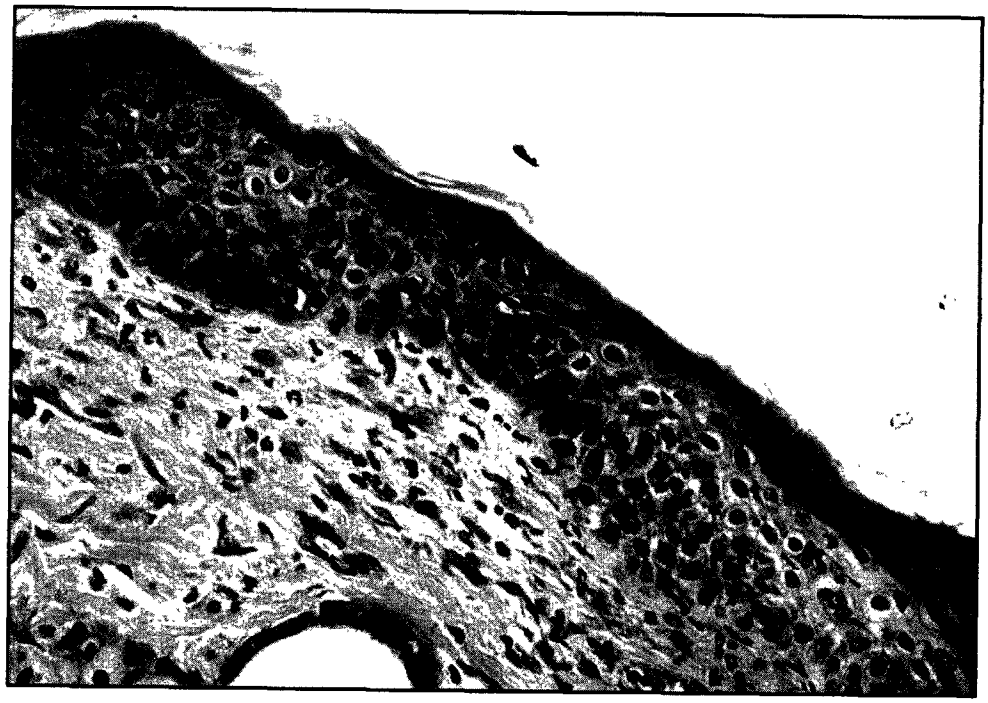

Fig. 20. Exocytosis. Suppurative inflammatory cells are migrating through the acanthotic epidermis. A similar inflammatory response is noted in the superficial dermis. vinylcyclohexene diepoxide. 100 mg/ml, acetone vehicle. Mouse. x80

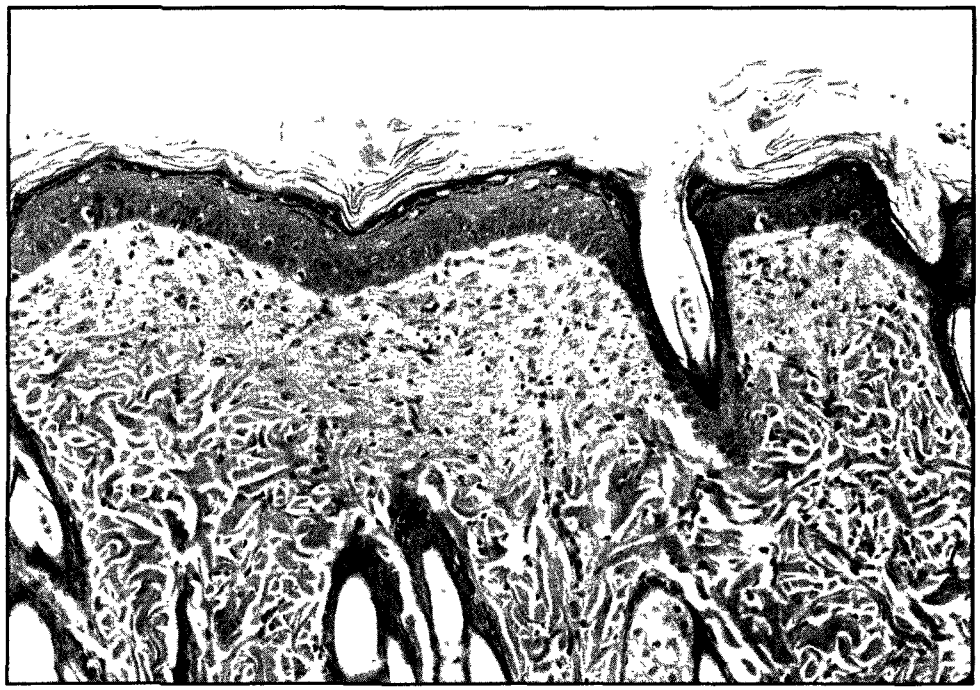

Fig. 21. Dermal fibroplasia. Immature fibrocytes proliferating in a lichenoid pattern beneath the acanthotic, hyperkeratotic epidermis. triethanolamine. 4 gm/kg, acetone vehicle. Mouse. x40

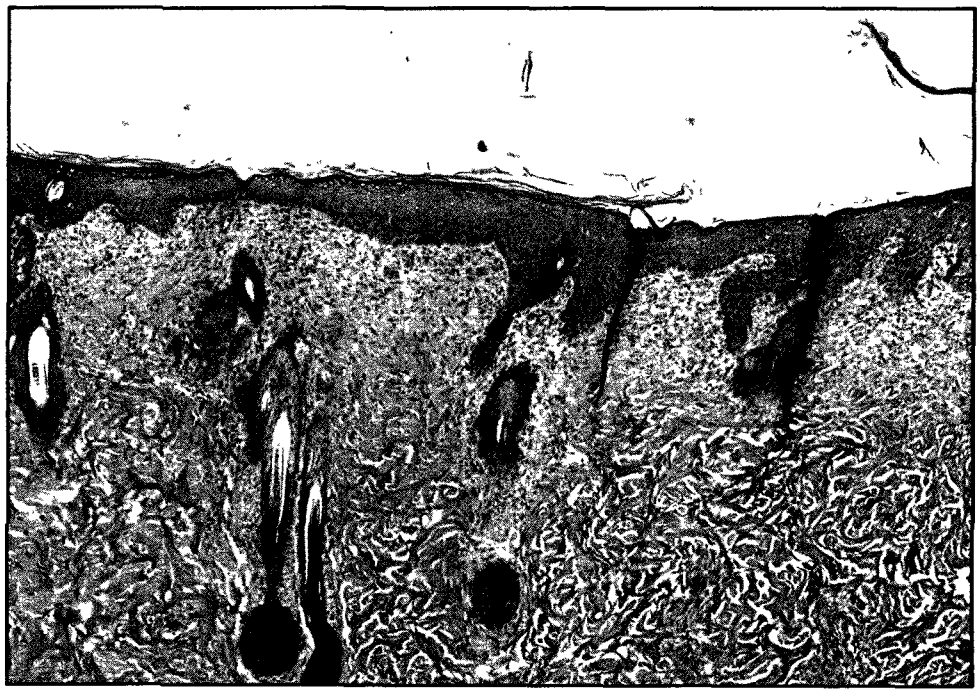

Fig. 22. Dermal fibroplasia, lichenoid distribution. Marked acanthosis with mild hyperkeratosis is evident. triethanolamine. 4 gm/kg, acetone vehicle. Mouse. x16

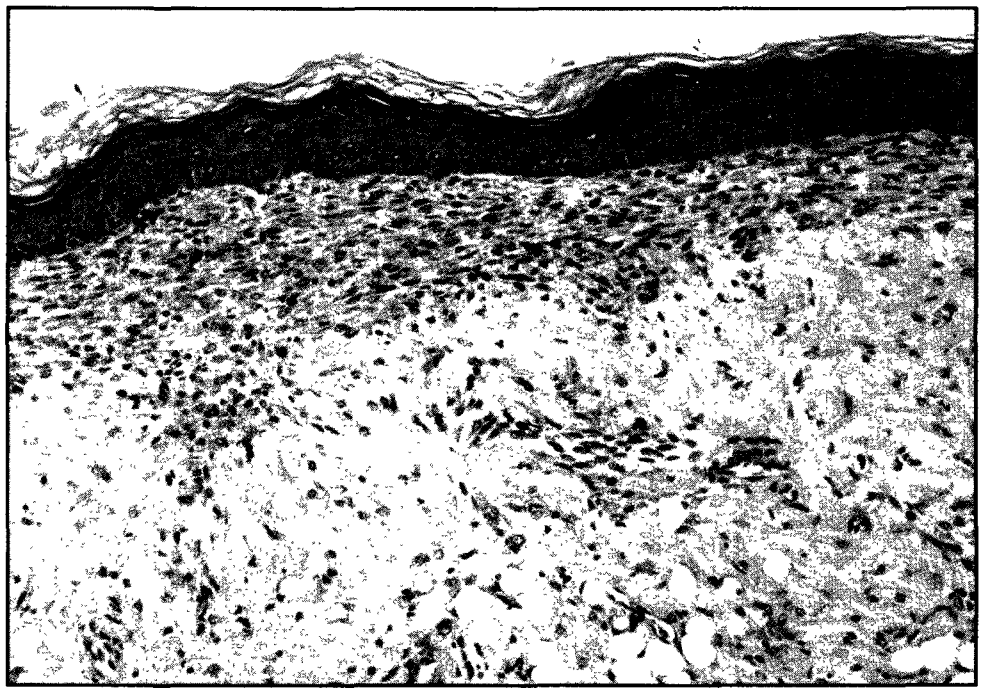

Fig. 23. Dermal fibroplasia associated with mild inflammation and hemorrhage. The epidermis is moderately acanthotic and hyperkeratotic. triethanolamine. 4 gm/kg, acetone vehicle. Mouse. x40

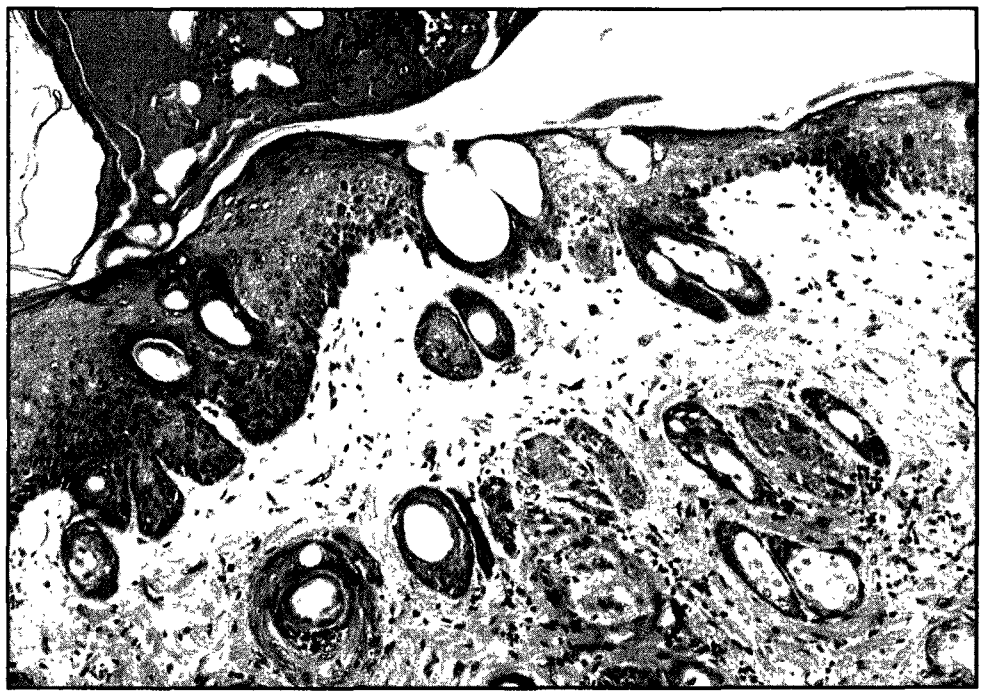

Fig. 24. Dermal edema. A pale staining zone of interstitial edema is evident in the superficial dermis. Dilatation of small lymphatic vessels is noted in this area. The epidermis shows marked acanthosis with rete peg formation at the left. A large unattached crust is above the epidermis. vinylcyclohexene chloride. 100 mg/ml, acetone vehicle. Rat. x40

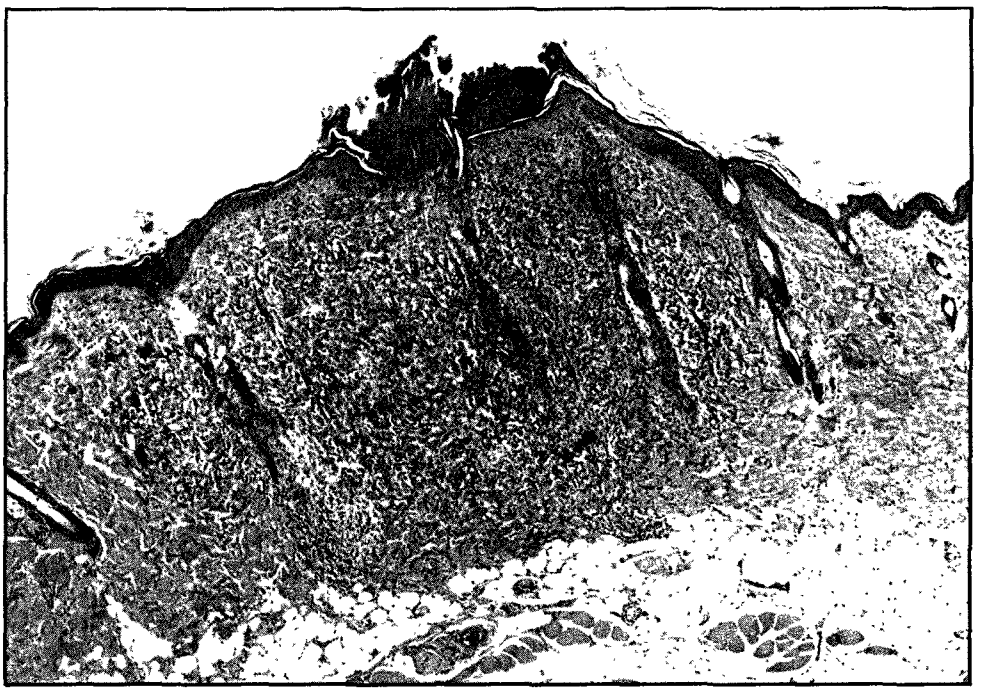

Fig. 25. Epidermal ulceration, crust formation and marked, focal dermal inflammation. The inflammatory reaction extends into the subcutis and the overlying epidermis shows acanthosis and hyperkeratosis. benzethonium chloride. 25 mg/kg, ethanol vehicle. Rat. x13.2

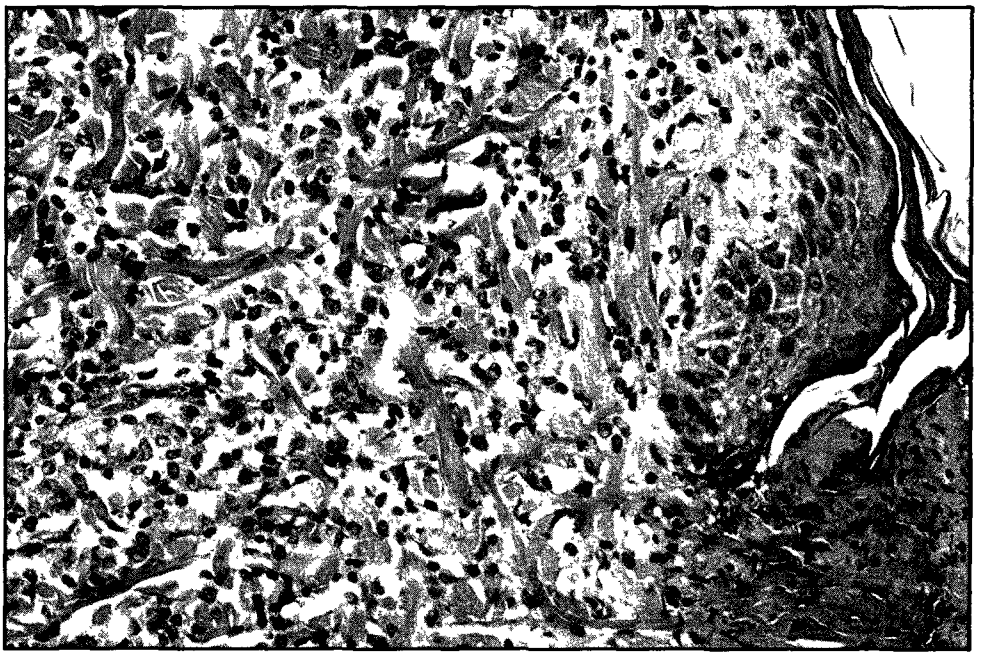

Fig. 26. Higher magnification of Fig. 25. Epidermal ulcer with attached crust is at the right, acanthotic hyperkeratotic epidermis is at the left, and a marked chronic, active inflammatory response is present in the dermis. benzethonium chloride. 25 mg/kg, ethanol vehicle. Rat. x100

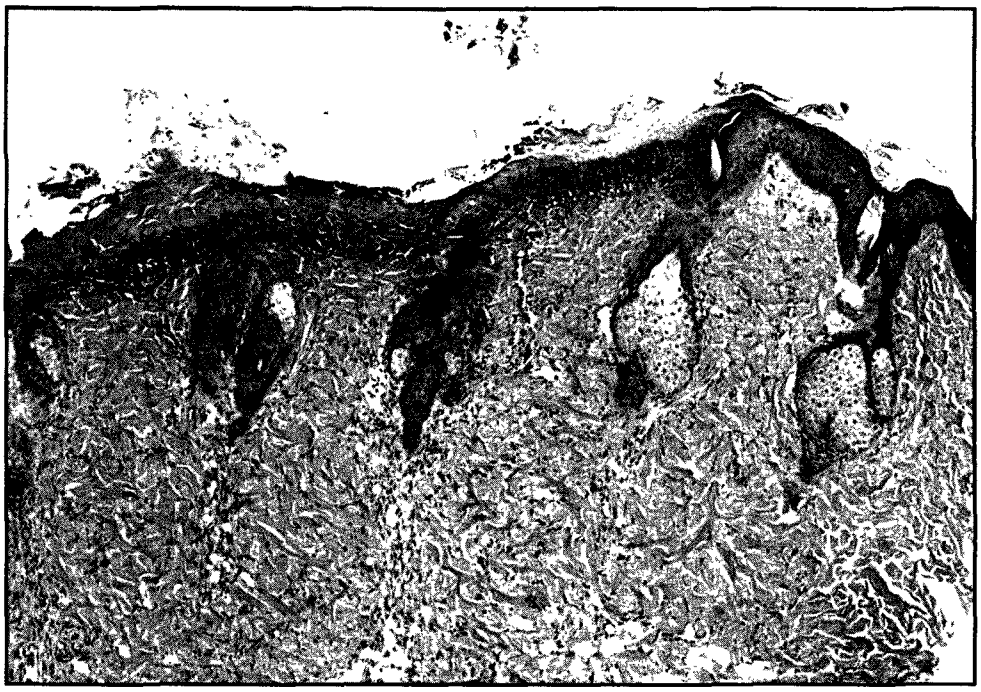

Fig. 27. Hyperplasia (at right) and atrophy (at left) of sebaceous glands. The atrophied glands lie beneath an area of extensive ulceration; the hyperplastic glands beneath acanthotic and hyperkeratotic epidermis. benzethonium chloride. 25 mg/kg, ethanol vehicle. Rat. x33

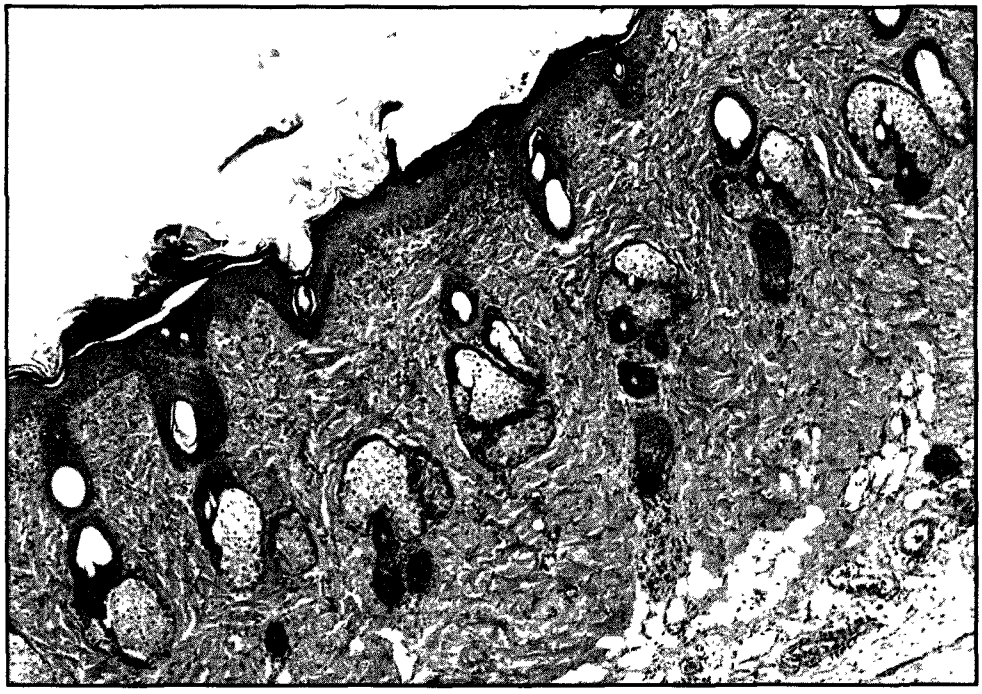

Fig. 28. Hyperplasia of sebaceous glands. Acanthosis, hyperkeratosis, crust formation and a small focal ulcer are seen in the epidermis. Mild dermal inflammation is also present. benzethonium chloride. 25 mg/kg, ethanol vehicle. Rat. 33

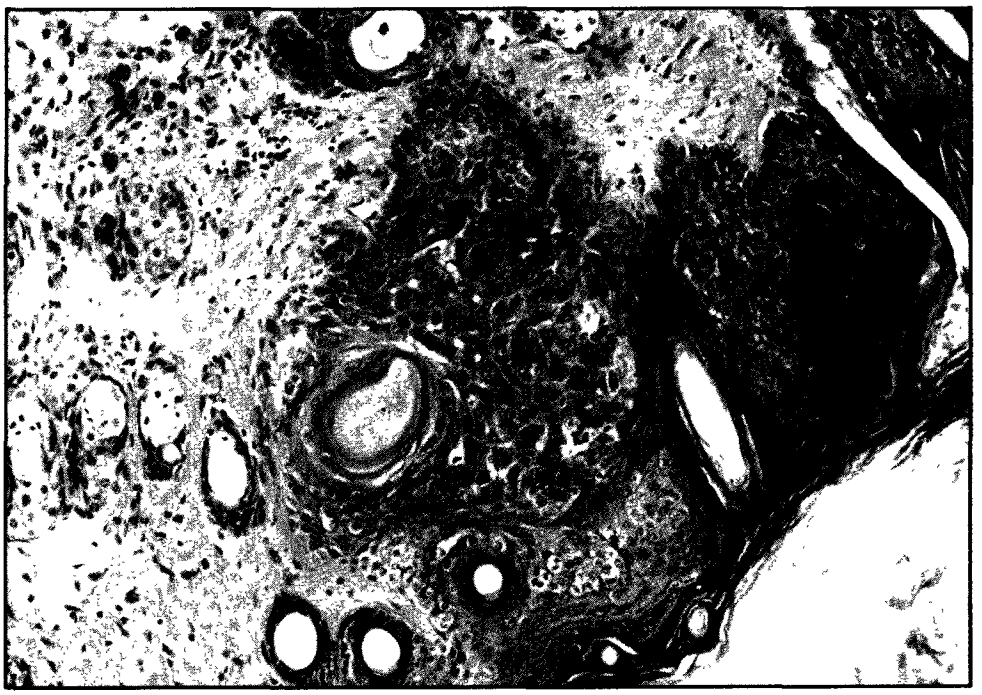

Fig. 29. Dysplasia. Focally disorganized growth pattern of epithelial cells. Loss of polarity (lack of stratified growth) and mild nuclear atypia characterize this change. Acanthosis and hyperkeratosis of adjacent epidermis is evident. vinylcyclohexene diepoxide. 100 mg/ml, acetone vehicle. Mouse. x50

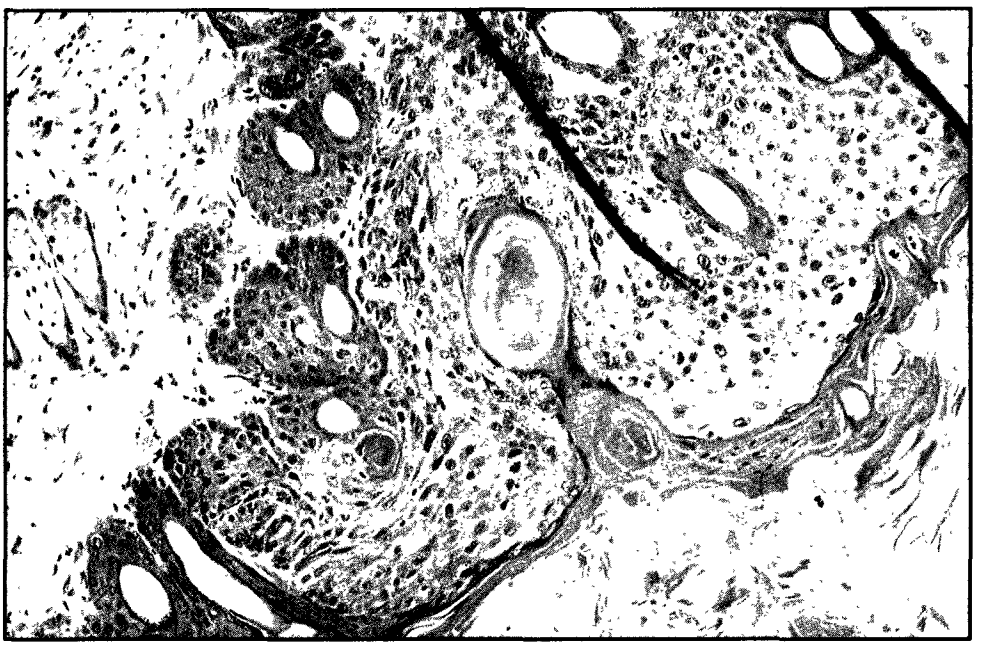

Fig. 30. Dysplasia. Faulty stratification of the epidermis with nuclear atypia. Keratinization is abrupt above this disorganized area of epidermal growth. Moderate hyperkeratosis and minimal parakeratosis are noted. vinylcyclohexene diepoxide. 100 mg/ml, acetone vehicle. Mouse. x60