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Dermal Dysplasia, Hypotrichosis, and Dorsal Skin Ulcers in Adult NMRI-Mice After X-Irradiation in Utero

W. Schmahl[1], E. Senft[1], V. Erfle[2], and H. Kriegel[1]

[1] Abteilung für Nuklearbiologie und
[2] Abteilung für Pathologie der Gesellschaft für Strahlen- und Umweltforschung München (GSF-Munich), D-8042 Neuherberg, Federal Republic of Germany

Summary. Prenatal X-irradiation in mice leads to a marked incidence of hypotrichosis and alopecia in offspring, when irradiation occurs during the stage of late organogenesis (day 11–13 p.c.). In addition, severe ulcerative dermatitis occurs in offspring starting at 2 months of age, with marked preference for those animals, which have been irradiated at least during days 11–13 p.c. This occurs without any dose dependence; application of doses between 2.4 Gy and 7.2 Gy results in approximately similar incidence rates of skin ulcers (range between 39.1 and 48.0%). There is no sex preference and no dependence on housing. At autopsy no special abnormalities were found in the internal organs with the exception of frequent signs of amyloidosis. This disease pattern could also be produced in germ-free animals. The intracutanous administration of skin extracts from affected animals into unirradiated mice leads to a marked infiltration of leukocytes. It is therefore suggested that prenatal X-irradiation induces a distinct dysplasia of the epidermis, which is followed by an endogenous leukotactic activity.

Key words: Skin dysplasia – X-irradiation – In utero.

Introduction

Prenatal exposure of the fetus with ionizing rays leads to growth retardation of the whole animal and especially – dependent on the day of exposure – to growth disturbances of certain organs, to various anomalies and malformations (for complete review see UNSCEAR-report, 1977). Special effects have been reported for the CNS by Hicks et al. (1953), Hicks (1958) and Kriegel et al. (1964), for the skeletal system by Russell (1956), and for the visceral organs by Russell (1950). To date there are no reports of radiation effects on the fetal or newborn animal's skin. Only in long-term experiments where irradiated offspring have been observed for their life span are skin lesions

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mentioned, but only casually. Upton et al. (1966) described ulcerative dermatitis in offspring of RF mice which were X-irradiated at day 14 post conception (p.c.) with 300 R (=3 Gy). However, these skin alterations were considered to have originated from biting due to the increased aggressiveness of the experimental animals. In the experiments of Lathrop et al. (1977) with CF1-mice, applying high doses of ^{99}Tc (500 μCi pertechnetate/day) throughout the gestational and lactating period, marked alopecia occurred in about 20% of the offspring at weaning. Unfortunately this finding was only mentioned and not discussed.

The relevance of these animal studies to human medicine is made clear by the very comprehensive compilation of data on similar diseases in children which was presented by Thalhammer (1967): he refers to 20 cases of dermal lesions (alopecia, skin atrophy, and ulcers) in newborn babies, who were heavily exposed to X-rays between the fifth and the eighth gestational month.

In this report we describe the occurrence and the pathogenesis of alopecia and skin ulcers in juvenile and adult NMRI-mice, which were exposed to fractionated X-irradiation during organogenesis and/or the fetal period. We looked for both exogenous and endogenous causes of the skin inflammation. In so doing we also tested proteinase-enriched extracts from healthy and diseased animals' skin for their leucotactic activity in vivo, by analogy with similar findings described for psoriatic skin by Lazarus et al. (1977).

Materials and Methods

A. Animals

1. Female virgin specific pathogen free NMRI-mice were kept in a barrier system. All animals received standard diet and water ad libitum. At 8 weeks of age they were mated between 8 a.m. and 10 a.m. The morning after a vaginal plug was found is considered as day 1 p.c. The pregnant mice were divided into 7 experimental groups in single cages in air-conditioned animal rooms at 23° C with artificial light from 6 a.m. to 6 p.m.

2. 14 germfree NMRI dams were reared in a flexible plastic isolator and were X-irradiated under germfree conditions (see B. 1. b). An additional 8 unirradiated dams served as controls. The offspring were weaned at 28 days of age and were kept then in single cages under germfree conditions until 3 months of age.

B. Experimental Procedure

1. Irradiation of the Animals. Irradiation of the pregnant mice was carried out with a therapeutic Roentgen (X-ray)-unit at 180 kV and 10 mA at 9a.m. (dose rate 0.01 Gy/sec). We used a copper plate of 0.3 mm diameter as filter. The focus-target distance was 40 cm. For irradiation, five pregnant animals were caged together in a round, flat plastic restrainer. Registration of the applied radiation dose was performed at a central hole of this restrainer by a Victoreen dosimeter.

a) For survival studies the following X-irradiation doses were applied:
group 1:0 (controls)
group 2:3 × 0.8 Gy at days 11–13 p.c.
group 3: 3 × 1.2 Gy at days 11–13 p.c.
group 4:6 × 0.8 Gy at days 11–16 p.c.

group 5: 6×1.2 Gy at days 11–16 p.c.
group 6: 3×0.8 Gy at days 14–16 p.c.
group 7: 3×1.2 Gy at days 14–16 p.c.

On day 19 p.c. approximately equal numbers of male and female offspring were born to all groups. The offspring were weaned at 28 days of age and observed throughout the whole lifespan (till 30 months). Most of these animals were kept in single cages.

b) Another 14 germfree dams were irradiated with 3×0.8 Gy at days 11–13 p.c. (see sections, 2, 3, and 5).

2. Patho-Histological Examination. All animals were autopsied and the major organs, the skin, the endocrine glands and the pituitary gland were examined histologically. The skin of these animals, with exception of the diseased parts and the samples taken for histology, were used for the preparation of proteinase extracts (see section 5).

3. Bacteriological Examination. At the end of the observation period bacteriological samples were taken from the skin of the mice. They were cultivated on 10% sheep blood agar, McConkey-agar, Sabouraud-agar and in thioglycolate-broth. The media were incubated at 37° C and 20° C respectively for 48 h. The bacteria grown were differentiated according to the Cowan-Steel scheme.

4. Autoradiographic Studies. 5 dams irradiated in utero (see gr. 2) and 5 control dams were injected intraperitoneally at day 17 p.c. with 5 μCi/g body weight ^{3}H-thymidine (aqueous solution 5 Ci/mmol; Amersham Buchler). The dams were autopsied at day 18 p.c., the fetuses removed and fixed in neutral buffered formaline. From each litter 3 fetuses were used for histological studies. The sections at 6 μm from different regions (head, chest and abdomen) were dipped in Kodak NT2 emulsion and exposed to the cold for 4 weeks. After developing in Kodak D 19 the sections were stained with hematoxylin and eosin.

5. Preparation of Skin Extracts for Studying Chemotactic Activity. Skin of the back from the descendents of irradiated and nonirradiated germfree mice was shaved and depilated with Pilca cream (Olivin, Wiesbaden, Germany). Subsequently the skin was freed of the muscle and fat. Unaltered skin pieces from a) control animals and from irradiated mice either b) with distinct lesions or c) no visible alterations were pooled separately. We used the KBr epidermal preparation technique, as described by Levine et al. (1976). This included immersion in 2M KBr at 37° C for 1 h, removal of the epidermis, washing in cold PBS, then placing the epidermal pieces in 50mM phosphate buffer pH 7.5, containing 1M KCl, 0.1% Triton X100, and sodium azide (0.1%). This mixture was homogenized, centrifuged at $15000 \times g$, and the supernatant solution was dialyzed against sterile saline. The chemotactic activity of the extracts was determined by assaying histologically the accumulation of polymorphonuclear (PMN) leucocytes in the dermis of the foot pad from 12 young mice for each extract. Observation times were at 24, 48, and 72 h after application of 0.05–0.1 ml of the extracts.

Results

The incidence rate of stillbirths and the neonatal mortality was outstandingly high in group 3 (69.7%) and group 5 animals (37.1%), which received 3×1.2 Gy or 6×1.2 Gy during days 11–13 or 11–16 p.c., respectively (Table 1). The newborn mice of these groups showed the most drastic reduction in birth weights. Further, the immediate postnatal and the longterm mortality was significantly higher than in all other experimental groups. Finally, at 24 months of age 84% of those offspring which had received 6×1.2 Gy during days 11–16 p.c. had died. However, animals from these 2 groups did not reveal significantly different disease incidences. We will restrict our discussion to the development of diseases of the skin and its appendages.

Table 1. Treatment schedule during pregnancy, postnatal development and main pathological conditions of offspring till 30 months of age

Group No.	Treatment (Gy)	During days p.c.	No. of dams	Stillbirths (%)	Living offspring	neonatal weights (g)	Mortality (%) until 24 months	Hypotrichosis + alopecia (%)	Ulcerative dermatitis (%)
1	0	–	17	5 (3.1%)	157	1.42±0.06	43.9	0.8	0.9
2	3×0.8	11–13	14	13 (8.7%)	137	1.24±0.04*	73.0	9.5	43.5
3	3×1.2	11–13	25	212 (69.7%)	92	0.97±0.04***	76.5	6.8	39.1
4	6×0.8	11–16	21	7 (2.8%)	239	1.00±0.05***	64.9	4.3	42.3
5	6×1.2	11–16	15	63 (37.1%)	107	0.83±0.03***	84.0	8.4	48.0
6	3×0.8	14–16	13	2 (1.6%)	125	1.37±0.05	66.4	2.4	5.6
7	3×1.2	14–16	14	9 (5.7%)	150	1.15±0.05**	62.7	2.6	8.2

Significance levels against controls (t-test): * $P<0.05$, ** $P<0.01$, *** $P<0.001$

From 3 weeks of age on, in 2.4–9.5% of the experimental animals lightning of the fur could be observed (see Table 1). In severe cases quite distinct circumscribed hairless areas could be seen. This occurred almost exclusively in the cranio-dorsal parts of the head (Fig. 1).

Starting at an age of 2 months severe inflammation of circumscribed skin areas developed in 39–48% of those mice X-irradiated in utero, which were exposed either during days 11–13 p.c. or days 11–16 p.c. This occurred irrespective of the applied radiation dose (experimental groups 2–5; detailed percentages see Table 1) and could also be seen in animals which were kept in isolation. The same pathological conditions could also be found in the irradiated germfree animals starting at 6 weeks after birth. In contrast, mice which had been irradiated during days 14–16 p.c. showed a markedly smaller incidence of skin ulcers (5.6–8.2% in groups 6 and 7, respectively). Similar alterations in control animals were quite rare (0.9%). There was obviously no sex preference in the development of skin lesions in any animal group. The distribution pattern of these skin lesions showed a remarkable tendency for the dorsal parts of the body, as especially the neck, ears, snout, cheeks, and the lumbar region were stricken (Fig. 2).

These ulcerative inflammations of the skin on the upper legs and the back were uncommon, but were never seen on the lower legs, the toes, or the thoracic or the abdominal regions. In all cases skin ulceration started with hair loss

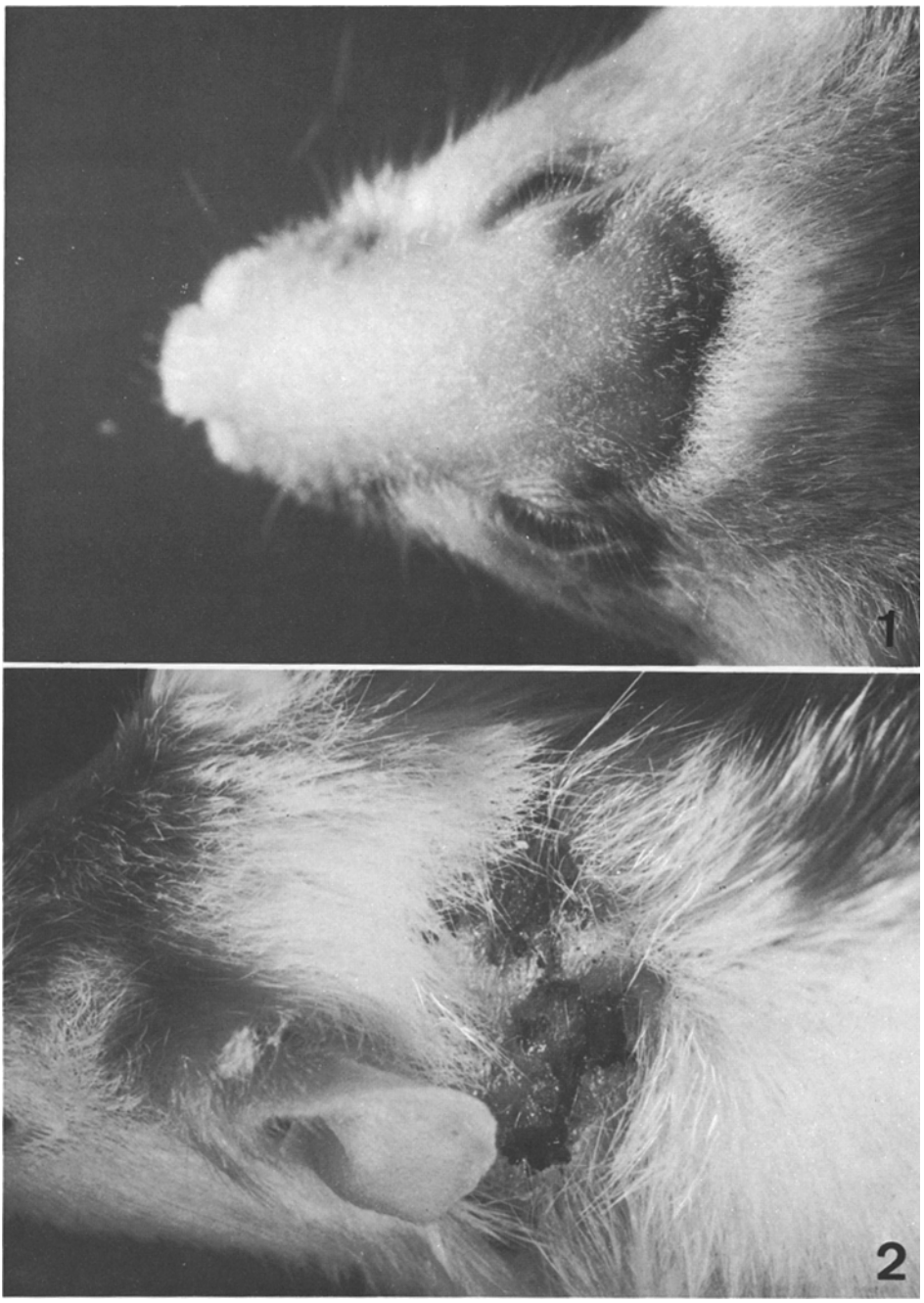
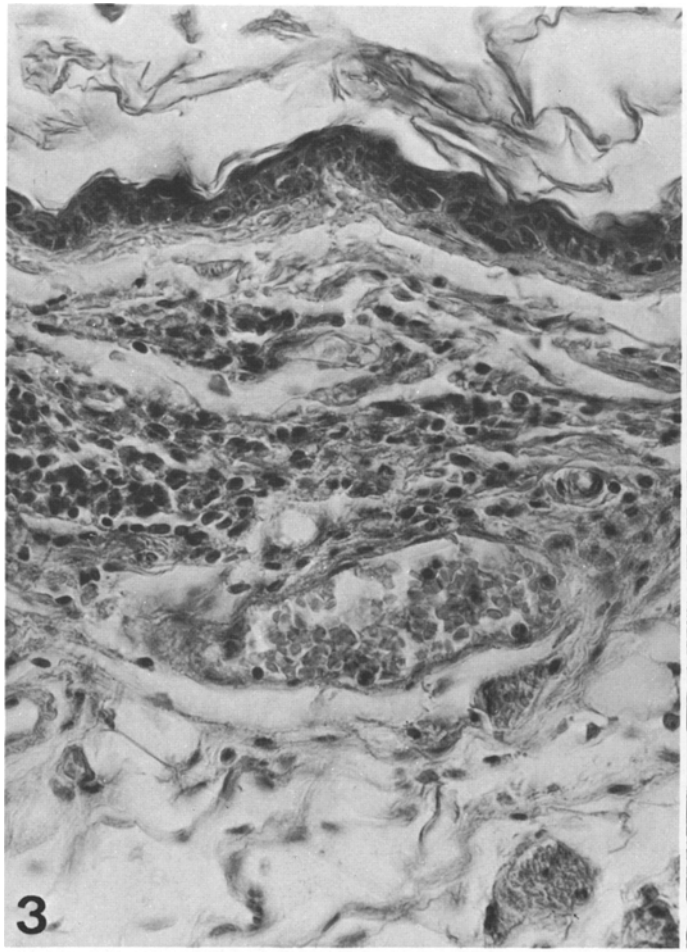


Fig. 1. Dorsal view of mouse offspring, aged 1.5 months, X-irradiated in utero with 3×0.8 Gy at days 11–13 p.c. Marked and distinctly circumscribed alopecia at the whole skull region

Fig. 2. Dorsolateral view of mouse offspring, aged 11 weeks, X-irradiated in utero with 3×0.8 Gy at days 11–13 p.c. Profound ulcerative dermatitis at the nape with surrounding alopecia



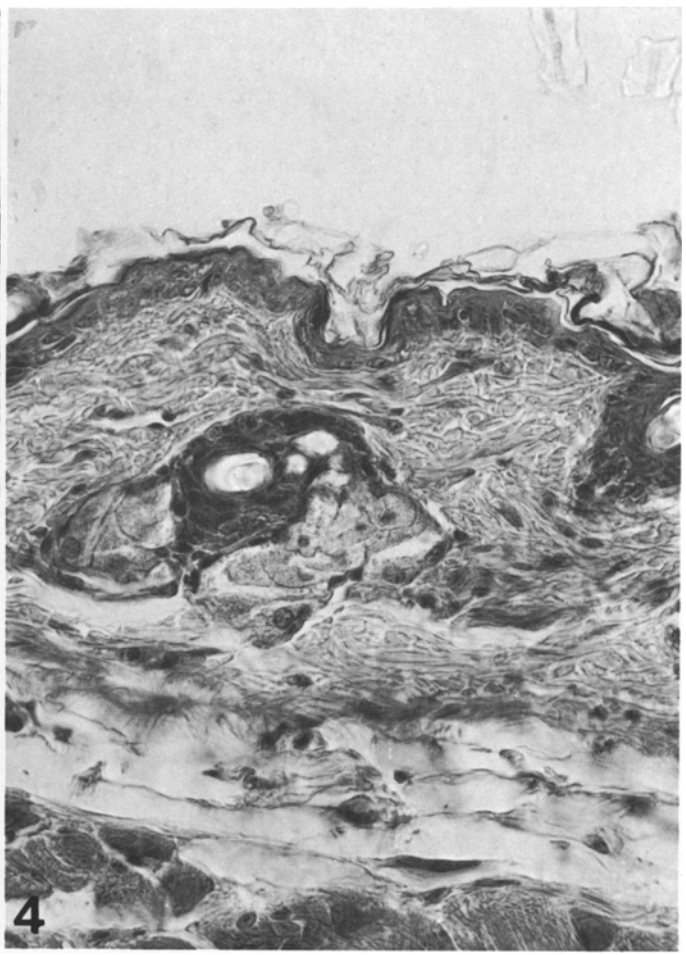


Fig. 3. Histology of an inconspicuous skin area, baso-occipitally to the ear of a germfree mouse offspring (X-irradiated in utero with 3×0.8 Gy at days 11–13 p.c.) at an age of 12 weeks. Distinct inflammation of the corium with extensive dilatation of the blood vessels, poor edema, and with a marked infiltration by PMN leucocytes and lymphocytes. The epidermis is unaltered. (H.E., $\times 560$)

Fig. 4. Histology of the ventral abdominal skin of the same animal as in Fig. 3, without any signs of skin inflammation. (H.E., $\times 560$)

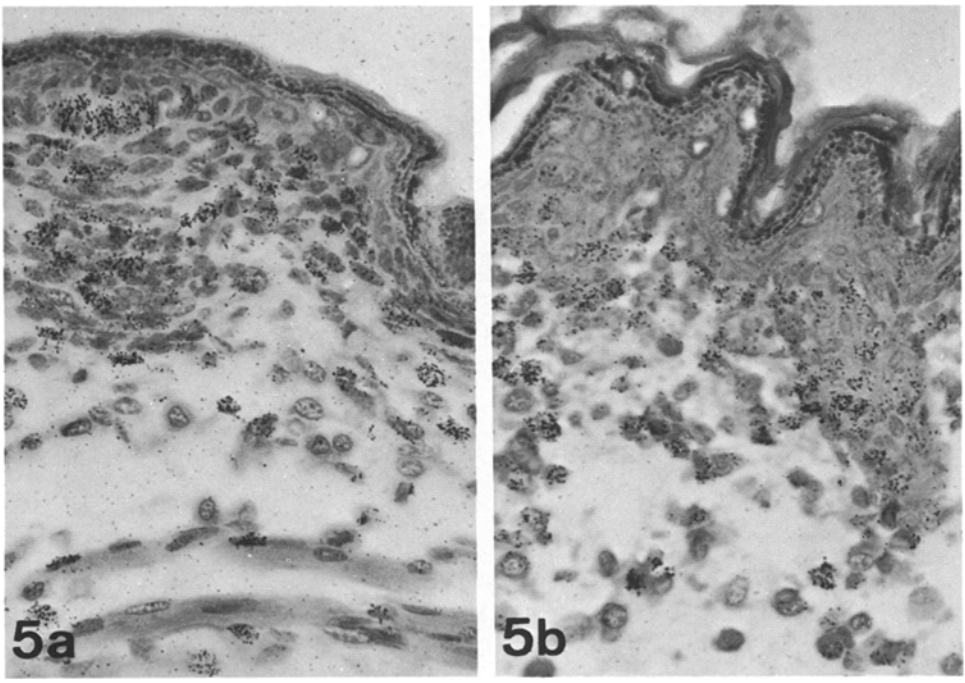


Fig. 5 a and b. Autoradiography of fetal skin sections at day 18 p.c., 24 h after ^{3}H-thymidine application **a** of a control fetus, **b** of a fetus x-irradiated with 3×0.8 Gy at days 11–13 p.c. No differences in labelling density and intensity between **a** and **b**) (H.E., × 560)

and signs of inflammation and developed into deep ulcers within 2 weeks. A tendency for healing was present to a fair extent within a period of 2 to 7 months.

At autopsy of those animals from the long-term study which showed severe skin ulcerations we observed a marked swelling of the lymph nodes and of the spleen, and also a lighter colour of the liver and the kidneys than in controls. Histological examination showed these alterations to be due to marked amyloidosis (Fig. 6). We did not find any pathological alterations of the pituitary, the adrenals or of the testes. Ovarian cysts were quite frequent both in controls and in experimental animals, without any dependency on treatment.

Bacteriological examination of the skin lesions of the SPF-mice revealed the isolation of coagulase – negative staphylococci *(St. epidermidis)*. These bacteria could not be found in the skin lesions of the germfree mice. In no instance could fungi be isolated.

The histology of the fetal skin at day 18 p.c., accompanied by autoradiography, revealed no differences between the controls and the irradiated animals in utero with respect to the structure of the epidermis. The formation of the cell layers and the degree of keratinization was undistinguishable between the different groups. Neither was there any difference in the distribution of labelled corium cells or of the labelling intensities (Fig. 5).

Hair morphogenesis was also quantified in the histological sections by counting the hair follicles in the dorsal region at 3 mm to each side of the midline.

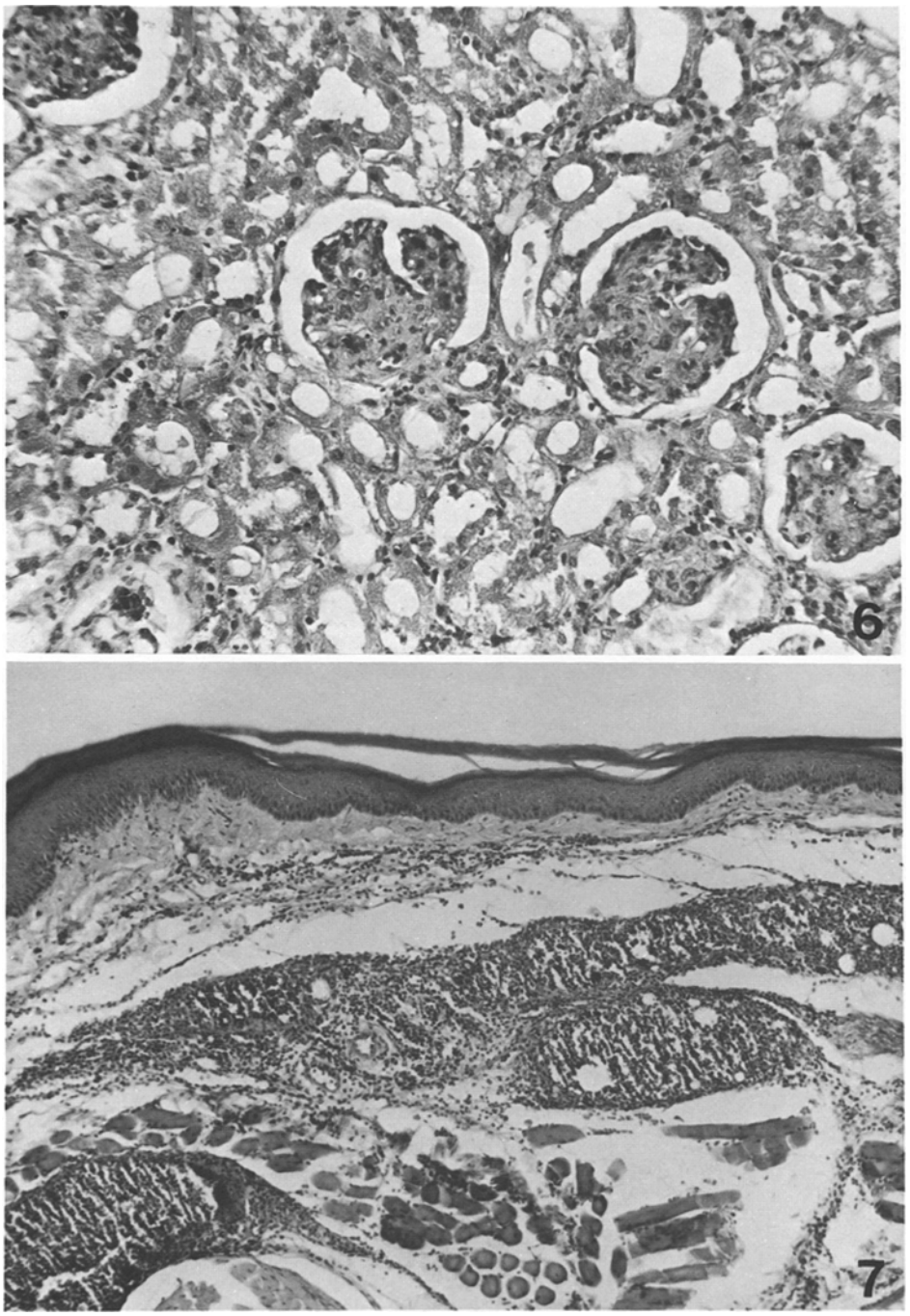


Fig. 6. Marked amyloid nephrosis of an 11 months old descendant from group 2 (X-irradiated in utero with 3×0.8 Gy at days 11–13 p.c.), which developed severe skin ulcerations at an age of 2.5 months (Kongo red, $\times 350$)

Fig. 7. Extensive leucocyte accumulation in the foot pad of a young mice, 24 h after application of 0.05 ml of a skin extract from experimental animals with severe skin lesions. (H.E., $\times 140$)

Table 2. Histological results of the cutaneous test of several skin extracts of controls and animals X-irradiated in utero

	Reaction after											
	24 h				48 h				72 h			
	Animals observed				Animals observed				Animals observed			
	1	2	3	4	1	2	3	4	1	2	3	4
1. Skin extract derived from												
a) control animals	–	–	–	–	–	(+)	–	–	–	–	(+)	(+)
b) unaffected X-irrad. offspring	–	–	(+)	–	+	(+)	(+)	–	–	+	++	+
c) offspring revealing severe skin lesions	+++	+++	+	++	++	++	+++	++	+++	+++	+++	+++
2. Phosphate buffered saline	–	–	–	(+)	–	–	–	–	–	(+)	–	–

Scale of judgement:
(+) few, small infiltrates consisting maximally of 10–15 PMN leucocytes
\+ some small infiltrates consisting of about 10–15 PMN leucocytes
++ multiple infiltrates in the corium with a diffuse tendency for spreading
+++ very intense diffuse PMN leucocytic infiltration

The mean control value was 16.3, the mean follicle number in the irradiated animals was 12.4 per counting area. Thus the reduction in hair follicles was 23.9% after irradiation in utero (days 11–13 p.c.).

The histology of the skin from various body regions of the in utero irradiated germfree mice revealed the presence of PMN leucocytes in the macroscopically intact skin of the ears (Fig. 3) and of the neck at 3 months of age. However, similar infiltrates were not observed in the skin of the extremities or of the ventral body regions (Fig. 4). Controls were free of leucocytic cell assemblies in the corium in all cases.

The leucotactic activity of skin proteinase extracts revealed a very different reaction pattern which depended on the origin of the crude material (Table 2). While saline, or an extract from control animals' skin led only to a very mild reaction within 48–72 h of application, an extract from skin of irradiated but not diseased offspring induced a marked reaction after 72 h. A very severe reaction occurred within 24 h of application of an extract from unaffected parts of skin from X-irradiated and subsequently diseased animals (Fig. 7).

Discussion

Our study presenting animal data on congenital skin defects caused by exogenous harm, should be compared with Demmel's review (1975) on this topic. Demmel argued that "the exogenic cause of congenital skin defects appears more and more impossible."

The high incidence rates of hypotrichosis, alopecia and skin ulcers in the prenatally X-irradiated animals indicates a potential pathogenesis, largely restricted to the mice which were irradiated at least during days 11–13 p.c. (groups 2–5). Irrespective of the doses applied, these animals revealed skin alterations at a very high incidence while those irradiated only during days 14–16 p.c. (groups 6 and 7) were much less susceptible to post-natal skin diseases.

This is reasonable with regard to the skin development of the mouse (Gruneberg, 1943; Hansen, 1947). The dorsal integument arise from the somitic dermatome. The stratum germinativum consists of rather flat cells until day 11 p.c. Differentiation into epidermal layers then begins, while at the same stage the squamous cells become progressively cuboidal. This transformation spreads progressively to the dorsal regions (Sengel, 1976). We suggest that X-irradiation during days 11–13 p.c. preferentially interferes with this differentiation step, during which the flat cells of the dorsal stratum germinativum start proliferating. Thus dysplasia of the skin will be situated mainly in the most dorsal part. Obviously any interaction of X-irradiation with epidermal proliferation is repaired within a short period, since in our studies the labeling intensities at day 18 p.c., the histological structure and also the layer formation are about the same both in controls and irradiated animals. The same explanation also accounts for the occurrence of hypotrichosis in the dorsal head and neck regions, for the studies of Wessells and Roessner (1965) and of Hardy (1969) pointed out that the pelage hairs of the head are the first ones to develop (about days 12–13 p.c.) in the mouse.

We may further speculate that these irradiated offspring have an increased tendency for fighting and biting (Upton et al., 1966), and perhaps a reduced

healing tendency (Fox, 1977). Similar skin lesions have also been reported to occur as a result of excessive grooming and associated self mutilation (Wagner et al., 1977). However, we observed marked signs of inflammation in the presence of a completely intact epidermis. Another pathogenetic possibility is the occurrence of the staphylococcal scalded skin syndrome (Reid et al., 1974; Elias et al., 1974). This disease occurs in mice in response to a toxin (exfoliatin) from coagulase-positive staphyloccocci and is mainly restricted to newborn animals, mainly because of a lower renal excretion of this toxin and therefore a higher accumulation in the newborn animal's skin (Fritsch et al., 1976). However, this disease could be ruled out by the experiments with germfree mice and also by very different symptoms of the disease described here, especially with respect to age distribution and body area restriction.

The appearance of PMN infiltrates in the corium of intact skin strongly indicates a (functional) dysplasia of the integument. We wondered whether there is an endogenous chemotactic mechanism, originating from the epidermis itself. Indeed, the very intense leucotactic reaction, which can be induced by a crude homogenate or by a proteinase extract from irradiated and affected animals' skin as soon as 24 h after application, clearly points to the presence of a leucotactic substance in X-irradiated animal's skin. This pathogenesis bears some resemblance to an hypotheses of the causation of human psoriasis, although the morphological picture of skin disease in mice is quite different. In psoriatic skin Lazarus et al. (1977) found an elevated level of serin-proteinase, while Penneys et al. (1976, 1977a) described the occurrence of inhibitors of the prostaglandin synthesis and consequently an elevated level of free arachidonic acid (Hammarstrom et al., 1975), which is known to be of high leucotactic activity (Turner et al., 1975; Penneys et al., 1977b). To date we have not been able to prove these biochemical details in our animals.

The pathogenesis of the skin lesions can also be discussed in the light of a functional deficit of the pituitary. Haeffner and Privett (1973) reported on scaly tails and feet, similar to those seen in essential fatty acid deficiency, in immature hypophysectomized rats. According to Tan and Privett (1973) these rats fail to convert arachidonic acid to prostaglandin and will thus evolve skin lesions. As we did not find morphological alterations in the pituitary and the other endocrine glands we are inclined to reject this indirect pathogenetic path to dermal inflammation.

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