Full-Thickness Skin Grafts from Flaky Skin Mice to Nude Mice: Maintenance of the Psoriasiform Phenotype

John P. Sundberg, Robert W. Dunstan, Dennis R. Roop*, and Wesley G. Beamer
The Jackson Laboratory, Bar Harbor, Maine; and *Baylor College of Medicine, Houston, Texas, U.S.A.

Flaky skin *(fsn)* is an autosomal recessive mouse mutation with papulosquamous disease features similar to human psoriasis. In *fsn/fsn* skin, one sees marked acanthosis and hyperkeratosis with focal parakeratosis, subcorneal pustules, dermal capillary dilation, and a marked diffuse dermal infiltration of mixed inflammatory cells, predominantly lymphocytes. To determine if these pathologic features are a characteristic of the skin or a chronic autoimmune attack, we placed full-thickness skin grafts from affected homozygous *(fsn/fsn)* and normal littermate control (+/?) mice on the dorsal skin of genetically athymic nude *(nu/nu)* mice. After 10 weeks of observation, the grafts maintained the histologic phenotype of the donor animal. In the *fsn/fsn* grafts, there was persistence of both epidermal proliferation and dermal inflammation, characteristics of the mutation. The *fsn/fsn* phenotype was also confirmed by immunohistochemical evaluation for specific mouse keratinocyte marker expression. Based on tritiated thymidine uptake, we found DNA synthesis rates elevated threefold or more in *fsn/fsn* epidermis compared to littermate control mouse skin. Elevated rates of DNA synthesis remained a feature of the *fsn/fsn* grafts but not that of littermate control skin grafts. This study demonstrates that the psoriasiform phenotype of this mouse mutation can persist independent of the host thymic-derived immune system. *J Invest Dermatol 102:781–788, 1994*

Psoriasis is believed to have a genetic basis, although the mode of inheritance and number of genes involved remain to be defined [1–3]. Progress in understanding the mechanisms of psoriasis has long been hampered by the obvious difficulty in obtaining samples from human subjects and the lack of a suitable animal model system [4]. Although sporadic cases of psoriasiform dermatitides have been described in non-human primates [5,6], dogs [7], and pigs [8], the spontaneous nature and infrequent occurrence of these diseases discourage their use for detailed scientific investigation.

Establishment of an animal model system of a psoriasiform dermatitis using an inbred mouse strain would resolve many of the problems associated with other purported animal models of psoriasis, particularly the availability of large numbers of affected animals. Although there are several spontaneous mouse mutations in which hyperkeratosis is part of the phenotype, such as asebia *(ab)* and ichthyosis *(ic)* [9], the hyperkeratosis in these animals is not associated with inflammation. Therefore, they are not suitable to investigate the interaction of the epidermis and inflammatory cells, which is central to defining the pathogenesis of psoriasis. Recently, there have been reports of transgenic mice and rats with inflammatory and hyperkeratotic skin disease suggestive of psoriasiform dermatitis [10–12]. The relevance of these lesions to human psoriasis awaits further characterization.

In the fall of 1985, a spontaneous autosomal recessive mouse mutation, designated flaky skin (gene symbol *fsn*), was found at The Jackson Laboratory [9,13,14]. Extensive longitudinal characterization studies of skin from *fsn/fsn* mice have demonstrated a high degree of correlation between the mouse skin pathology and human psoriasis [13,14]. The flaky skin mouse has changes in the stratum corneum characteristic of guttate psoriasis and a prominent dermal inflammatory cell infiltrate similar in composition to psoriasis in humans.

Current hypotheses suggest that psoriasis arises as a result of a complex interaction between cytokines and various cells of the immune system [15,16]. Discriminating between these hypotheses requires experimental isolation of the psoriasiform skin and maintaining it in an environment free of an immune system. Although this is precluded by both ethical and practical issues in humans, the role of host inflammatory cells on the maintenance and progression of the disease in flaky skin mice can be analyzed by grafting affected *fsn/fsn* skin onto genetically athymic nude *(nu)* mice. Homozygous *nu/nu* mice lack a thymus and thus do not have T cells necessary to reject cutaneous allographs or xenographs of wide phylogenetic disparity [17,18]. This method has been used to study the biology of permanent skin grafts of normal adult and fetal human skin and adnexa [19–21]. Human allografts onto *nu/nu* mice have also been used to define the pathogenesis of a number of human skin diseases including psoriasis [22–24]. Transplantation of skin from *fsn/fsn* to *nu/nu* mice would test the hypothesis that an abnormal immune system was required for maintenance of the psoriasiform phenotype and would also provide a comparison of the *fsn/fsn* phenotype with human psoriasis.

We describe here the successful transplantation of full-thickness skin grafts from *fsn/fsn* and +/? littermate control mice to *nu/nu* mice. The mutant phenotype was maintained, as determined by histopathology, immunohistochemistry, and epidermal kinetic studies. No influence on the normal littermate control grafts was identified.

Manuscript received November 10, 1993; accepted for publication December 20, 1993.

Dr. Dunstan did the work while on sabbatical from the Department of Pathology, Michigan State University, East Lansing, MI 48824-1316.

Reprint requests to: Dr. John P. Sundberg, The Jackson Laboratory, 600 Main Street, Bar Harbor, ME 04609.

Abbreviations: *fsn*, flaky skin mouse mutation; *nu*, nude mouse mutation; +/?, flaky skin heterozygote or wild type littermate control.

0022-202X/94/$07.00

MATERIALS AND METHODS

Animals Skin graft donor mice consisted of six female CBy.A N1F2-*fsn*/*fsn* and six female +/? (may be either +/*fsn* or +/+) littermate control mice that were 7–9 weeks old. In addition, unmanipulated female *fsn*/*fsn* and +/? mice at 6 weeks of age (three each) and 16 weeks of age (two each) were necropsied for comparison to the donor and 10-week-old grafted skin. Mice were obtained from the small research colony developed and maintained at The Jackson Laboratory, Bar Harbor, ME. Recipients consisted of twelve 7–8 week old, male CByB6F1/J-*nu*/*nu* mice obtained from production colonies of The Jackson Laboratory. Mice were fed Wayne sterilizable Rodent Blox (Tecklab, Premier Laboratory Diets, Bartonville, IL), provided chlorinated water (10–20 ppm residual chlorine) *ad libitum*, and maintained on a 12:12 light:dark cycle.

Skin Grafts The grafts were performed according to the methods described by Briggaman [25]. Briefly, recipient and donor mice were each anesthetized with pentobarbital (80 mg/kg body weight; Nembutal, Abbott Laboratories, North Chicago, IL) diluted in phosphate-buffered saline (pH 7.2) administered intraperitoneally (IP). A circular piece of skin (epidermis and dermis), approximately 1 cm in diameter, was aseptically removed from the dorsal cervical and lumbar regions of *nu*/*nu* recipients. To these sites we transplanted 1-cm-diameter biopsies of the cutis obtained from the dorsal cervical and dorsal lumbar regions of the donor mice. Grafts were held in place with tape cut to form a vest around the mouse. Each recipient received one skin graft from a *fsn*/*fsn* and one from a +/? littermate control mouse. Each donor provided grafts for transplantation to two *nu*/*nu* recipients. At the same time, additional samples of skin were fixed from the donor mice for histopathologic comparison of the donor skin with transplanted skin.

Epidermal Kinetics Seventy days after transplantation, the recipient mice were administered 1 μCi/gm body weight of ^{3}H-thymidine (specific activity 20 μCi/mM; New England Nuclear, Boston, MA) IP, to label cells entering the "S" phase of the cell cycle. Forty minutes after injection, the mice were euthanized by CO_2 asphyxiation. The transplantation sites and peripheral skin from the *nu*/*nu* mouse host were removed, attached by gentle pressure to heavy paper, and fixed by immersion in Fekete's acid alcohol formalin for 12 h. The tissues were subsequently transferred to 70% ethanol, trimmed for histology, embedded in paraffin, and sectioned at 5 μm. Serial sections were either stained with hematoxylin and eosin, prepared for immunohistochemistry, or processed for autoradiography.

Autoradiographs were prepared by immersing the slides in a liquid photographic emulsion (Kodak NTB-2; Eastman Kodak Co., Rochester, NY) under darkroom conditions, exposed at 4°C for 39 d, developed (Kodak D19 developer, Eastman Kodak Co.) and stained with Mayer's hematoxylin. On microscopic examination, an epidermal cell was defined as labeled (synthesizing DNA) if it contained five or more silver grains over the nucleus. Two labeling indices were defined for each transplantation site: 1) the epidermal basal cell labeling index, which represents the labeled epidermal basal cells/total epidermal basal cells $\times 100$ (estimated by counting 2000 labeled and unlabeled basal cells); and 2) the epidermal nucleated cell-labeling index, which represents the total labeled epidermal nucleated cells/epidermal nucleated cells $\times 100$ (established by counting 5000 labeled and unlabeled nucleated cells [26]). The cell-renewal time was estimated from these data using the method of Leblond *et al* [27]. Data were analyzed by the t test; differences were considered significant at $p < 0.05$.

Immunohistochemistry Serial sections, obtained as described above, were stained with a panel of rabbit affinity-purified polyclonal antibodies directed against mouse specific keratinocytes markers (K1, K5, K6, K10, K13, K14, filaggrin, and loricrin) using the avidin-biotin method. Diaminobenzidine was used as the chromagen and Mayer's hematoxylin as the counterstain as previously described [28]. Dark brown cytoplasmic staining was scored as positive with blue as a negative result. Results were compared to staining of host skin taken adjacent to the excision site.

RESULTS

Skin Grafts Representative photographs of host mice and photomicrographs of full-thickness skin graft from *fsn*/*fsn* and +/? littermate controls are presented in Figs 1 and 2. The histologic and immunohistochemical results, as well as labeling index data, were essentially identical for the duplicate grafts even though they were on separate recipients. The data are summarized in Tables I and II.

The *fsn*/*fsn* and +/? grafts could be distinguished from adjacent *nu*/*nu* mouse skin by microscopic differences in the hair follicles

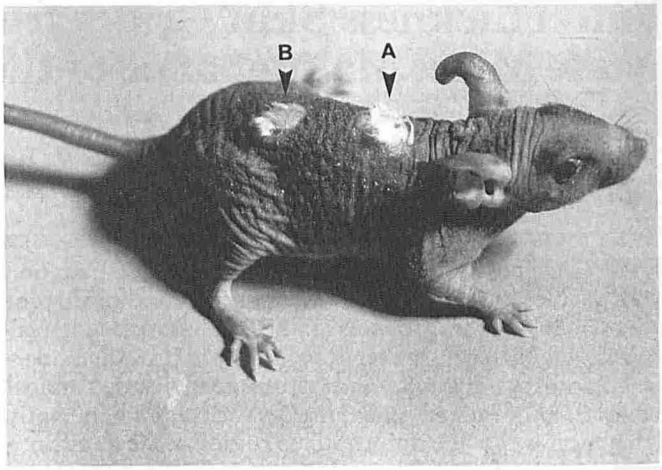

Figure 1. The *nu*/*nu* mouse with with a *fsn*/*fsn* graft *(A)* and +/? control skin graft *(B)*, 10 weeks after surgery.

(Fig 2). The donor grafts were from an albino background and accordingly had hair follicles with normal hair shafts devoid of melanin pigment. The *nu*/*nu* mouse background is pigmented and thus skin had abundant melanosomes in the hair bulbs and the hair shafts in the follicular infundibulum were characteristically distorted and malacic [29].

Normal +/? control skin and +/? grafted onto *nu*/*nu* mice had no substantive differences other than mild dermal and panniculer fibrosis and rare, scattered lymphocytes and macrophages. These were judged to be a consequence of the surgical procedures.

In contrast, *fsn*/*fsn* donor skin and grafts had marked laminated orthokeratosis alternating with mounds of parakeratosis and occasionally contained neutrophils (Fig 2). The nucleated epidermal layers had moderate to marked epidermal hyperplasia with prominence of the granular cell zone. The pattern of hyperplasia in the grafts was often more papillated than donor skin and there was prominent keratin plugging of the follicular infundibula. In both donor and graft biopsies, there was an interstitial and perivascular inflammatory response involving the entire dermis. The reaction was somewhat less severe in the grafts (but much more intense than the scattered inflammatory cells noted in the littermate control grafts). The inflammatory reaction was composed primarily of small lymphocytes and macrophages. Neutrophils were occasionally present in the subepidermal adventitial dermis. There was dermal and panniculer fibrosis as a consequence of the grafting procedure.

Immunohistochemistry Immunohistochemical evaluation of keratinocyte markers of the transplanted and non-transplanted controls (+/?), had a consistent staining pattern. The results, summarized in Table I, represent data from six donor biopsies rather than 12 recipient grafts for each group. This was done because of the identical staining patterns of the respective grafts. Markers for K5 and K14 stained the lower half of the epidermis (primarily basal cells) and the keratinocytes of the outer root sheath of the hair follicle (Fig 3*a–d*). Anti-K6 stained the cells comprising the inner layer of the outer root sheath of the follicular isthmus (Fig 3*e,f*) Staining for K1 and K10 was specific for the upper half of the non-cornified epidermis (Fig 4*a–d*). Anti-K13, which normally stains only the mucous membranes of the oral cavity, did not stain skin cells. Anti-loricrin and filaggrin staining was limited to the cytoplasm of the epidermal and infundibular granular cell layer, the expression of filaggrin being specific for keratohyalin granules (Fig 4*e,f*)

The immunohistochemical staining patterns of the *fsn*/*fsn* mice

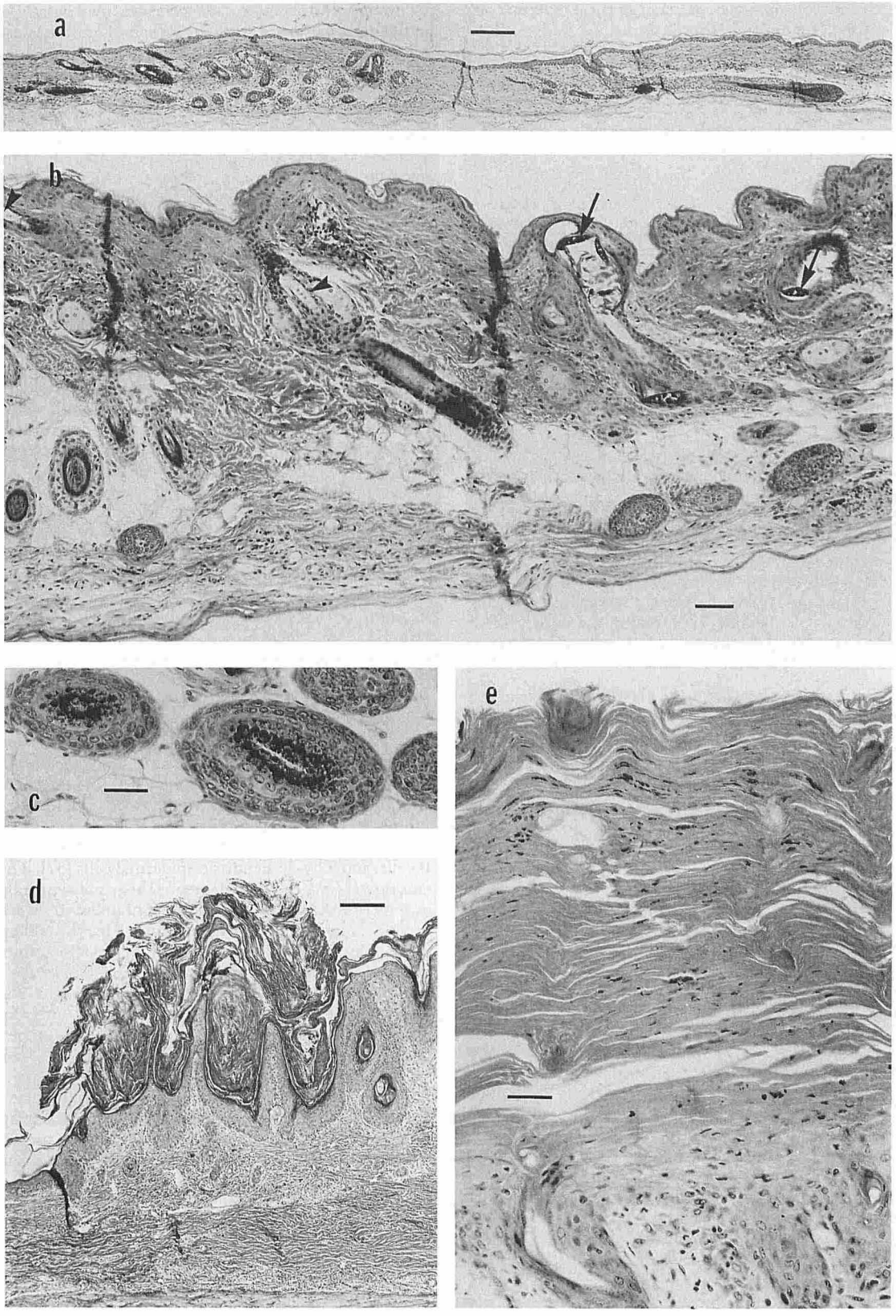

Figure 2. Skin grafts from littermate control (+/?) and affected *fsn/fsn* mice. Abrupt change in orientation of follicles identified location of normal grafts (*a, bar,* 200 μm). Normal unpigmented hair follicles and shafts *(arrowheads)* of the +/? mice could be differentiated from the pigmented, dystrophic hair shafts *(arrows)* (*b, bar,* 100 μm). Heavily pigmented *nu/nu* bulbs (*c, bar,* 50 μm) could be easily differentiated from +/? bulbs *(b)*. In the *fsn/fsn* graft there was more intense inflammation, marked epidermal hyperplasia, laminated orthokeratosis, and keratin plugging of the follicular infundibula (*d, bar,* 100 μm; *e, bar,* 50 μm).

Table I. Keratinocyte Marker Expression in the Epidermis of Grafted and Host Skin[a]

Keratinocyte Marker	Immunohistochemical Expression		
	fsn/fsn	+/?	*nu/nu*
Keratin K1	Patchy to negative	Positive	Positive
Keratin K5	Positive	Positive	Positive
Keratin K6	Positive	Negative[b]	Negative[b]
Keratin K10	Patchy to negative	Positive	Positive
Keratin K13	Negative	Negative	Negative
Keratin K14	Positive	Positive	Positive
Filaggrin	Increased	Positive	Positive
Loricrin	Increased	Positive	Positive

[a] Immunohistochemistry was done on skin from *fsn/fsn* and +/? mice as well as the grafted skin from both mutant and control mice and the *nu/nu* host skin to determine if phenotypic expression of these keratinocyte markers remained the same in the grafts as donor skin.

[b] Staining limited to outer root sheath of the hair follicle at the level of the follicular isthmus.

were consistent between the donor and the grafts, as summarized in Table I. Keratinocyte marker proteins K5, K13, and K14 stained similarly to that of the +/? controls. Filaggrin and loricrin staining was more prominent than in controls, a change consistent with the hypergranulosis noted on sections stained with hematoxylin and easin. K1 and K10 staining was patchy where the epidermis was moderately hyperplastic and minimal to absent where the epidermis was markedly hyperplastic. K6 was expressed in the noncornified epidermis and in the entire outer root sheath.

Epidermal Kinetics The results of the ^{3}H-thymidine labeling studies are presented in Table II and illustrated in Fig 5. The grafts from the *fsn/fsn* mice had significantly higher cell labeling indices than +/? control grafts ($p < 0.005$), with calculated cell renewal times of 1.9 d and 6.9 d, respectively. As a consequence of factors associated with surgical grafting, the grafts from both *fsn/fsn* and +/? control mice had significantly more proliferative activity when compared to biopsies from their respective genotype controls ($p < 0.05$).

DISCUSSION

Grafting psoriatic human skin onto *nu/nu* mice has been developed as a system that can be manipulated to study the biology and potential treatment of the disease [22–24]. With the discovery of a new mouse mutation that resembles psoriasis, it was possible to use skin grafting to ask fundamental questions about the pathogenesis of the disease. It was essential to use *nu/nu* mice as recipients because the *fsn* gene was not on an inbred background, thus precluding syngeneic grafting. This study demonstrated that grafting of *fsn/fsn* skin to *nu/nu* mice would maintain the clinical phenotype for periods of at least 10 weeks. This has advantages as a test system, but also implies that the thymic-derived T lymphocytic part of the immune system is not required for maintenance of the lesion.

Maintenance and progression of the *fsn/fsn* phenotype in grafts may be caused by host factors produced by the *nu/nu* mouse that support already inherently abnormal *fsn/fsn* keratinocytes. Grafting of human psoriatic skin to *nu/nu* mice has yielded conflicting results and interpretations. Thus, Briggaman *et al*† were successful in their studies and concluded that host factors were important for supporting the skin disease. Others have achieved intermediate results [22–24] and concluded that only some factors are present in *nu/nu* mice. Finally, Baker *et al* [30] reported loss of the psoriatic phenotype, and by immunohistochemical markers identified putative mouse T cells in the human grafts, raising the specter of graft-versus-host response confounding the interpretation of skin graft proliferation as evidence for abnormal keratinocytes [23]. This latter conclusion must be tempered by the fact that several cell types including NK cells, all T cells, and Thy-1$^+$ dendritic epidermal cells also express Thy 1.2 antigen [13,31–33]. The confusion may stem from several sources, such as variability of the human grafts, unidentified species differences in host factors, and substantial differences in genetic backgrounds of the *nu/nu* mice used for grafting studies [22–24,30]. It is well known that a mutant phenotype can be subtly or dramatically altered by background modifying genes [34].

Variation in endogenous factors may play a role in changes in phenotypes between allograph versus xenographs in this type of iatrogenic model system. Dermal-epidermal recombination grafts of human psoriasis skin onto *nu/nu* mice duplicated psoriasis only in recombinants composed of psoriatic epidermis and dermis. The human recombination study indicated that generalized (exfoliative) psoriasis resides within the skin and not just the epidermis.† Neonatal or fetal *fsn/fsn* skin grafts combined with dermal-epidermal recombination grafts are in progress to determine if both mutant dermis and epidermis are required for phenotypic expression.

Patients with severe, generalized psoriasis, had complete and permanent regression of skin lesions following bone-marrow transplants from unaffected siblings for diseases unrelated to the psoriasis [35,36]. Therefore, it appears that bone-marrow–derived cells and growth factors are involved in the pathogenesis of at least some forms of psoriasis. We have found that bone marrow grafted from *fsn/fsn* mice to severe combined immunodeficiency *(scid/scid)* mice resulted in the development of a proliferative skin disease in the recipients [13]. This experiment suggests that the papulosquamous disease in *fsn/fsn* mice has a pathogenesis similar to that of some forms of human psoriasis. Alternatively, cells or factors residing in the dermis or epidermis in the full-thickness grafts might be adequate to maintain the phenotype during the observation period. The *fsn/fsn* grafts to *nu/nu* hosts in this study did have lymphocytic infiltrates (probably B cells of *nu/nu* origin) in the dermis 10 weeks after the surgery. The source of these cells was not identified. Some studies suggest that T lymphocytes mediate keratinocyte proliferation in psoriasis [5]. The *scid/scid* mutation lacks functional T cells, B cells, and Thy-1$^+$ dendritic epidermal cells [37]. The double mutation *(scid/scid, fsn/fsn)* maintains the papulosquamous phenotype in spite of the lack of a functional immune system [13]. Therefore, functional lymphocytes are not required for the pathogenesis of the *fsn* papulosquamous disease. These observations initially indicate that the mechanisms underlying the *fsn* phenotype are different from those of human psoriasis. This may be the case with some forms of psoriasis; however, because patients with acquired immunodeficiency syndrome (lacking a functional immune system) have been reported with severe cases of psoriasis [38], this hypothesis should be re-examined.

Immunohistochemical evaluation of keratinocyte markers has proved to be useful for evaluating naturally occurring mouse skin tumors [39] and carcinogen-induced mouse skin tumors [40–42], as well as xenografts to nude mice [43]. Some of the markers, such as K13, are detected in squamous cell carcinomas of the skin and may prove to be valuable in the mouse for differentiating hyperplastic versus neoplastic changes in naturally occurring or induced skin tumors [40,44–46] or various biochemically related processes in mutant mice. K13 was not expressed in either the donor or grafted *fsn/fsn* skin, suggested that there is no inherent transformational defect in this mutant mouse. Another keratinocyte marker, K6, has been associated with nonspecific hyperplasia of the epidermis and papilloma formation [42,47,48], whereas expression of others such as K1 and K10 are decreased or absent [42,49,50]. Expression in the *fsn/fsn* epidermis was consistent with these types of observations. K6 in mice without epidermal hyperplasia is only expressed in the inner cell layer of the outer root sheath of the follicular isthmus whereas K1 and K10 are present in normal suprabasal cells. These

† Briggaman RA, Wheeler CE: Nude mouse-human skin graft model III. Studies on generalized psoriasis (abstr). *J Invest Dermatol* 74:262, 1980.

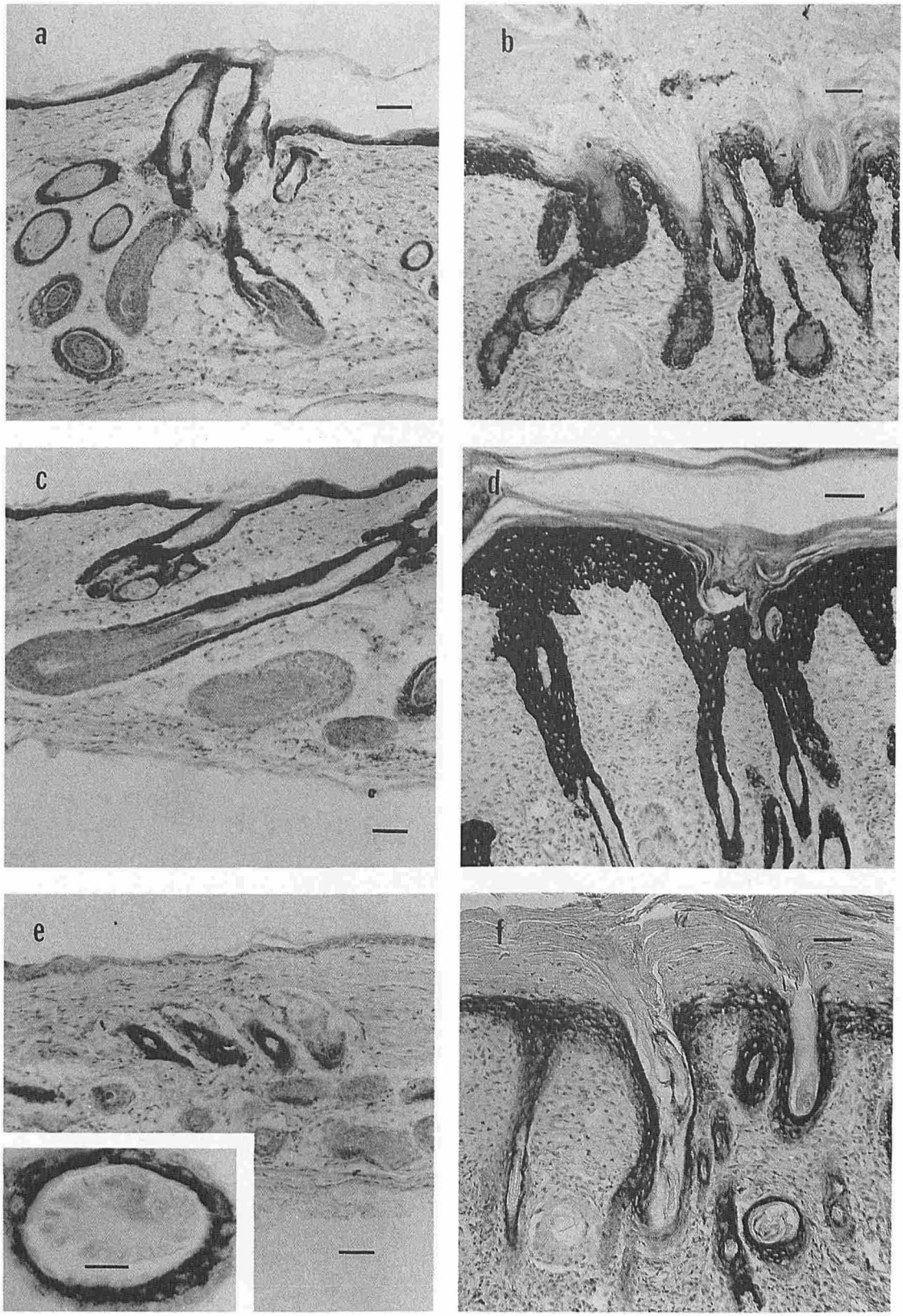

Figure 3. Antibodies directed at mouse keratins K5 (*a, b, bar,* 100 μm) and K14 (*c, d, bar,* 100 μm) stained basal and suprabasal epidermal cells and the outer root sheath of the hair follicle. Patterns between controls *(a, c)* and *fsn/fsn (b, d)* grafts were similar. Staining for K6 was localized to the follicular isthmus in control grafts (*e, bar,* 100 μm; *inset, bar,* 20 μm) but extended to the proliferative suprabasal epidermis in the *fsn/fsn* grafts (*f, bar,* 100 μm).

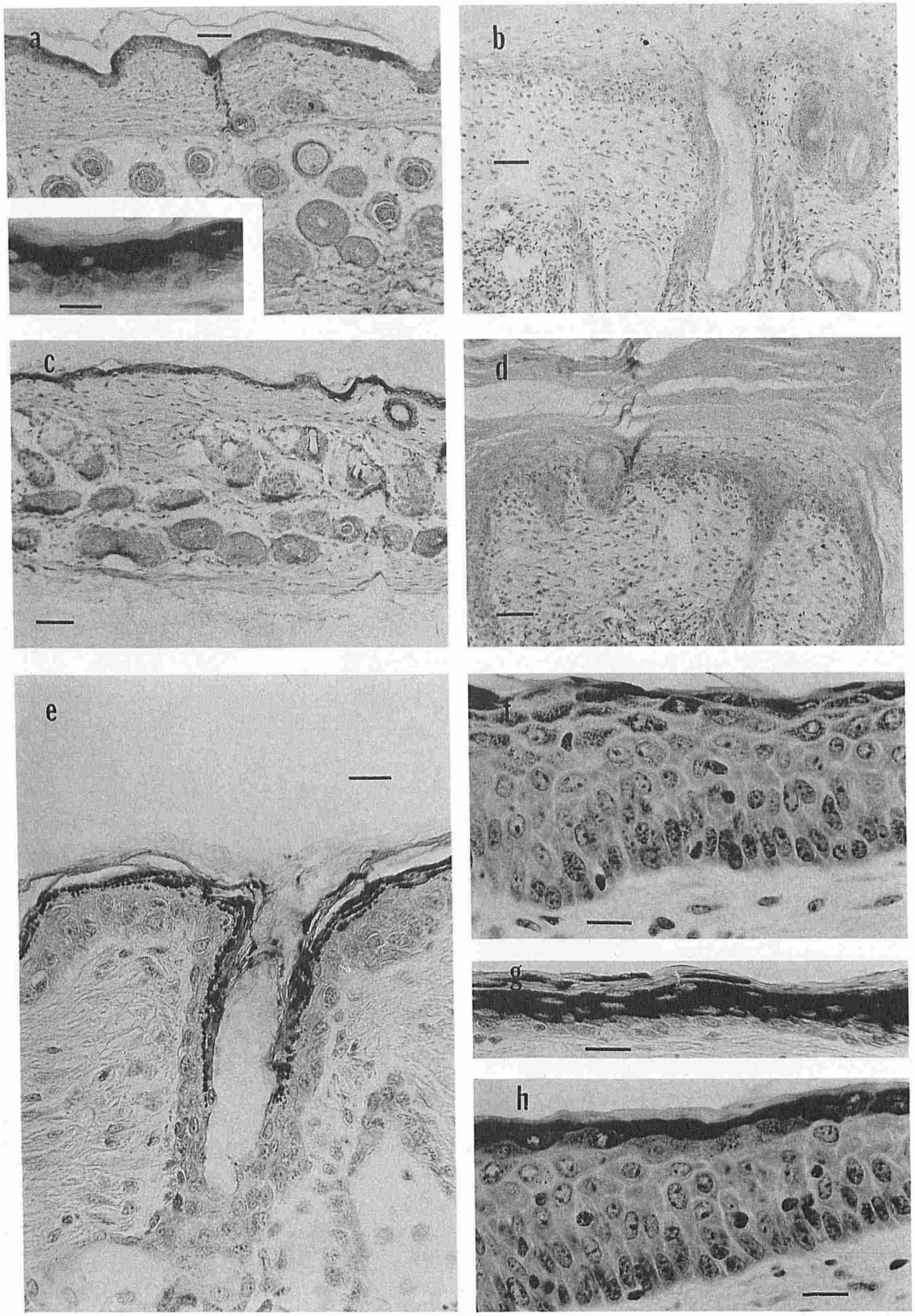

Figure 4. K1 (*a, b, bar,* 100 μm) and K10 (*c, d, bar,* 100 μm) were detected in suprabasilar epidermis of control grafts (*a, insert, bar,* 20 μm, *c*) but not in the proliferating epidermis of the *fsn/fsn* skin grafts (*b, d*). Filaggrin staining was limited to the keratohyalin granules within the cytoplasm of cells in the stratum granulosum of both control (*e, bar,* 20 μm) and *fsn/fsn* skin grafts (*f, bar,* 20 μm). Loricrin staining was limited to the cytoplasm of cells in the stratum granulosum of both controls (*g, bar,* 20 μm) and *fsn/fsn* (*h, bar,* 20 μm) grafts.

Table II. Cell Kinetic Data Based on Tritiated Thymidine Uptake for 42-Day-Old Flaky Skin Mice or Littermate Controls or Comparable Grafted Skin to Nude Mice[a]

Criteria	*fsn/fsn*	+/?
Basal cell labeling index		
Skin graft	31.7 ± 4.6[b]	6.9 ± 3.7
Unmanipulated skin	18.6 ± 7.7	2.9 ± 0.3
Nucleated cell labeling index		
Skin graft	13.6 ± 1.3	4.2 ± 1.7
Unmanipulated skin	7.8 ± 2.4	3.1 ± 0.7
Calculated cell renewal time in days		
Skin graft	1.9 ± 0.2	6.9 ± 2.3
Unmanipulated skin	3.6 ± 0.9	8.9 ± 1.9

[a] Mice were injected with tritiated thymidine to determine if epidermal kinetics of both the *fsn/fsn* donor and grafted skin remained elevated compared to that of the control skin.
[b] Standard deviation.

observations in both *fsn/fsn in situ* skin and grafted skin parallel similar observations of human psoriatic skin [51,52].‡

The ^{3}H-thymidine labeling indexes of the *fsn/fsn* and +/? littermate controls were significantly different ($p < 0.005$); duplicate biopsies grafted onto each of two *nu/nu* mice yielded essentially identical results. The labeling indices of the grafted sites were higher than the donor skin of the affected and control mice. This observation can most reasonably be explained by the dermal fibrosis and other processes of wound healing, which can stimulate increased epidermal turnover. There is an inherent variability in the labeling index of humans with and without psoriasis.† This could reflect the background genetic variation between humans (an outbred species) and the variation of the purported human genetic mutation(s) as well [34]. However, by grafting of human psoriatic skin from one individual onto several *nu/nu* mice, similar results were obtained within that group of nude mice [22], as was the case with *fsn/fsn* grafts to *nu/nu* mice in this study.

There is increasing evidence that supports the flaky skin mouse mutation as a potentially useful animal model that will serve as a useful tool to unravel the mechanisms involved in papulosquamous diseases, such as psoriasis. In this study we have demonstrated that skin grafts onto *nu/nu* mice will maintain the mutant phenotype as measured by histopathology, keratinocyte markers, and epidermal kinetics. All of these parameters parallel similar studies utilizing human psoriatic skin grafts to *nu/nu* mice, further supporting the value of this new mouse mutation.

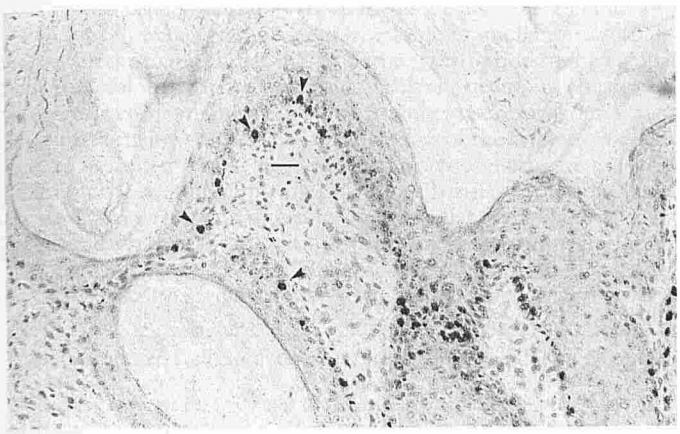

Figure 5. ^{3}H-thymidine labeled nuclei *(arrowheads)* were numerous in *fsn/fsn* grafts (*bar*, 20 μm).

‡ Holland DB, Wood EJ, Goodfield MJD, Cunliffe WJ: Epidermal differentiation in pre-lesional psoriatic skin (abstr). *J Invest Dermatol* 92:446, 1989.

We wish to thank D.L. Adkison, K.S. Brown, and P. Jewett for their technical assistance. This work was supported by grant AR40324 from the National Institutes of Health and Institutional Research funds from the Jackson Laboratory.

REFERENCES

1. Creagh TM, Wright NA, McKee PH: Inflammatory Dermatoses. In: McKee PH (ed.). *Pathology of the Skin with Clinical Correlations.* J.B. Lippincott, Philadelphia, 1989, pp 8.3-8.8
2. Farber EM, Nall L: Epidemiology: natural history and genetics. In: Roenigk HH, Maibach HI (eds.). *Psoriasis.* Marcel Dekker, New York, 1991, pp 209-258
3. Marcusson J: Psoriasis and arthritic lesions in relation to the inheritance of HLA genotypes. *Acta Dermato-Venereol* 82 (suppl 59):5-78, 1979
4. Krueger GG, Bergstresser PR, Lowe NJ, Voorhees JJ, Weinstein GD: Psoriasis. *J Am Acad Dermatol* 11:937-947, 1984
5. Lowe NJ, Breeding J, Kean C, Cohn ML: Psoriasiform dermatoses in a rhesus monkey. *J Invest Dermatol* 76:141-143, 1981
6. Jayo MJ, Zanolli MD, Jayo JM: Psoriatic plaques in *Macaca fascicularis. Vet Pathol* 25:282-285, 1988
7. Mason KV, Halliwell RE, McDougal BJ: Characterization of lichenoid-psoriasis-form dermatosis of springer spaniels. *J Am Vet Med Assoc* 189:897-901, 1986
8. Dunstan RW, Rosser ER: Does a condition like human pityriasis rosea occur in pigs? *Am J Dermatopathol* 8:86-89, 1986.
9. Sundberg JP, Beamer WG, Shultz LD, Dunstan RW: Inherited mouse mutations as models of human adnexal, cornification, and papulosquamous dermatoses. *J Invest Dermatol* 95:62S-63S, 1990
10. Hammer RE, Maika SD, Richardson JA, Tang J-P, Taurog JD: Spontaneous inflammatory disease in transgenic rats expressing HLA-B27 and human B2 M: an animal model of HLA-B27-associated human disorders. *Cell* 63:1099-1112, 1990
11. Leonard JM, Abramczuk JW, Pezen DS, Rutledge R, Belcher JH, Hakim F, Shearer G, Lamperth L, Travis W, Fredrickson T, Notkins AL, Martin MA: Development of disease and virus recovery in transgenic mice containing HIV proviral DNA. *Science* 242:1665-1670, 1988
12. Wilson JB, Weinberg W, Johnson R, Yuspa S, Levine AJ: Expression of the BNLF-1 oncogene of Epstein-Barr virus in the skin of transgenic mice induces hyperplasia and aberrant expression of keratin 6. *Cell* 61:1315-1327, 1990
13. Sundberg JP, Boggess D, Sundberg BA, Beamer WG, Shultz LD: Epidermal dendritic cell populations in the flaky skin mutant mouse. *Immunol Invest* 22:389-401, 1993
14. Sundberg JP, Boggess D, Shultz LD, Beamer WG: The flaky skin *(fsn)* mutation, chromosome? In: Sundberg JP (ed.). *Handbook of Mouse Mutations with Skin and Hair Abnormalities: Animal Models and Biomedical Tools.* CRC Press, Boca Raton (in press)
15. Baadsgaard O, Fisher G, Voorhees JJ, Cooper KD: The role of the immune system in the pathogenesis of psoriasis. *J Invest Dermatol* 95:32S-34S, 1990
16. Nickoloff B, Karabin G, Barker J, Griffiths C, Sarma V, Mitra R, Elder J, Kunkel S, Dixit V: Cellular localization of interleukin-8 and its inducer, tumor necrosis factor-alpha in psoriasis. *Am J Pathol* 138:129-140, 1991
17. Manning DD, Reed ND, Shaffer CF: Maintenance of skin xenografts of widely divergent phylogenetic origin on congenitally athymic (nude) mice. *J Exp Med* 138:488-494, 1973
18. Spang-Thomsen M, Visfeldt J: Transplanted malignant tumors. Human disease: malignant tumors. Animal model: homozygous *nu/nu* mice with transplanted human malignant tumors. *Am J Pathol* 84:193-196, 1976
19. Reed ND, Manning DD: Long term maintenance of normal human skin on congenitally athymic (nude) mice. *Proc Soc Exp Biol Med* 143:350-353, 1973
20. Lane AT, Scott GA, Day KH: Development of human fetal skin transplanted to the nude mouse. *J Invest Dermatol* 93:787-791, 1989
21. Petersen MJ, Zone JJ, Krueger GG: Development of a nude mouse model to study human sebaceous gland physiology and pathophysiology. *J Clin Invest* 74:1358-1365, 1984
22. Krueger GG, Manning DD, Malouf J, Ogden B: Long-term maintenance of psoriatic human skin on congenitally athymic (nude) mice. *J Invest Dermatol* 64:307-312, 1975
23. Krueger GG, Chambers DA, Shelby J: Involved and uninvolved skin from psoriatic subjects: are they equally diseased? Assessment by skin transplanted to congenitally athymic (nude) mice. *J Clin Invest* 68:1548-1557, 1981
24. Haftek M, Ortonne J-P, Staquet M-F, Viac J, Thivolet J: Normal and psoriatic human skin grafts on "nude" mice: morphological and immunochemical studies. *J Invest Dermatol* 76:48-52, 1981
25. Briggaman RA: Human skin graft—nude mouse model: techniques and application. In: Skerrow D, Skerrow CJ (eds.). *Methods in Skin Research.* John Wiley & Sons Ltd, Chichester, 1985, pp 251-276.
26. Kwochka KW, Rademakers AM: Cell proliferation of epidermis, hair, follicles, and sebaceous glands of beagles and cocker spaniels with healthy skin. *Am J Vet Res* 50:587-591, 1989
27. Leblond CP, Greulich RC, Pereira JPM: Relationship of cell formation and cell migration in the renewal of stratified squamous epithelia. In: Montagna W,

Billingham RE (eds.). *Advances in Biology of Skin*. Pergamon Press, New York, 1964, pp 39–67
28. Sundberg JP, Roop DR: Optimizing histology and immunohistochemistry for mouse skin. *J Histochem Cytochem* (in press)
29. Kopf-Maier P, Mboneko VF, Merker HJ: Nude mice are not hairless. *Acta Anat* 139:178–190, 1990
30. Baker BS, Brent L, Valimarsson H, Powles AV, Al-Imara L, Walker M, Fry L: Is epidermal cell proliferation in psoriatic skin grafts on nude mice driven by T-cell derived cytokines? *Br J Dermatol* 126:105–110, 1992
31. Aoki T, Hammerling U, deHarven E, Boyse EA, Old LJ: Antigenic structure of cell surfaces. An immunoferritin study of the occurrence and topography of H-2'Θ, and TL alloantigens on mouse cells. *J Exp Med* 130:979–1001, 1969.
32. Owen JJT, Raff MC. Studies on the differentiation of thymus-derived lymphocytes. *J Exp Med* 132:1216–1232, 1970
33. Scheid M, Boyse EA, Carswell EA, Old LJ: Serologically demonstratrable alloantigens of mouse epidermal cells. *J Exp Med* 135:938–954, 1972
34. Sundberg JP: Conceptual evaluation of inbred laboratory mouse models as tools for the study of diseases in other species. *Lab Animal* 21:48–51, 1992
35. Jowitt SN, Yin JAL: Psoriasis and bone marrow transplantation. *Br Med J* 300:1398–1399
36. Eedy DJ, Burrows D, Bridges JM, Jones FGC: Clearance of severe psoriasis after allogenic bone marrow transplantation. *Br Med J* 300:908, 1990
37. Shultz LD: Immunological mutants of the mouse. *Am J Anat* 191:303–311, 1991
38. Horn TD, Herzberg GZ, Hood AF: Characterization of the dermal infiltrate in human immunodeficiency virus-infected patients with psoriasis. *Arch Dermatol* 126:1462–1465, 1990
39. Sundberg JP, Hanson CA, Roop DR, Brown KS, Bedigian HG: Myoepitheliomas in inbred laboratory mice. *Vet Pathol* 28:313–323, 1991
40. Gimenez-Conti I, Aldaz CM, Bianchi AB, Roop DR, Slaga TJ, Conti CJ: Early expression of type I K13 keratin in the progression of mouse skin papillomas. *Carcinogenesis* 11:1995–1999, 1990
41. Huitfeldt HS, Heyden A, Clausen OPF, Thrane EV, Roop DR, Yuspa SH: Altered regulation of growth and expression of differentiation-associated keratins in benign mouse skin tumors. *Carcinogenesis* 12:2063–2067, 1991
42. Sundberg JP, Erickson AA, Roop DR, Binder RL: Ornithine decarbocylase expression in cutaneous papillomas in SENCAR mice is associated with altered expression of keratins K1 and K10. *Cancer Res* (in press)
43. Loning TH, Mackenzie IC: Immunohistochemical studies of basal cell carcinomas transplanted into nude mice. *Arch Dermatol Res* 279:37–43, 1986
44. Nelson KG, Slaga TJ: Keratin modifications in epidermis, papillomas, and carcinomas during two-stage carcinogenesis in the SENCAR mouse. *Cancer Res* 42:4176–4181, 1982
45. Winter H, Rentrop M, Nischt R, Schweizer J: Tissue-specific expression of murine keratin K13 in internal stratified squamous epithelia and its aberrant expression during two-stage mouse skin carcinogenesis is associated with the methylation state of a distinct CpG site in the remote 5'-flanking region of the gene. *Differentiation* 43:105–114, 1990
46. Nischt R, Roop DR, Mehrel T, Yuspa SH, Rentrop M, Winter H, Schweizer J: Aberrant expression during two-stage mouse skin carcinogenesis of a type I 47-kDa keratin, K13, normally associated with terminal differentiation of internal stratified epithelia. *Mol Carcinogenesis* 1:96–108, 1988
47. Stoler A, Duvic M, Fuchs E: Unusual patterns of keratin expression in the overlying epidermis of patients with dermatofibromas: biochemical alterations in the epidermis as a consequence of dermal tumors. *J Invest Dermatol* 93:728–738, 1989
48. Klijanienko J, Micheau C, Carlu C, Caillaud JM: Significance of keratin 13 and 6 expression in normal, dysplastic and malignant squamous epithelium of pyriform fossa. *Virchows Archiv A Pathol Anat* 416:121–124, 1989
49. Ivanyi D, Ansink A, Mooi WJ, de Kraker NW, Heintz APM: Absence of differentiation-related expression of keratin 10 in early stages of vulvar squamous cell carcinoma. Differentiation 42:124–129, 1989
50. Ivanyi D, Ansink A, Groeneveld E, Hageman PC, Mooe WJ, Heintz APM: New monoclonal antibodies recognizing epidermal differentiation-associated keratins in formalin-fixed, paraffin embedded tissue. Keratin 10 expression in carcinoma of the vulva. *J Pathol* 159:7–12, 1989
51. De Mare S, De Jong E, Van Erp PEJ, Van De Kerkhof PCM: Markers for proliferation and keratinization in the margin of the active psoriatic lesion. *Br J Dermatol* 122:469–475, 1990
52. Placek W, Haftek M, Thivolet J: Sequence of changes in psoriatic epidermis. *Acta Derm Venereol (Stockh)* 68:369–377, 1988