(2) "The Pharmacological Basis of Therapeutics," L. S. Goodman and A. Gilman, Eds., Macmillan, New York, N.Y., 1975
(3) V. P. Shah, V. K. Prasad, B. E. Cabana, and P. Sojka, *Curr. Ther. Res.*, **24**, 366 (1978).
(4) V. P. Shah, J. Lee, V. K. Prasad, J. Hunt, and B. E. Cabana, "Abstracts, 27th Academy of Pharmaceutical Sciences National Meeting," Kansas City, Mo., 1979.
(5) B. Beermann, M. Groschinsky-Grind, and B. Lindstrom, *Eur. J. Clin. Pharmacol.*, **11**, 203 (1977).
(6) D. C. Hobbs and T. M. Towmey, *Clin. Pharmacol. Ther.*, **23**, 241 (1978).
(7) G. J. Yakatan, R. B. Smith, E. L. Frome, and J. T. Doluisio, *J. Clin. Pharmacol.*, **17**, 37 (1977).
(8) B. Beermann, M. Groschinsky-Grind, and B. Lindstrom, *Clin. Pharmacol. Ther.*, **22**, 385 (1977).
(9) T. H. Maren, *Physiol. Rev.*, **47**, 595 (1967).
(10) E. Redalieu, V. V. Tipnis, and W. E. Wagner, Jr., *J. Pharm. Sci.*, **67**, 726 (1978).

*Vinod P. Shah* ˣ
*John P. Hunt*
*Vadlamani K. Prasad*
*Bernard E. Cabana*
Biopharmaceutics Laboratory Branch
Food and Drug Administration
Washington, DC 20204

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## Technique for Preparing Appendage-Free Skin (Scar) on Hairless Mouse

**Keyphrases** □ Scar tissue—technique for preparing appendage-free skin on the hairless mouse □ Burns—examination of scar tissue, technique for preparing appendage-free skin on the hairless mouse □ Skin—technique for preparing appendage-free skin on the hairless mouse, examination of scar tissue

*To the Editor:*

Scar formation is, minimally, a reconstruction of skin that has undergone total destruction of its epidermal elements through disease or physical trauma (1). Since epidermal elements such as hair follicles often penetrate deeply into and beyond the dermal structure, significant repair of dermal and subdermal damage also is associated with the appearance and function of the scarred surface. When cells of epidermal origin are obliterated within the surface, including those deep within the follicular invaginations, the epidermis of a small wound is repaired by lateral migration of cells from its periphery. Based on histological examination of actual injuries, an epidermal structure is formed, which, as a minimally functional renewed surface, is without normal skin lines and is devoid of pilosebaceous and eccrine appendages. It has a flattened interface with the dermis. The dermis is repaired by fibroblasts that appear in large numbers in the wound. Depending on the nature and extent of the damage, the scar may be raised or depressed and is usually schlerotic (hard) due to the synthesis of new collagen.

An appendage-free structure such as scar tissue should be useful for sorting out transfollicular and transepidermal contributions to percutaneous absorption by studying it side by side with normal skin. To do this study with the least possible complications, experimental wounds need to be developed that result in scarring but that also represent minimal damage and restructuring of the dermal matrix.

Many researchers have developed methods to produce experimental wounds in laboratory animals. These procedures include excision of surface tissues (2–7), branding (8–10), severe chemical burning (11), thermal burning (12), and X-ray and UV irradiation (13, 14). The major emphasis of these investigations has been to study the healing process; the end result, the scarred surface, has been of only incidental concern. Where scar tissue has been purposefully studied histologically and otherwise, tissue samples normally have been of etiological rather than of experimental origin (15, 16). Therefore, we attempted to develop a simple reliable technique to produce scars with minimal dermal involvement in small laboratory animals for the purpose of studying the physicochemical (barrier) properties of scar tissue itself.

Male hairless mice[1], 60–80 days old, were anesthetized with methoxyflurane[2], and their dorsal surfaces were scalded using a previously reported technique (17). Essentially, the dorsal surface of an animal was immersed for 30 sec in water maintained at 60°. These conditions were chosen because they produce a borderline full-thickness burn on hairless mouse skin (17) and are routinely used to separate epidermis from dermis in preparing epidermal membranes for mass transfer studies (18). At the outset, the conditions appeared to be at or near the threshold to accomplish the stated goal.

The scalded mice were placed on a table with the burned surfaces exposed. An area was marked on the traumatized dorsal surface roughly approximating 6–8 $cm^2$ of the body surface area. With the blade of a spatula, the epidermis was scraped off the surface. Occasionally, the epidermal layer was separated as a single piece, but it usually came off in fragments. The blade was moved back and forth on the exposed skin several times, exposing the outlines of superficial blood vessels. The skin was uniformly erythematous. The animals then were returned to individual

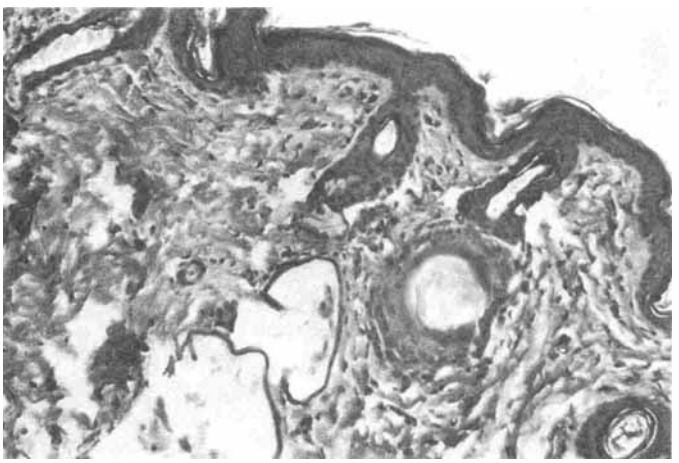

**Figure 1**—*Histological appearance of the hairless mouse normal skin.*

[1] SKH-hr$^{-1}$ strain, Skin Cancer Hospital, Philadelphia, Pa.
[2] Metofane, Pitman-Moore, Washington Crossing, N.J.

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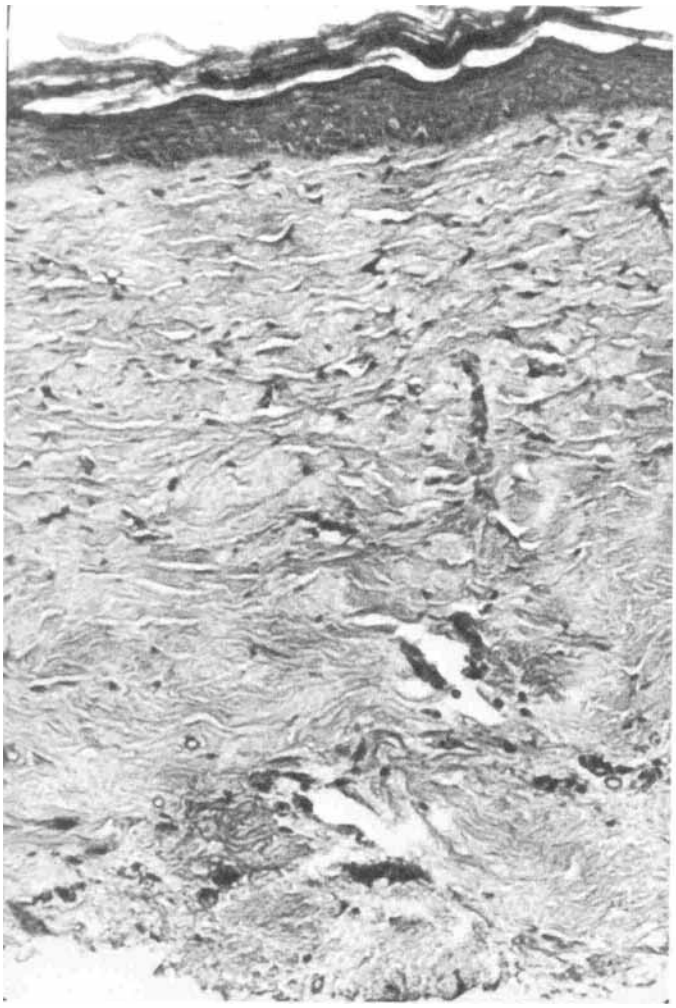

**Figure 2**—*Histological appearance of scar tissue obtained ~3 months postburn.*

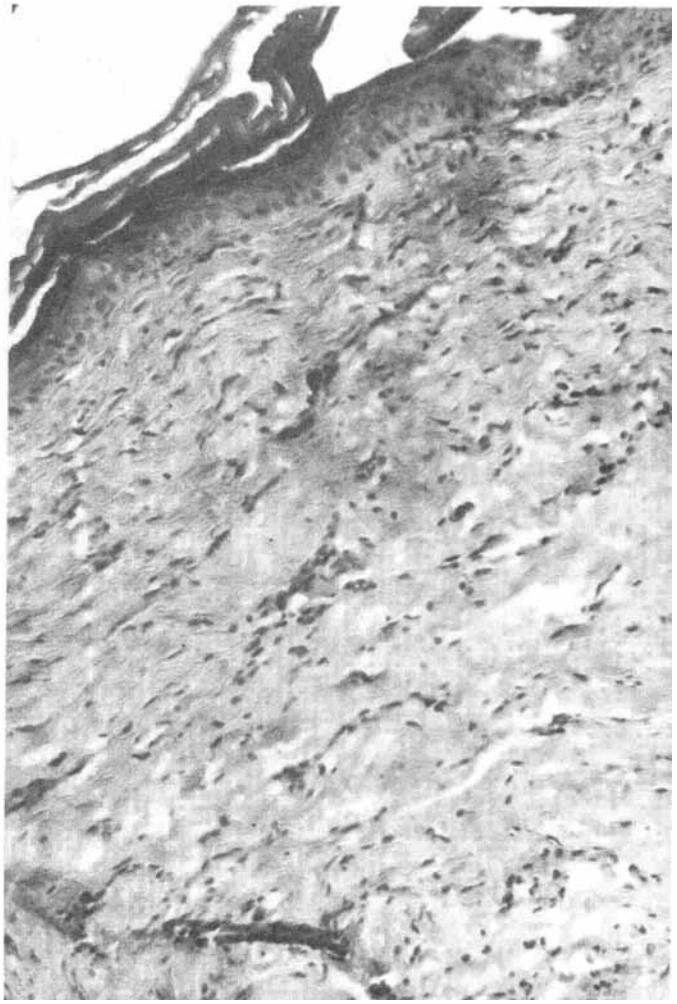

**Figure 3**—*Histological appearance of scar tissue obtained ~4 months postburn.*

cages and were supplied food and water *ad libitum*.

The traumatized animals were examined daily. A clearly defined wound was evident on the 1st day after inflicting the burn. In 1 week, a thick eschar covered the affected area. This eschar desiccated gradually and finally sloughed by about the 4th week postburn. The newly exposed surface appeared smooth and pinkish and refracted light in a manner typical of scarred surface. The scarred area was substantially contracted relative to the initial area from which the epidermis was removed. The wounds appeared to heal inward from thin margins, a process typical of full-thickness wound reepithelialization.

For purposes of histological examination, mice were sacrificed by spinal cord dislocation. Small scar biopsies were taken, and microscopic slides were prepared using standard hematoxylin and eosin staining techniques. Figure 1 represents the normal skin of the hairless mouse, and Figs. 2 and 3 represent the scar tissues obtained ~3 and 4 months, respectively, after inflicting the wound. The normal skin has a distinct epidermis and dermis containing loosely arranged connective tissue and numerous cystic pilosebaceous glands extending through the epidermis. The epidermal–dermal junction is convoluted. This normal slide can be contrasted to the 3-month-old burn scar (Fig. 2), which evidences a somewhat thickened epidermis and a more compact dermis (greater cellulosity and deposited collagen). The absence of the cystic pilosebaceous glands is notable, as is the flatness of the epidermal–dermal interface. Both features are typical of a scarred surface. The 4-month-old scar (Fig. 3) is less cellular with compact dermal collagen, a more developed stratum corneum, and a thinner viable epidermis, all features normally associated with a mature scar.

In separate experiments, attempts were made to produce scarring on the Swiss mouse and the rat. A similar procedure was employed with one minor variation. Before burning the skin for 30 sec at 60°, the anesthetized animal's dorsal surfaces were scalded briefly (60°) for ~ 5 sec, and all hair was plucked by hand. However, in these animals, the surface healed without scarring and with only a slight decrease in the density of hair. The necrotizing conditions apparently were not sufficient to destroy epidermal cells seated deeply on the follicular islands upon burning of these pellaged species. Rather, their more prominent, more deeply anchored hair follicles provided for survival of cells capable of regenerating a normal-appearing integument.

The methodology described produces the desired result in the hairless mouse[1]. A scar tissue is obtained that is being used to study permeation and other properties of skin devoid of its usual appendages. These studies should

reveal the impact of scar formation on the bioavailability of drugs and irritants applied topically over the scarred surface.

(1) T. B. Fritzpatrick and D. P. Johnson, in "Dermatology in General Medicine," T. B. Fritzgerald *et al.* Eds., McGraw-Hill, New York, N.Y., 1971, p. 20.

(2) M. Abercrombie, M. H. Flint, and D. W. James, *J. Embryol. Exp. Morphol.*, **2,** 264 (1954).

(3) T. S. Argyris, *Arch. Pathol.*, **61,** 31 (1956).

(4) A. M. Cuthbertson, *Surg. Gynecol Obstet.*, **108,** 421 (1959).

(5) T. Gillman, T. Penn, D. Bronks, and M. Roux, *Br. J. Surg.*, **43,** 141 (1955).

(6) C. Breedis, *Cancer Res.*, **14,** 575 (1954).

(7) H. C. Grillo, G. T. Watts, and J. Gross, *Am. Surg.*, **148,** 145 (1958).

(8) L. Dann, A. Glucksmann, and K. Tansley, *Br. J. Exp. Pathol.*, **22,** 1 (1941).

(9) W. W. Washburn, *J. Invest. Dermatol.*, **23,** 97 (1954).

(10) B. E. Zawacki and R. J. Jones, *Br. Plast. Surg.*, **20,** 347 (1967).

(11) G. H. Bishop, *Am. J. Anat.*, **76,** 153 (1945).

(12) J. Moserova, E. Behounkova, and Z. Konickova, *Acta Chir. Plast.*, **18,** 135 (1976).

(13) H. B. Chase and W. Montagna, *Proc. Soc. Exp. Biol. Med.*, **76,** 35 (1951).

(14) D. Tarin and C. B. Croft, *J. Anat.*, **106,** 79 (1970).

(15) T. Moriguchi and D. Fujimoto, *J. Invest. Dermatol.*, **72,** 143 (1979).

(16) M. L. Biryukov, T. N. Belyakov, and G. I. Dmitriev, *Acta Chir. Plast.*, **21,** 86 (1979).

(17) C. R. Bèhl, G. L. Flynn, T. Kurihara, O. Gatmaitan, W. I. Higuchi, N. F. H. Ho, and C. L. Pierson, *J. Invest. Dermatol.*, **75,** 340 (1980).

(18) G. L. Flynn, H. H. Durrheim, and W. I. Higuchi, *J. Pharm. Sci.*, **70,** 52 (1981).

*Charanjit Rai Behl* *
*Ann Wittkowsky*
*Michael Barrett*
*Carl L. Pierson*
*Gordon L. Flynn* ˣ
College of Pharmacy
University of Michigan
Ann Arbor, MI 48109

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* Present address: Pharmacy Research, Roche Laboratories, Hoffmann–La Roche Inc., Nutley, NJ 07110.

# BOOKS

## REVIEWS

**Controlled Release of Bioactive Materials.** Edited by RICHARD BAKER. Academic, 111 Fifth Ave., New York, NY 10003. 1980. 473 pp. 15 × 23 cm. Price $34.50.

This book constitutes a collection of 27 papers delivered at the sixth International Symposium on Controlled-Release Materials in New Orleans in 1979. The first 12 papers deal with various aspects of controlled drug delivery systems.

In the first paper, Heller and Baker review the theory and practice of controlled drug delivery from biodegradable polymers. The mechanisms of drug release from these polymers are discussed in depth, and several illustrative examples are presented. Applications of biodegradable polymers are discussed further in the ensuing two papers by Pitt *et al.* and Petersen *et al.*

In the fourth paper, Theeuwes and Echenhoff present the applications of osmotic drug delivery systems. The design and experimental performance of two osmotic devices are described. The generic osmotic pump (Alzet) is designed to deliver the contents of 170 μl at the rate of either 1 μl/hr over a 1-week period or 0.5 μl/hr over 2 weeks. The other device is the elementary osmotic pump, which is generally fabricated in the shape of a tablet, with a single-delivery orifice. A paper by Chandrasekaran and Shaw is concerned with controlled, transdermal drug delivery.

Other papers of pharmaceutical interest deal with polymers that include poly(lactic acid) and the hydrogels. Rhine and coworkers present a new approach to achieve zero-order release kinetics from diffusion-controlled polymer matrix systems. The theoretical basis for these kinetics is presented as is a comparison of kinetics from matrix devices of other geometries.

The second half of the book is concerned essentially with topics not directly related to drug delivery systems. Controlled-release systems containing insecticides, molluscicides, and plant growth regulators are discussed and described. Implantable systems for the delivery of insect growth regulators to livestock are evaluated by Jaffe and coworkers. The basic technology used to design several of these systems is very similar to drug-containing devices.

This book is a collection of high quality research papers, prepared by scientists in widely different fields. As such, the book is highly recommended for both academic and industrial pharmaceutical scientists, chemists, biologists, and chemical engineers who have an interest in controlled-release technology.

*Reviewed by* James W. McGinity
*College of Pharmacy*
*University of Texas at Austin*
*Austin, TX 78712*

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**British National Formulary 1981: Number 1.** The Pharmaceutical Press, 1 Lambert St., London, SE1 7JN, England. 1981. 387 pp. 12 × 23 cm. Price £3.80

*The British National Formulary* is designed for use by doctors, pharmacists, and nurses in the National Health Service in the United Kingdom. Unlike earlier editions that were published every 2 or 3 years and contained only those drugs and preparations having the confidence of the Joint Formulary Committee, the 1981 edition is an outgrowth of the Committee's response to requests for a wider coverage of drugs available in the United Kingdom and more detailed guidance in prescribing and dispensing.

This new edition provides more descriptive information to assist the prescriber in selecting the appropriate treatment for a particular patient. A double-column format was followed to accommodate the increased volume of information and to allow the book to "still fit into the doctor's pocket."

The BNF begins with sections on Guidance on Prescribing and Emergency Treatment on Poisoning. The main text consists of classified notes divided into 15 chapters: Gastro-intestinal System; Cardiovascular System; Respiratory System; Central Nervous System; Infections; Endocrine System; Obstetrics and Gynaecology; Malignant Disease and Immunosuppression; Nutrition and Blood; Musculoskeletal and Joint Diseases; Eye; Ear, Nose, and Oropharynx; Skin; Immunological Products and Vaccines; and Anaesthesia. Each chapter begins with appropriate notes for prescribers to facilitate selection of suitable treatment followed by detailed monographs of the relevant drugs and preparations (indications, contraindications, cautions, side-effects, doses, dosage forms, routes of administration, and relative prices). Drugs appear under their pharmacopoeial titles or British Approved Names and are listed alpha-