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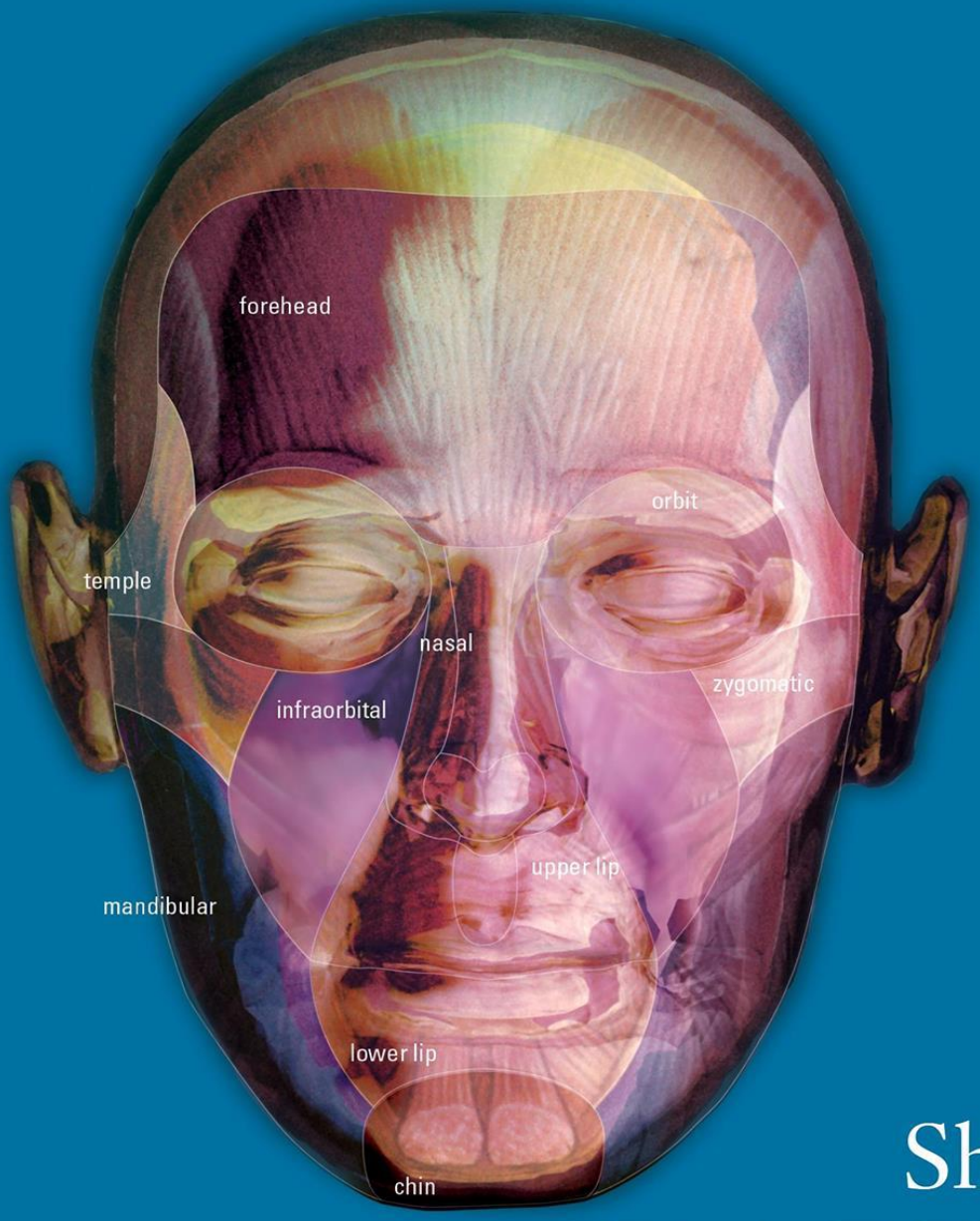

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LOCAL FLAPS IN FACIAL RECONSTRUCTION

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FOURTH EDITION

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To Catherine Belle Baker, Alexander Ray Baker,
and Monica Catherine Baker and to the thousands
of patients who have trusted me to make their
faces whole

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PREFACE

This textbook provides an in-depth discussion of the use of local flaps for reconstructing the face, scalp, and neck. Like the third edition, it is designed to be a "working man's" manual for repair of cutaneous defects of the head and neck, providing practical and effective methods of reconstructing skin defects of a variety of sizes, configurations, and locations. It is unique in that the contributors are from the surgical specialties of facial plastic and reconstructive surgery, ophthalmology, and dermatology. The authors are individuals with exceptional knowledge and experience using local flaps in facial reconstruction. They are some of the most prominent surgeons in their respective specialties.

I am fully cognizant of the political and philosophic differences among the various surgical specialties involved with reconstructing the face. Nevertheless, it is important to set aside any conflicts of interest and disagreements to promote the interchange of ideas and knowledge that will be both educational to physicians and beneficial to patients. This textbook represents an example of mutual interest and cooperation among a diverse group of surgeons. This is the fourth edition of the book, which was originally published in 1995 and is printed in three languages.

Although the majority of the illustrations used in this edition are the same as those that appeared in the third edition, all of the chapters have been upgraded through the introduction of new concepts or additional information. In many of the chapters, new clinical cases and photographs have been added or used to replace previous cases and photographs. Many of the photographs from the third edition have been enlarged for improved visualization of critical aspects of flap design. The bibliographies have been updated to include recent publications on local flaps. Many chapters have added algorithms to help surgeons select the preferred method of wound repair based on the size and location of the cutaneous defect.

As with the third edition, I authored a number of chapters in this book. This is because of a conscious effort on my part to present my personal surgical techniques and philosophy of using local flaps in facial reconstruction. To impart my philosophy toward surgical repair of Mohs defects, I have authored or coauthored 12 of the 28 chapters comprising this edition. Although this may have restricted the diversity of surgical approaches available for discussion, it has enabled the textbook to have a more homogenous narrative and consistent message. Similar to the third edition, there are videos that accompany many of the chapters. The videos are available on ExpertConsult.com. The videos demonstrate the design and transfer of a multitude of local flaps. Included in the videos are actual surgical procedures performed in the operating room. In addition to showing uncomplicated cases using simple cutaneous flaps, very complex defects requiring multiple flaps and grafts are included in the video library.

This work represents the culmination of 42 years of cooperative interaction between me and the dermatologic surgeons at the University of Michigan. During this time, we have shared the care of a few thousand patients, which I believe was to the patient's benefit. This cooperative arrangement facilitated the interchange of knowledge and experience, leading to a hybrid of surgical approaches for the repair of facial cutaneous defects. This cross-fertilization of ideas has been a direct benefit to me and my ability to care for patients; it is also the source of my desire to publish this textbook. This book would not have been possible without the cooperation of all of the surgeons in the Department of Dermatology at the University of Michigan. For this reason, I express my sincere gratitude to all of them for their continued support and confidence in me.

Shan R. Baker, MD, FACS

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I thank Timothy M. Johnson, MD, past director of Dermatological Surgery at the University of Michigan, and his colleagues Darius J. Karimipour, MD; Christopher K. Bichakjian, MD; Jennifer L. Schwartz, MD; Sandra C. Paek, MD; Marcus Frohm, MD; and Jeffrey S. Orringer, MD. Thank you all for the referrals of your patients throughout the many years we have been professionally associated. Without your support and trust, this book would not have been possible.

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Finally, I would like to thank all of the authors of this textbook for devoting hundreds of hours toward preparing and updating their chapters. The quality of this textbook is directly related to your contributions.

Shan R. Baker, MD, FACS

CHAPTER 1

ANATOMY OF THE SKIN

Noah R. Smith • Alison B. Durham • Christopher K. Bichakjian • Timothy M. Johnson

INTRODUCTION

The skin is a complex organ that is essential for all forms of mammalian life. It may be viewed as a double-layered sheath, cushioned by the underlying subcutaneous adipose tissue, that covers the entire surface of the body. The outer layer of skin, known as the *epidermis*, is separated from the inner layer, or dermis, by the basement membrane zone. The dermis is attached to the subcutaneous adipose tissue and underlying musculature by fibrous insertions. On the scalp, the skin overlies a dense connective tissue layer composed of fibrous and adipose tissue, followed by the galea aponeurotica, loose areolar tissue, and pericranium. Important structures, including hair follicles, sebaceous glands, sweat glands, nerves, blood vessels, and immunologic cells, are present in the skin (Fig. 1.1). As an organ, the skin has many important physiologic and immunologic properties: it provides a barrier to the environment, regulates body temperature, and serves as an important component of the immune system.

A complete understanding of anatomy is the cornerstone of surgery. Moreover, an awareness of cutaneous anatomy is essential for a full appreciation of the human body's functional, social, and aesthetic relationship with its environment. The purpose of this chapter is to provide a basic knowledge of the normal anatomy of the skin.

GENERAL CHARACTERISTICS

Skin is highly variable from one person to another and, within the same individual, from one anatomic region to another, with differences to be observed in color, texture, thickness, and content of hair follicles and sebaceous glands. Skin may be divided into smooth, non–hair-bearing (glabrous) and hair-bearing (nonglabrous) areas, although it is virtually always hair-bearing.

Considerable variation in skin thickness and content of appendages and elastic fibers exists with respect to anatomic region, age, and sex. An appreciation of these variations is clinically important for understanding wound healing and aesthetics. These variations play an integral role in the definition of facial aesthetic regions, boundaries, and junctions. The surgeon must apply knowledge of these factors to the task of determining the best reconstructive option during flap or graft surgery. Careful examination of the skin is essential for making the best tissue match for aesthetic reconstruction. Discrepancies in the thickness of skin edges should be observed before wound closure for exact reapproximation of the edges. The best donor site for a full-thickness skin graft is determined by an examination of all potential donor sites with respect to skin thickness, color, texture, and content of hair follicles and sebaceous glands. Careful examination of the skin before surgery may uncover several clues that could influence the outcome. Individuals with fair skin, light hair, and blue eyes may develop postoperative scars that remain pink for an extended period. People with dark skin, hair, and eyes may develop scars that remain pigmented for a prolonged period after surgery. An assessment of previous scars and keloids should be made. Individuals with hyperelastic skin features are characterized by hyperextensibility of the joints (elbows, wrists, and knees), anterior hooding of the navel, and lax skin (Figs. 1.2 to 1.4). These individuals are at a higher risk for the development of wide scars, permanent railroad tracking suture marks, hypertrophic scars, and prolonged erythema of scars lasting up to 1 year, eventually resulting in a porcelain-colored white scar. Although it is also present in Ehlers-Danlos syndrome, hyperelastic skin is most often simply a relatively common normal variant within the population.

Patients with common skin conditions, such as atopic dermatitis, psoriasis, and unusually dry skin, may have high counts of staphylococcal organisms on their skin and thereby increased risk for wound infections. In essence, basic knowledge of skin anatomy is something that is applied daily in reconstructive surgery.

EPIDERMIS

The epidermis, the outermost layer of the skin, is a continually renewing, keratinizing, stratified, squamous epithelium. All epidermal appendages, including hair follicles, sebaceous glands, and eccrine and apocrine sweat glands, derive from this layer. The epidermis consists of four distinct cell types: keratinocytes, melanocytes, Langerhans cells, and Merkel cells. The predominant cell type is the keratinocyte, which constitutes at least 80% of epidermal cells. Four clearly defined layers are identified in the epidermis (Fig. 1.5): the basal layer (stratum germinativum), the spinous layer (stratum spinosum), the granular layer (stratum granulosum), and the cornified layer (stratum corneum). The basal layer is the deepest layer in the epidermis. It is composed of a single germinative layer of columnar-shaped keratinocytes that attach

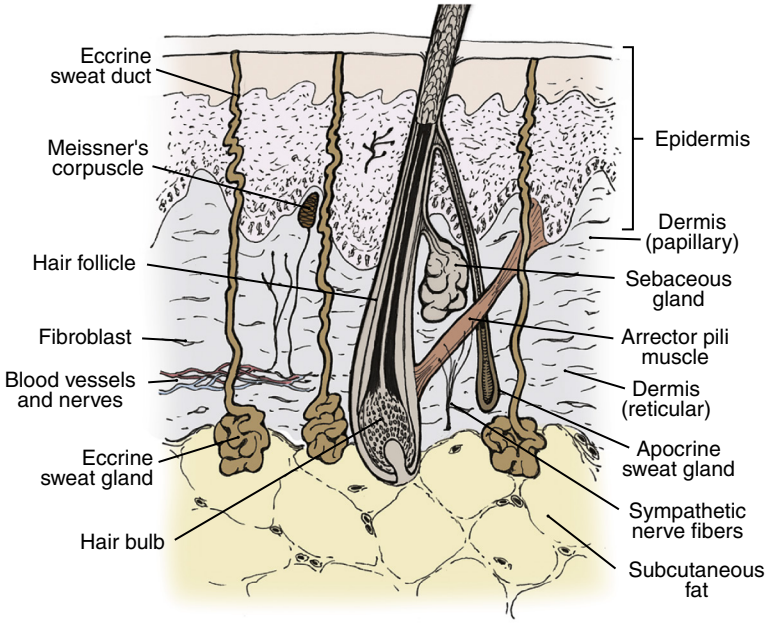

FIG. 1.1 ■ Schematic vertical cross section of skin.

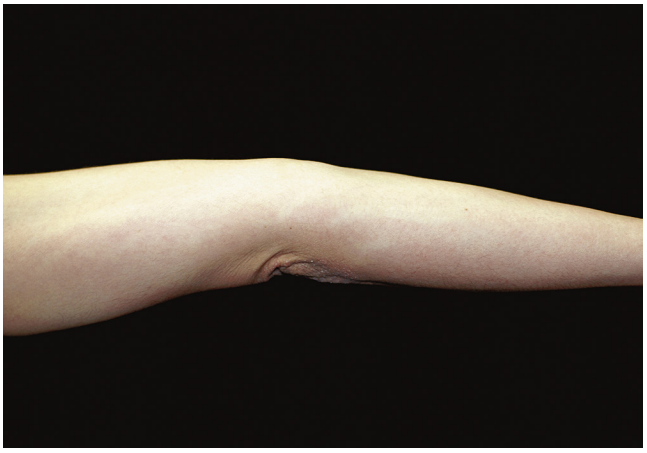

FIG. 1.2 ■ Hyperextensibility of the elbow in a healthy, 28-year-old woman with hyperelastic skin features.

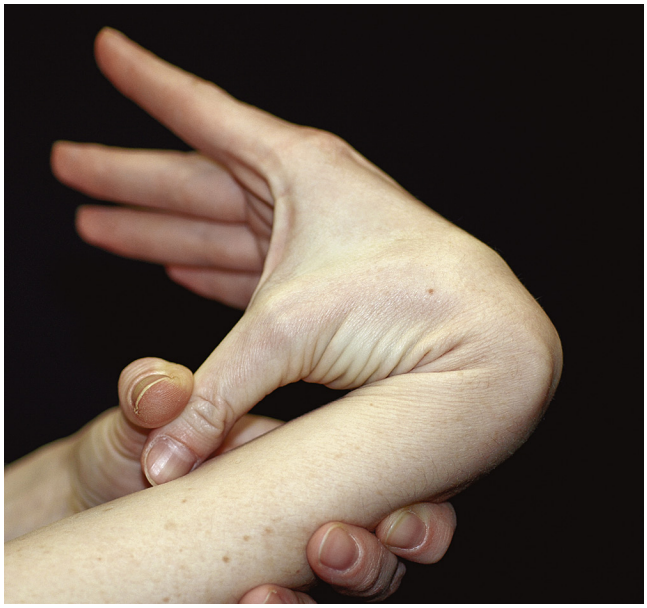

FIG. 1.3 ■ Hyperextensibility of the wrist in a healthy, 36-year-old woman with hyperelastic skin features.

to the basement membrane zone and give rise to the more superficial epidermal layers. The next layer, the spinous layer, is several cells thick and composed of polygonal cells with abundant eosinophilic cytoplasm. Small spiny desmosomal attachments between the spinous cells are evident under light microscopy. As the spinous cells migrate superficially and differentiate into granular cells, they become larger and flatter. The granular layer, usually one to four cells thick, is composed of cells with deeply basophilic keratohyalin granules. Further maturation occurs in the outermost stratum corneum, which is highly variable in thickness. In this layer, keratinocytes lose their nuclei and flatten to form plates of keratin, which are shed as "dead skin." The stratum corneum is thickest on the palms and soles and thinnest on the eyelids and genitalia. Total epidermal turnover time from the basal layer to the stratum corneum is approximately 30 days. The thickness of the epidermis is generally about 0.075 to 0.15 mm.

Melanocytes

Melanocytes are dendritic, pigment-synthesizing cells of neural crest origin with clear cytoplasm confined to the basal layer. The ratio of melanocytes to basal cells ranges from 1:4 on the cheek to 1:10 on the limbs. The function of melanocytes is to produce protective melanin pigment. Melanin is packaged in the form of melanosomes, which are transported through stellate dendritic projections to a group of adjacent keratinocytes in the basal and spinous layers (epidermal melanin unit). The keratinocytes engulf the melanosomes and arrange the pigment in an umbrella-like distribution over the nuclei, protecting them from potentially harmful ultraviolet irradiation (Fig. 1.6). This partly explains why people with less skin

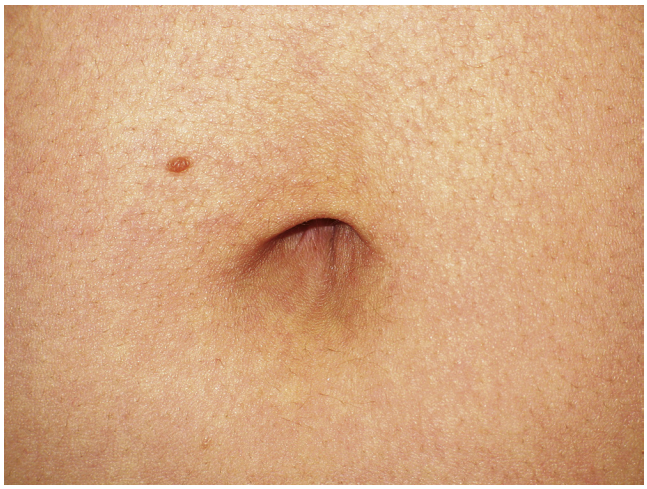

FIG. 1.4 ■ Anterior hooding of the navel in a healthy, 30-year-old woman with hyperelastic skin features.

pigmentation are at greater risk for developing cutaneous malignant neoplasms, such as basal cell carcinoma, squamous cell carcinoma, and melanoma.[1,2] The number of melanocytes does not differ between races; however, the number and size of melanosomes is greater in individuals with more skin pigmentation. In vitiligo, melanocytes are completely absent. In albinism, melanocytes are present but lack the enzyme tyrosinase. Without tyrosinase, tyrosine cannot be transformed into melanin. Tyrosinase activity and melanocyte density decrease with age.[3]

Langerhans Cells

Langerhans cells are bone marrow–derived, antigen-processing, and antigen-presenting cells found mainly in the suprabasal epidermal layers. They are, however, not unique to the epidermis and are found in other squamous epithelia and in the normal dermis. In routine histologic preparations, Langerhans cells are pale-staining cells that are difficult to identify and more readily demonstrated with special stains or immunohistochemistry. Like melanocytes, Langerhans cells are characterized by dendritic processes. The cytoplasm, as seen by electron microscopy, contains small racket-shaped structures known as *Birbeck* or *Langerhans cell granules*. Langerhans cells are responsible for recognizing and presenting antigens to lymphocytes in the skin and lymph nodes and are implicated in the pathologic mechanism underlying allergic contact dermatitis and skin allograft reactions. The number of Langerhans cells decreases after ultraviolet irradiation. This results in a diminished capacity for immune surveillance, which may play a role in cutaneous carcinogenesis. The number of Langerhans cells also decreases with age.[4]

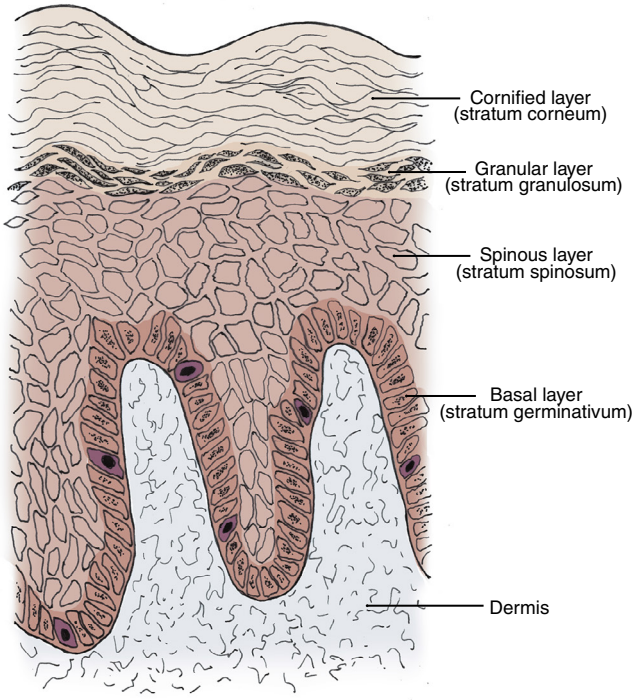

FIG. 1.5 ■ Layers of epidermis.

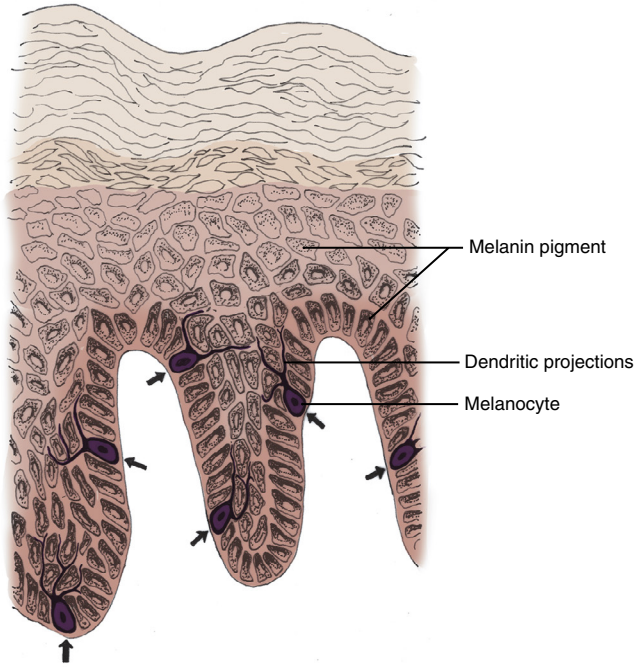

FIG. 1.6 ■ Melanocytes in basal layer *(arrows)* project stellate, dendritic processes to surrounding keratinocytes in basal and spinous layers (epidermal melanin unit). Note the umbrella-like distribution of melanin pigment over keratinocyte nuclei.

Merkel Cells

Merkel cells are neuroendocrine cells of epidermal origin that function as slow-adapting mechanoreceptors primarily concerned with touch sensation.[5,6] They are predominantly found among basal keratinocytes in areas of high tactile sensitivity, such as the lips, digits, oral cavity, and hair follicles. At these sites, Merkel cells often aggregate in specialized structures, called *tactile disks* or *touch domes*, in close association with peripheral nerve endings to form the Merkel cell–neurite complex. Merkel cells, like Langerhans cells, are difficult to identify in light microscopy without the use of immunohistochemical markers. Ultrastructurally, Merkel cells are characterized by membrane-bound, dense-core granules.

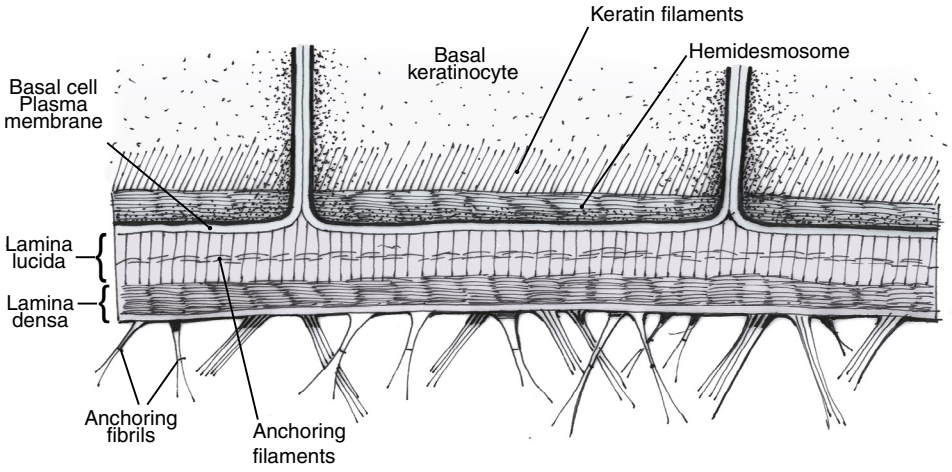

FIG. 1.7 ■ Dermal-epidermal junction.

These granules are similar to the neurosecretory granules found in neurons and contain neurotransmitter-like substances and markers of neuroendocrine cells. Merkel cell carcinoma (MCC), or cutaneous neuroendocrine carcinoma, is often associated with Merkel cell polyomavirus (MCPyV) and may arise from dermal fibroblasts in MCPyV-positive MCC versus epidermal keratinocytes in MCPyV-negative MCC.[7]

DERMAL-EPIDERMAL JUNCTION

The epidermis is attached to the dermis by a basement membrane zone known as the *dermal-epidermal junction* (Fig. 1.7).[8] By light microscopy, the dermal-epidermal junction is identified as a thin pink band that stains positive with periodic acid–Schiff stain. This complex zone provides mechanical support to the epidermis and acts as a semipermeable barrier to chemicals and other substances. Keratin filaments within the basal keratinocyte condense and attach to an electron-dense plaque at the inferior aspect of the cell membrane, known as the *hemidesmosome*. The hemidesmosomes are firmly anchored to the underlying lamina densa through connecting anchoring filaments in the lamina lucida. The lamina densa is attached to anchoring plaques in the underlying dermis by anchoring fibrils and elastic fibers. Anchoring fibrils, mainly composed of type VII collagen, are degraded by collagenases and are absent in new scars. The importance of the dermal-epidermal junction can be surmised from a variety of inherited and acquired diseases of the skin in which different components are absent, altered, or destroyed, resulting in dermal-epidermal separation, such as in epidermolysis bullosa.[9]

Hair Follicle

The hair follicle is the main component of a structure known as the *pilosebaceous unit*, which also includes the hair shaft, sebaceous gland, arrector pili muscle, and sensory end organ (Fig. 1.8). The pilosebaceous unit has motor and sensory functions and is responsible for the production of hair and sebum. On the scalp, the follicular component is predominant, resulting in thick, dense terminal hair. Fine, thin vellus hair is found on the temples and forehead. On the nasal tip, the sebaceous component predominates, and the total structure is sometimes termed the *sebaceous follicle*. The complete pilosebaceous unit is absent on the palms, soles, and mucous membranes. Re-epithelialization of partial-thickness wounds occurs not only from the wound edges but also from the pilosebaceous units and eccrine glands.[10]

Longitudinally, the hair follicle is divided into three regions (see Fig. 1.8). The uppermost portion, the infundibulum, extends from the skin surface to the opening of the sebaceous duct into the follicle. The segment between the follicular opening of the sebaceous duct and the bulge is known as the *isthmus*. The inferior portion lies below the area of the bulge and includes the lowermost part of the follicle and the hair bulb. The bulge is a region enriched with follicular epithelial stem cells and the insertion site of the arrector pili muscle. This muscle inserts into the perifollicular connective tissue sheath around the bulge and extends obliquely and upward into the papillary dermis. Contraction of the arrector pili muscle, innervated by sympathetic nerve fibers, makes the hair "stand up" (goose bumps) as it is pulled from an oblique to a vertical position, providing a greater thermal barrier to the skin. Sensory nerves are located around the isthmus and inferior portion of the hair follicle. These nerves are stimulated as a touch receptor when the hairs are touched.

The internal organization of the hair follicle is best conceptualized as a series of distinct concentric layers (Fig. 1.9). The most peripheral layer, the outer root sheath, is contiguous with the epidermis and is lined by the dermal-epidermal junction. In the infundibulum, the outer root sheath consists of all layers of the epidermis. Distal to the follicular opening of the sebaceous duct, the outer root sheath consists of a markedly vacuolated spinous layer because of the presence of glycogen. Next is the inner root sheath, which consists of three distinct layers: Henley's layer, Huxley's layer, and a cuticle. Innermost is the hair shaft, which also has three layers: its cuticle, the cortex that forms the bulk of the hair shaft, and the variable central medulla. The medulla is absent in lanugo and vellus hairs. The inner root sheath and hair shaft are derived from a proliferation of germinative cells, known as the *matrix*, at the base of the hair follicle. The distal hair bulb forms an invagination around the follicular papilla, which is richly vascularized and contains abundant nerve endings.

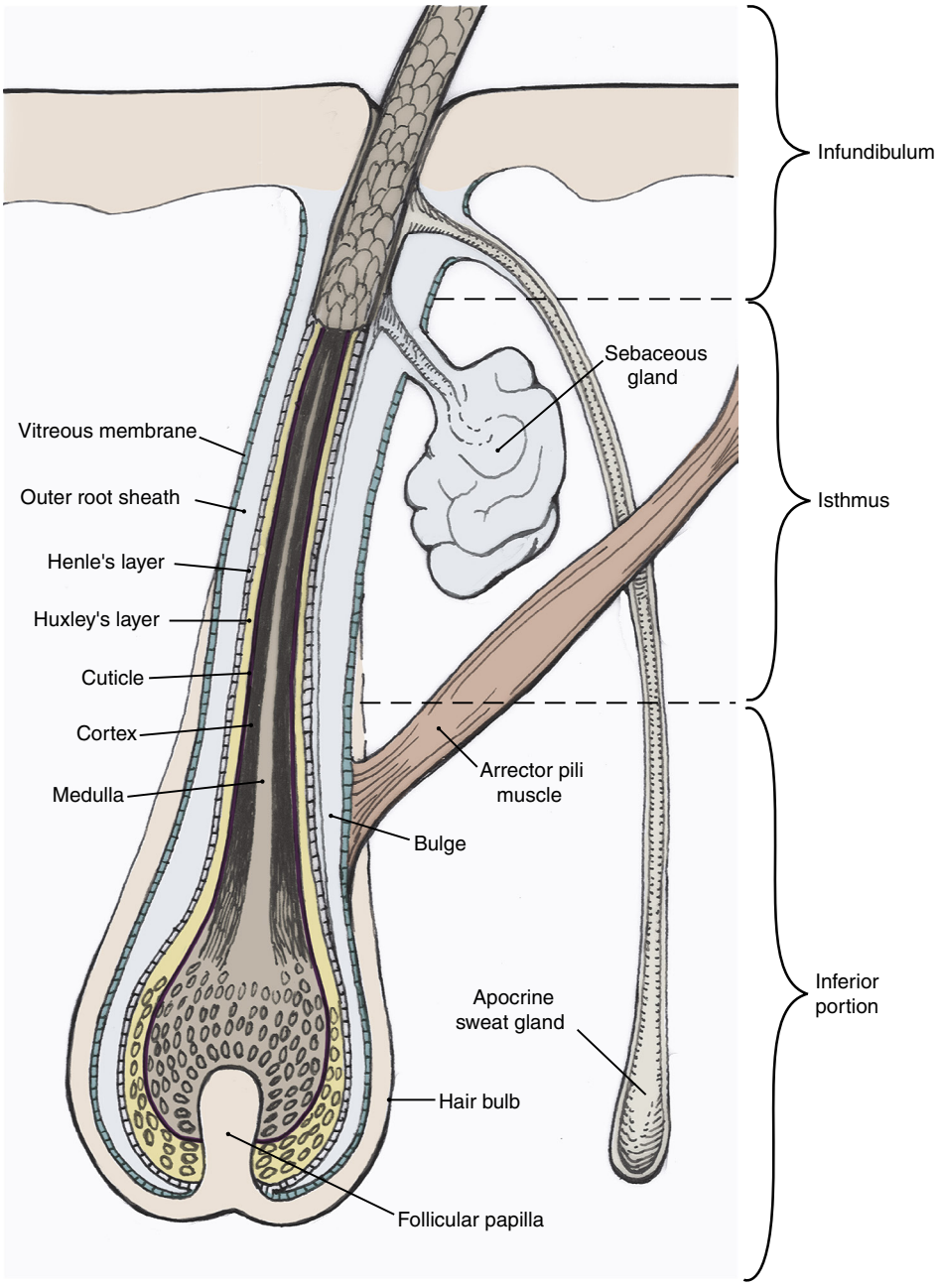

FIG. 1.8 ■ Pilosebaceous unit.

Hair follicles undergo cycles of growth, involution, and rest (Fig. 1.10). During the growing phase, or anagen, matrix keratinocytes in the bulb proliferate rapidly and produce the growing hair. During the involutional phase, or catagen, the matrix cells abruptly cease proliferating, and the lower portion of the hair follicle involutes. In telogen, the resting phase, the inferior portion of the follicle is lost, and the follicular papilla comes to rest at the height of the bulge. The club-shaped telogen hair is typically shed from the follicle during telogen or the subsequent anagen. Human hair growth is cyclic, but because each follicle functions independently, humans do not shed hair synchronously. On the human scalp, approximately 85% of hairs are in anagen, and the average length of the growing phase is 3 to 4 years. The number of hair follicles on the scalp is approximately 100,000 in people with brown or black hair, about 10% greater in blondes, and 10% less in redheads.

The follicular epithelium in the dermis provides an additional source of germinative cells for re-epithelialization of partial-thickness wounds. The follicular dermal extension of the epidermis also allows epidermal diseases, such as Bowen's disease (squamous cell carcinoma in situ), to extend into the dermis. This may result in a higher recurrence rate if superficial treatment methods (such as electrodesiccation and curettage or CO_2 laser) do not destroy the follicular downward extension of the disease process.

Sebaceous Glands

Sebaceous glands are unilobular or multilobular structures that connect to the hair follicle by a squamous

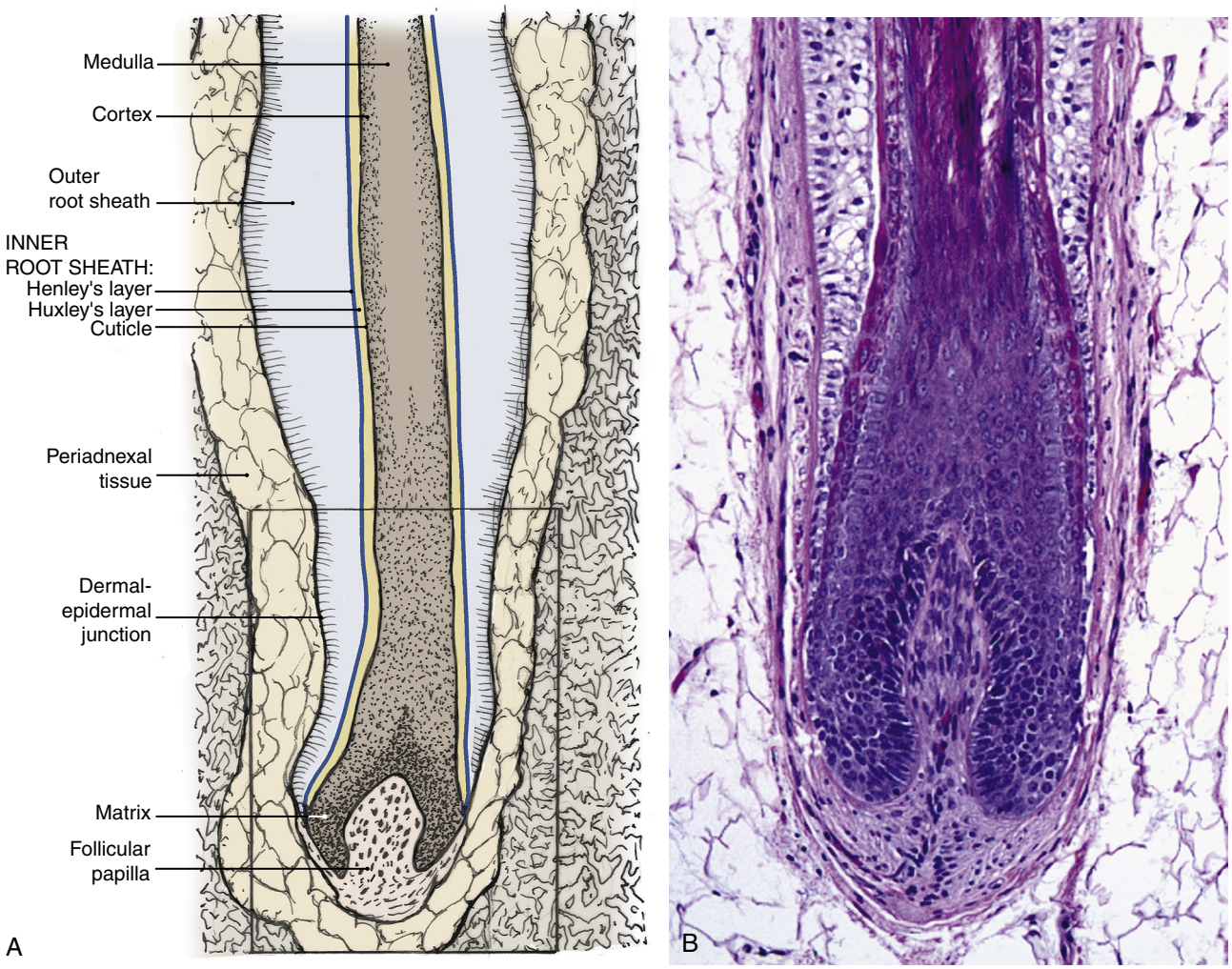

FIG. 1.9 ■ **A, B,** Vertical section of a normal hair follicle showing distinct concentric layers.

epithelial duct. Each lobule consists of a peripheral cuboidal or flattened germinative cell layer. These cells give rise to a central, lipid-laden, vacuolated cell population with characteristic clear to foamy cytoplasm. The glands secrete sebum through the sebaceous duct into the follicle and onto the surface of the skin. Sebum, a complex lipid mixture, acts as an emollient to the hair and skin and may have a protective function.

Sebaceous glands enlarge and become functionally active during puberty. They are found everywhere on the body, except the palms and soles, and are most abundant on the face and scalp. Sebum secretion is largely controlled by androgens and is associated with acne. Sebaceous glands may enlarge considerably in middle-aged and elderly persons, resulting in benign yellow papular lesions known as *sebaceous hyperplasia*. In certain locations, sebaceous glands arise independently and are not associated with a hair follicle, such as the vermilion border of the lip (Fordyce spots) or the eyelids (meibomian glands).

Eccrine Sweat Glands

Eccrine sweat glands are found everywhere on the skin, except the mucous membranes, and are most abundant on the palms, soles, axillae, and forehead. The eccrine sweat unit is composed of two segments, a coiled secretory gland and a duct. The secretory gland is located in the deep reticular dermis or the junction between the dermis and subcutaneous adipose tissue. The glandular lumen is lined by an inner layer of secretory cells and an outer layer of contractile myoepithelial cells. The dermal duct ascends upward to the coiled intraepidermal duct (acrosyringium), which opens directly to the skin surface. The eccrine sweat gland is innervated by cholinergic nerve fibers, which are stimulated by thermal, mental, and gustatory stimuli. A person can perspire as much as several liters per hour and 10 liters per day. The duct modifies the composition of sweat, which consists of water, sodium, chloride, potassium, urea, and lactate.

Apocrine Sweat Glands

Apocrine sweat glands are generally confined to the axillae, areolae, perineum, eyelids (Moll's glands), and external auditory canal (ceruminous glands). They do not become functional until just before puberty. Apocrine sweat glands respond to emotive stimuli by adrenergic innervation. They produce an odorless secretion, which requires

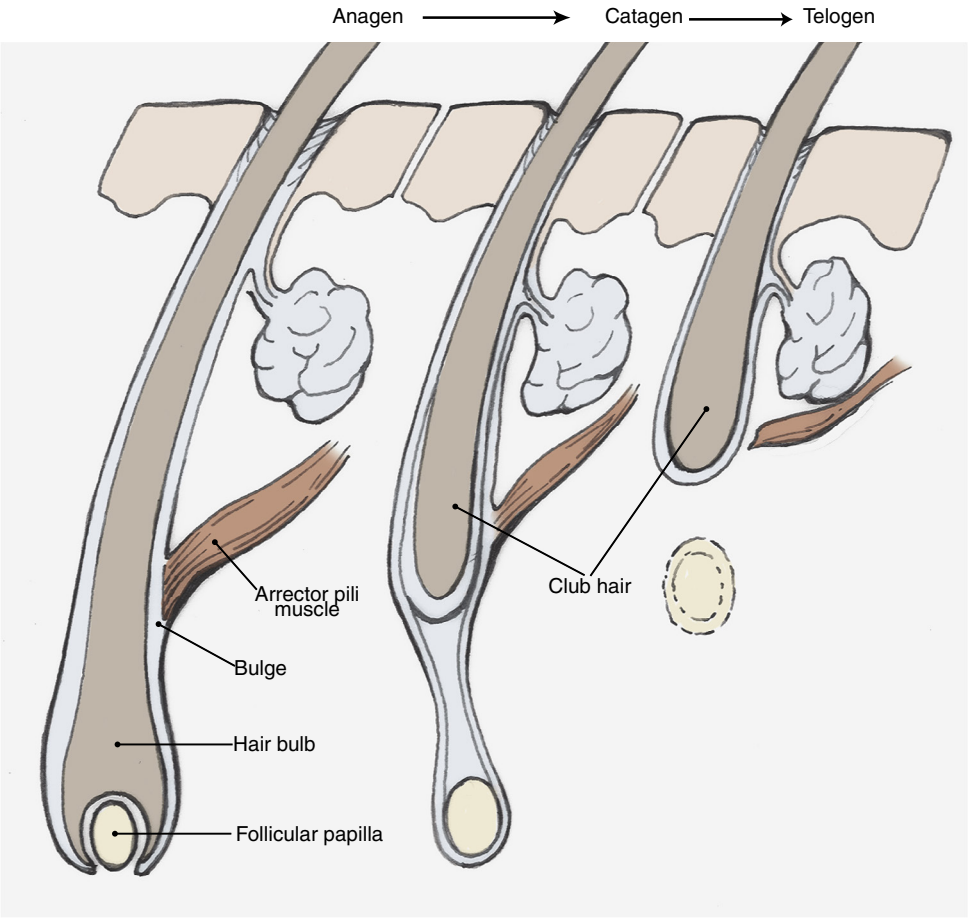

FIG. 1.10 ■ Hair growth cycle proceeding from anagen through catagen to telogen. Growth occurs during the longest anagen phase. The lower portion of hair follicle involutes during catagen. In telogen, the inferior portion of the follicle is lost and follicular papilla comes to rest at the height of the bulge.

bacterial action for odor production. Various functions including odiferous roles as sexual attractants and territorial markers have been attributed to apocrine glands.

The apocrine sweat unit consists of a secretory gland and a duct. The secretory gland is larger than its eccrine counterpart and lies in the deep reticular dermis or subcutaneous adipose tissue. It consists of an outer layer of myoepithelial cells and an inner layer of columnar or cuboidal eosinophilic cells. The inner layer of cells appears to secrete droplets into the lumen by decapitation secretion, which can be seen by light microscopy. The apocrine duct ascends upward through the dermis and connects to the infundibulum of the hair follicle superior to the sebaceous duct.

DERMIS

The dermis is an integrated connective tissue system between the epidermis and the subcutaneous adipose tissue that makes up the bulk of the skin. It accommodates nerve and vascular networks, epidermal appendages, fibroblasts, macrophages, mast cells, and other blood-borne cells. The extracellular dermal matrix is composed primarily of collagen, with lesser amounts of elastin, and filamentous and amorphous molecules known as *ground substance*. The dermis provides the skin its pliability, elasticity, and tensile strength. It is divided into the relatively thin, superficial papillary dermis and the deeper, thicker reticular dermis. There is great regional variation in thickness of the dermis, ranging from less than 1 mm on the eyelid to 1.5 mm on the temple, 2.5 mm on the scalp, and more than 4 mm on the back. The dermis is thin at birth, increases in thickness until the fourth or fifth decade, and then decreases.

Collagen

Collagen is the principal component of the dermis and accounts for approximately 75% of the dry weight of skin. Collagen fibers are synthesized by fibroblasts and provide both tensile strength and elasticity to the skin. Approximately 85% of dermal collagen is type I collagen, which is found predominantly as thick broad bands in the reticular dermis. Type III collagen constitutes roughly 10% of dermal collagen and forms the fine collagen fibers located primarily in the papillary dermis. Collagen types IV and VII are located mainly in the basement membrane zone.[11]

Collagen fibers are continuously being degraded by proteolytic enzymes called *matrix metalloproteinases*, such as collagenase, and replaced by newly synthesized fibers. Ultraviolet irradiation induces matrix metalloproteinases in the epidermis and dermis, leading to dermal collagen degradation. This is manifested histologically as the disorganization of collagen fibrils and clinically as skin wrinkling in photoaging. Topical tretinoin, or retinoic acid, inhibits the induction of matrix metalloproteinases and improves the appearance of photoaged skin by reducing

fine lines and wrinkles.[12,13] It is believed that matrix metalloproteinases are induced by CO_2 laser treatment to degrade photodamaged collagen. This degradation is followed by the formation and deposition of new collagen.[14]

Elastin

Elastic fibers in the dermis return the skin to its normal configuration after being stretched or deformed. The normal fibers are not readily seen on routine histology without the aid of special elastic tissue stains. Elastic fibers in the dermis are synthesized primarily by fibroblasts. In the papillary dermis, the fibers are thin and run perpendicular to the skin surface, whereas those in the reticular dermis are thicker and run parallel to the skin surface. Like collagen, elastic tissue is in a continuous state of synthesis and degradation by matrix metalloproteinases such as elastase. Elastic tissue is composed of a protein elastin and a microfibrillar matrix that contains fibrillin, a glycoprotein, and other components. The amino acids desmosine and isodesmosine are unique to elastin.[15]

Extracellular Matrix

The extracellular matrix (ECM), or ground substance, surrounds and embeds the fibrous components of the dermis. It consists predominantly of proteoglycans (such as chondroitin sulfate and dermatan sulfate), glycosaminoglycans (such as hyaluronic acid), and filamentous glycoproteins (such as fibronectin). In the dermis, the ECM is primarily synthesized by fibroblasts and appears as fine mucinous stroma on routine histologic stains. The ECM plays a role in skin hydration and helps preserve the tensile elasticity of compressed skin by redistributing the pressure forces. Relative dehydration of the skin because of displacement of fluids and the ECM is partly responsible for the phenomenon termed *mechanical creep*, or elongation of the skin beyond its intrinsic extensibility.[16] Mechanical creep plays a role in the physiologic factors of immediate intraoperative tissue expansion.[17]

Cellular Component

Fibroblasts constitute the main cellular component of the dermis and synthesize collagen, elastin, and ECM. They are abundant in the papillary dermis and scant in the reticular dermis. The function of this metabolically dynamic cell is to provide a structural extracellular matrix framework and to promote interaction between epidermis and dermis. Fibroblasts play a major role in wound healing and behave like a contractile cell during wound contraction. The number of fibroblasts in the skin decreases with age.

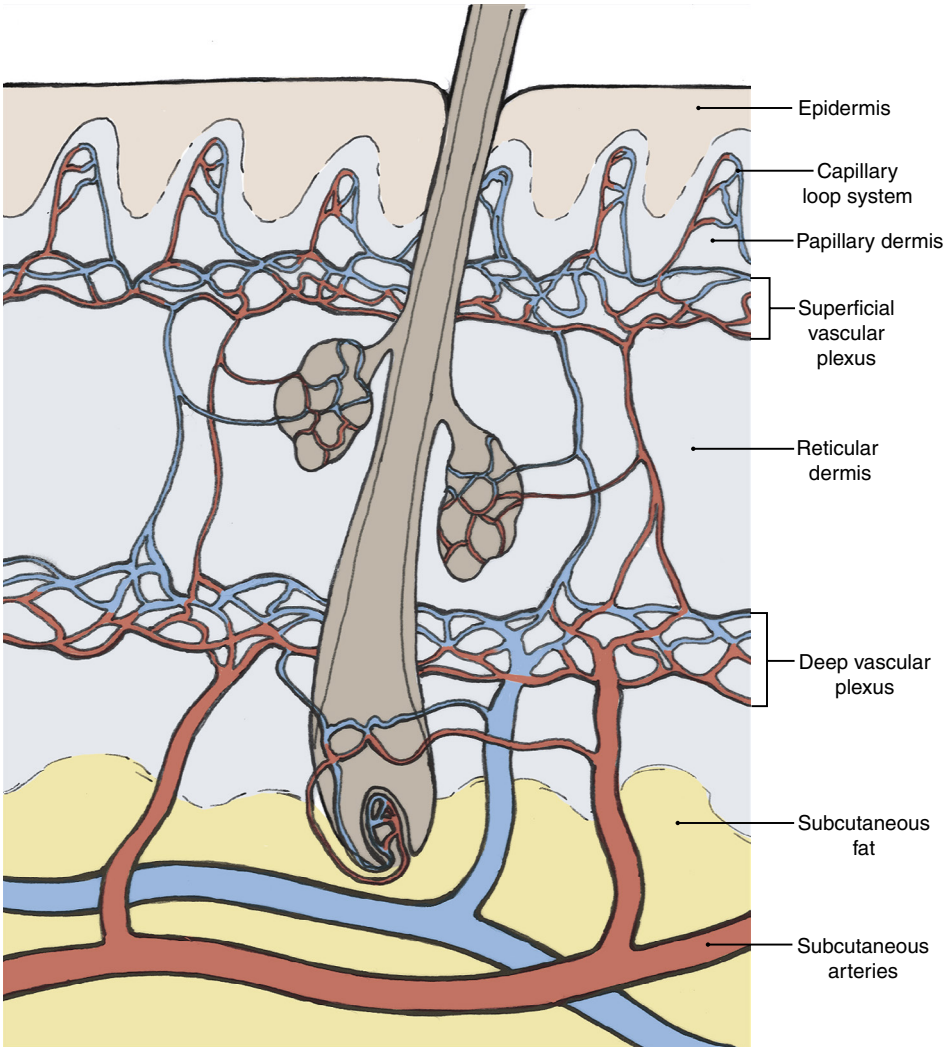

FIG. 1.11 ■ Vasculature of skin. Superficial and deep vascular plexuses provide nourishment to the skin and epidermal appendages.

Monocytes, macrophages, and dermal dendrocytes constitute the phagocytic cells in the dermis. Mast cells are specialized secretory cells present in greatest density in the papillary dermis; near the basement membrane zone; and around epidermal appendages, blood vessels, and nerves. Mast cells are the primary effector cells in the onset of an allergic reaction and may be important in initiating the repair of damaged skin.[18]

Vasculature

Soft tissue surgery on the head and neck usually heals particularly well because of a rich vascular supply. Most of the blood flow in the skin is directed toward the more metabolically active components, namely, the epidermis, the follicular papillae, and the epidermal appendages. Two vascular plexuses connected by communicating vessels are present in the dermis (Fig. 1.11).[19] At the junction of the dermis and subcutaneous adipose tissue lies the deep vascular plexus, which receives its vascular supply from musculocutaneous arteries perforating the subcutaneous adipose tissue. Arterioles from the deep vascular plexus supply the epidermal appendages and the superficial vascular plexus. The superficial vascular plexus lies in the superficial aspect of the reticular dermis and gives rise to a rich capillary loop system in the papillary dermis. This capillary loop system abuts the epidermis and provides it with nutrients by diffusion. The dermis also contains a lymphatic system that resembles the vascular plexuses.

Nerve Supply

A rich cutaneous nerve supply consisting of free nerve endings and specialized corpuscular receptors permits the body to accurately interpret the continuous bombardment of stimuli received from the external environment (Fig. 1.12).[20] Temperatures, pain, and itch are transmitted

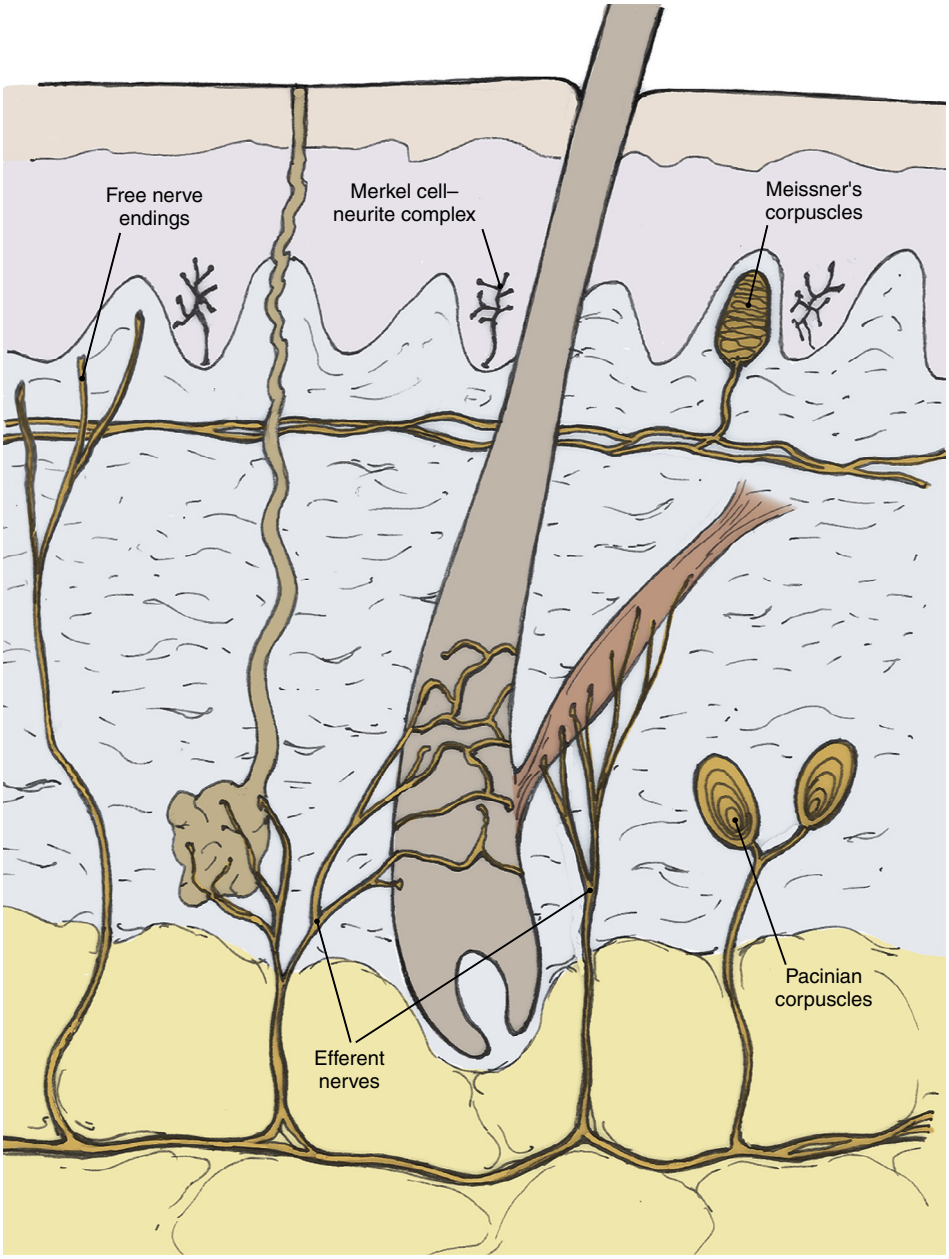

FIG. 1.12 ■ Nerve supply of skin.

by both myelinated and nonmyelinated free nerve endings, which are particularly common in the papillary dermis just beneath the epidermis. Specialized receptors include Meissner's and Pacinian corpuscles. Meissner's corpuscles mediate fine touch sensation and are predominantly found in the papillary dermis of the hands, feet, lips, and forearms. Pacinian corpuscles are involved in the appreciation of deep pressure and vibration. They are primarily found in the deep dermis and subcutaneous adipose tissue of the palms, soles, dorsal surfaces of digits, and genitalia. Efferent nerves in the dermis innervate blood vessels and appendageal structures and regulate their function.

SUMMARY

A basic knowledge of skin anatomy is required to fully understand skin tissue match, tissue stretch, skin thickness and elasticity, wound contraction, tumor cell derivation, and other concepts used on a daily basis by surgeons who perform skin cancer removal and reconstructive surgery.

The reference list can be found on the companion Expert Consult website at http://www.expertconsult.inkling.com.

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CHAPTER 2

SKIN FLAP PHYSIOLOGY

David B. Hom • George Goding, Jr.

INTRODUCTION

The creation of a cutaneous flap applies specific stresses to otherwise normal skin. These stresses include local tissue trauma and reduced neurovascular supply to the affected tissue. The extent to which skin can survive these injuries is a reflection of the anatomy and physiology of skin as well as the cutaneous response to injury. Knowledge of these principles has led to improved skin flap survival by means of flap design and flap delay. Increasing cutaneous flap survival by minimizing the deleterious physiologic effects of flap transposition is an area of active research.

PHYSIOLOGIC CHARACTERISTICS OF SKIN

The skin serves as a sensory and protective organ. The thick epidermal layers are largely impermeable to gases and to most liquids. Because of this, many agents that could result in beneficial effects are ineffective when they are applied topically to intact skin. Preservation of sensation in transferred cutaneous flaps is desirable, but its effect on the physiology of flaps is unclear.

The blood supply to the skin serves two important functions. It provides nutritional support and a thermoregulatory mechanism for the body. Primarily because of its thermoregulatory function, the rate of blood flow through the skin is one of the most variable in the body. Under ordinary skin temperatures, the amount of blood flowing through the skin (0.25 L/m^2 of body surface area) is approximately 10 times the flow required for nutritional support.[1] Blood flow can increase up to seven times this value with maximal vasodilation. When the body is exposed to extreme cold, blood flow can be reduced to levels that are marginal for cutaneous nutrition.

The nutrient capillary network in the reticular dermis and the arteriovenous shunts in the more superficial papillary dermis[2] perform the two functions of the cutaneous circulation. The amount of blood flow to the skin depends ultimately on arteriolar pressure and flow. Under conditions of adequate systemic vascular pressure, however, arterioles act as preshunt and precapillary sphincters that regulate the flow through each vascular network.[3]

The sphincters in the two vascular systems respond to different stimuli (Fig. 2.1). The precapillary sphincter, which controls the amount of nutritive[4] blood flow to the skin, responds to local hypoxemia and increased metabolic byproducts by dilation.[5] Under these conditions, the blood flow is increased (reactive hyperemia being an example). The preshunt sphincters are involved in regulating the changes in blood flow that affect thermoregulation and systemic blood pressure.[6] Release of norepinephrine by the postganglionic sympathetic fibers results in contraction of the preshunt sphincters. This diverts blood away from the skin surface, where heat loss can occur. With increased body temperature, the sympathetic vasoconstrictor impulses decrease, allowing increased blood flow to the skin.[4]

Vasodilation can also occur with excessive body temperature. Local release of acetylcholine by sympathetic nerve fibers may cause vasodilation by directly affecting vasodilator fibers or acting through the release of the potent vasodilator bradykinin from the sweat glands. The cutaneous circulation is also extremely sensitive to circulating norepinephrine and epinephrine. Even in areas of skin that have lost their sympathetic innervation, a mass discharge of the sympathetic system will still result in intense vasoconstriction in the skin.

NEUROVASCULAR SUPPLY TO LOCAL SKIN FLAPS

Blood vessels travel by one of two main routes to terminate in the cutaneous circulation. Musculocutaneous arteries pass through the overlying muscle to which they provide nutrition; septocutaneous arteries (also referred to as *direct cutaneous arteries*) travel through fascial septa, which divide the muscle segments (Fig. 2.2).

The cutaneous portion of septocutaneous arteries typically runs parallel to the skin surface, providing nutrition to a large area of skin. Septocutaneous arteries typically have a pair of veins accompanying them and run above the superficial muscular fascia. The more common musculocutaneous arteries leave the muscle and enter the subcutaneous tissue to supply a smaller region of skin.

Septocutaneous and musculocutaneous arteries empty into a diffuse interconnecting vascular network of dermal and subdermal plexuses. This network provides a redundancy in the vascular supply to the skin. A collateral blood supply supports the vascular territory of each musculocutaneous artery. Lymphatic vessels form a plexus running parallel and deep to the network of blood capillaries. The lymphatic capillaries end in blind sacs and conduct extracellular fluid back into the bloodstream.

The neural supply to the skin originates from both sensory nerves and sympathetic nerves. The sensory nerves are distributed in segmental fashion, forming dermatomes, and participate in the skin's protective function. The postganglionic terminals of cutaneous sympathetic

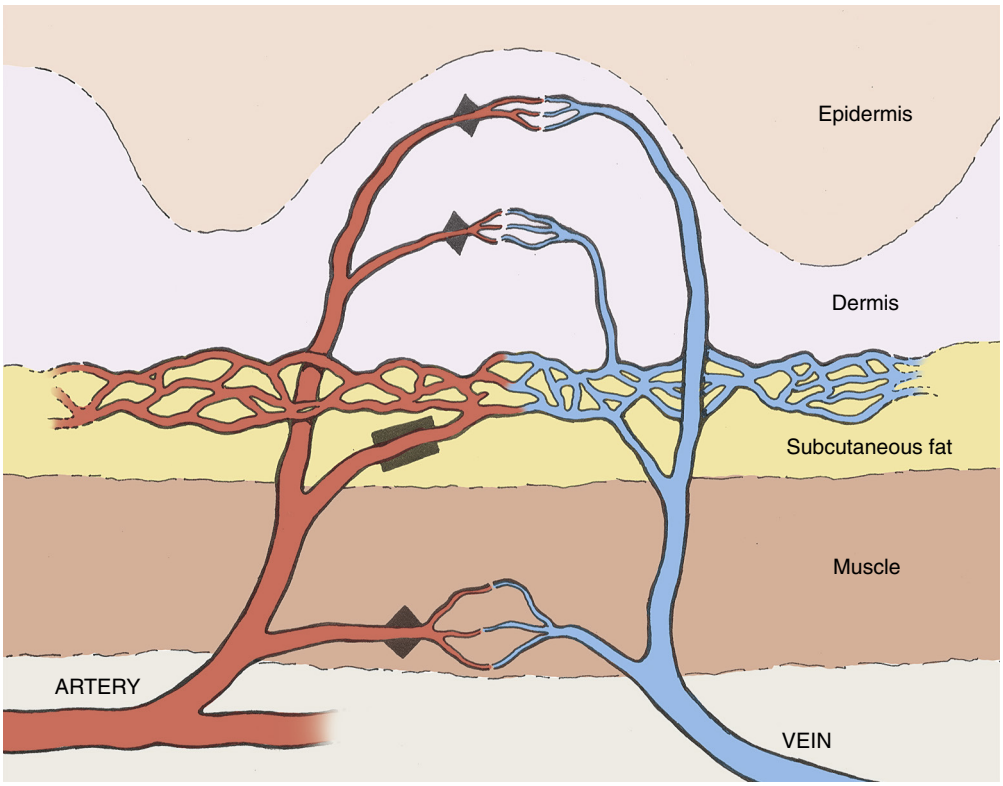

FIG. 2.1 ■ Precapillary (▲) and preshunt (■) sphincters in skin. The precapillary sphincter regulates nutritive blood flow to skin and responds to locally produced stimuli. The preshunt sphincter is involved in thermoregulation and is affected by sympathetic stimuli from the central nervous system.

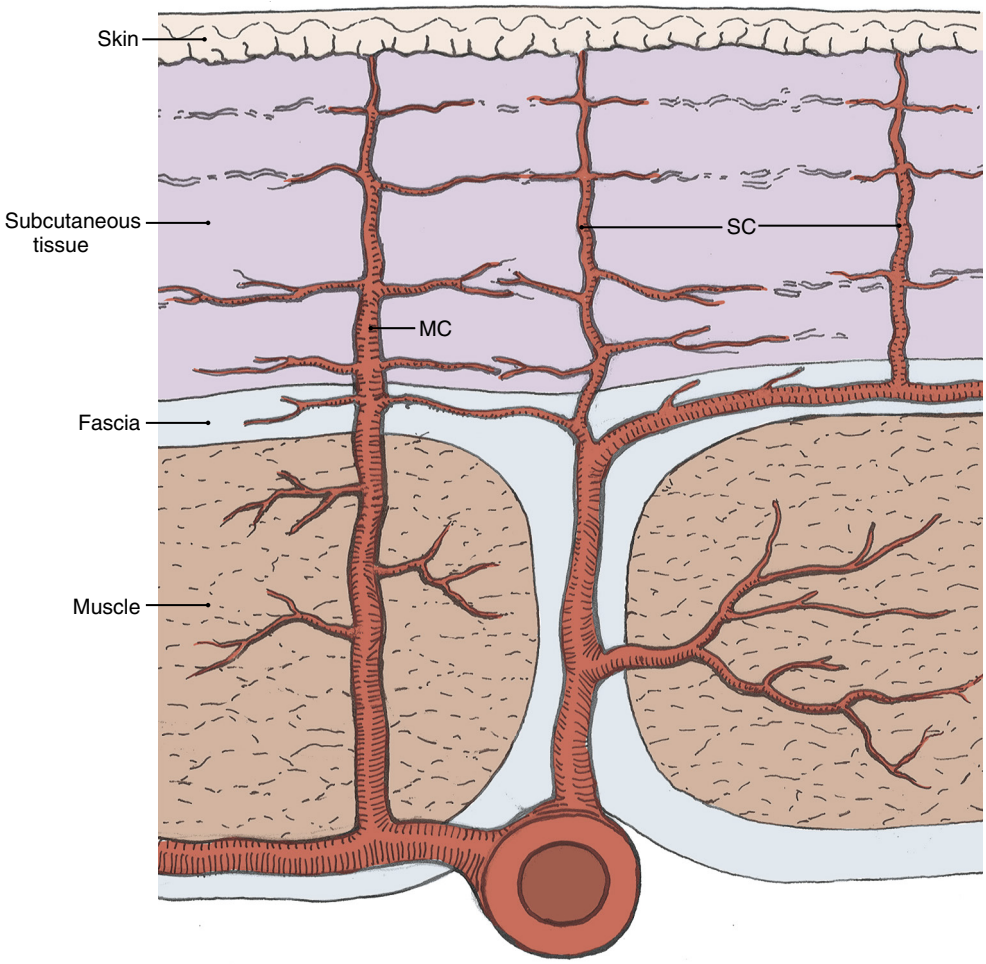

FIG. 2.2 ■ Depiction of varying pathways to skin that defines musculocutaneous (MC) and septocutaneous (SC) arteries.

nerves contain the neurotransmitter norepinephrine and are found in the area of cutaneous arterioles.[4]

VASCULAR DESIGN OF COMMON LOCAL SKIN FLAPS IN THE HEAD AND NECK

The vascular supply to a flap is critical to its survival and is the basis of one classification system of flaps (Fig. 2.3). Local flaps in the head and neck are primarily random or arterial cutaneous.

Random Cutaneous Flaps

The blood supply to a random cutaneous flap is derived from musculocutaneous arteries near the base of the flap. Blood is delivered to the tip of the flap by the interconnecting subdermal plexus. The random cutaneous flap is commonly used in local flap reconstruction and can be rotated, transposed, advanced, or tubed.

Length-to-width ratios of random cutaneous flaps have been recommended for various areas of the body. These differences reflect a regional variation of the neurovascular supply to the skin. Such a description can serve as a guide in designing random cutaneous flaps but should not imply that a wider flap would extend survival length.[7]

Arterial Cutaneous Flaps

Arterial cutaneous flaps (also called *axial pattern flaps* and *perforator flaps*) typically have an improved survival length relative to random cutaneous flaps.[8] This advantage results from the incorporation of a septocutaneous artery within the longitudinal axis. An island flap is an arterial flap with a pedicle consisting of nutrient vessels without the overlying skin. Island flaps can be useful to increase flexibility and to reduce pedicle bulk in certain reconstructive procedures.

Use of arterial cutaneous flaps is limited by the availability of direct cutaneous arteries. An example of an arterial cutaneous flap used in facial reconstruction is the paramedian forehead flap based on the supratrochlear artery.

The surviving length of arterial flaps is related to the length of the included septocutaneous artery. Survival beyond the arterial portion of the flap is based on the subdermal plexus and is essentially a random cutaneous extension of the flap. Flap necrosis secondary to ischemia can be said to occur only in the random portion of the flap (destruction of the arterial pedicle making the entire flap random). Preoperative imaging with computed tomographic angiography to evaluate the perforator distribution[9] and the subcutaneous arterial pattern[10] can further increase the usefulness of these flaps.

PHYSIOLOGIC CHANGES AFTER SKIN FLAP ELEVATION

A number of changes detrimental to skin survival occur when a cutaneous flap is created. That flap survival occurs at all is a testimony to the minimal nutritional requirements of skin. The primary insult affecting flap survival is impaired vascular supply and the resultant ischemia. In the presence of adequate blood flow, complete flap survival occurs. Nerve section and inflammation influence flap survival primarily by affecting blood flow. The formation of new vascular channels between the transposed flap and the recipient bed also influences flap survival.

Impairment of Vascular Supply

Partial interruption of the vascular supply to the skin is the most obvious and critical change that occurs with elevation of a cutaneous flap. This interruption results in a local decrease in perfusion pressure to the skin. In arterial or myocutaneous flaps, the blood supply to the skin overlying the vascular pedicle is usually adequate. In random flaps or random extensions of flaps, the decrease in perfusion pressure becomes more pronounced with increasing distance from the base of the flap.[11] When perfusion is reduced in one area of a random flap, the adjacent vascular territories supplied by a separate perforating vessel can provide a low-pressure blood supply through the subdermal plexus (Fig. 2.4). Because the nutritional requirements of skin are relatively low, a number of vascular territories can be compromised before necrosis will result.

The survival length of the random portion of the flap depends on the physical properties of the supplying vessels (intravascular resistance) and the perfusion pressure.[11] When the perfusion pressure drops below the critical closing pressure of the arterioles in the subdermal plexus, nutritional blood flow ceases and flap necrosis occurs. In the past, random cutaneous flaps were often designed relative to a desired length-to-width ratio, a wider base being needed to successfully transfer a longer flap. The wider random flap includes only additional vessels with the same perfusion pressure. The relationship between perfusion pressure and critical closing pressure is not altered, and no change in survival length occurs[7] (Fig. 2.5).

Myers has emphasized that "fresh flaps are always both viable and ischemic."[12] Depending on the degree of ischemia and the amount of time before the recovery of nutrient blood flow, the flap will either die or recover. In the pig model, arterial and random flaps can tolerate an average of 13 hours of total avascularity and remain viable.[13] In flaps with reduced perfusion, this time is probably much longer.

In surviving flaps, blood flow gradually increases. If the flap is in a favorable recipient site, a fibrin layer forms within the first 2 days. Neovascularization of the flap begins 3 to 7 days after flap transposition. Early neovascularization has been detected at 4 days in the pig and rabbit models[14] and at 3 days in the rat model.[15] Revascularization adequate for division of the flap pedicle has been demonstrated by 7 days in animal models and humans.[14,16]

During revascularization, vascular endothelial cells play a major role in the formation of new vessels. Normally, endothelial cells are in a quiescent state. When they are stimulated by angiogenic growth factors, however, these

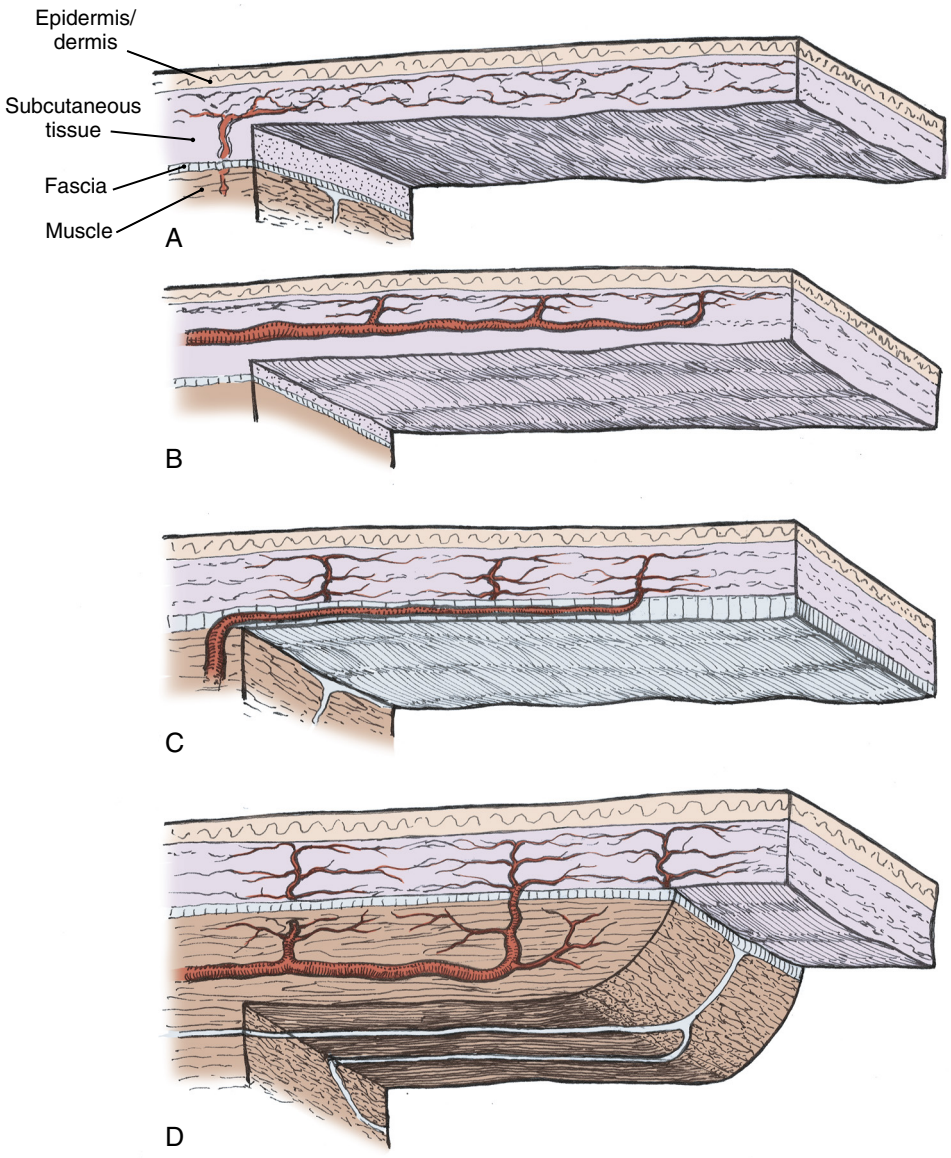

FIG. 2.3 ■ Classification of skin flaps based on vascular supply. **A**, Random. **B**, Arterial cutaneous. **C**, Fasciocutaneous. **D**, Musculocutaneous.

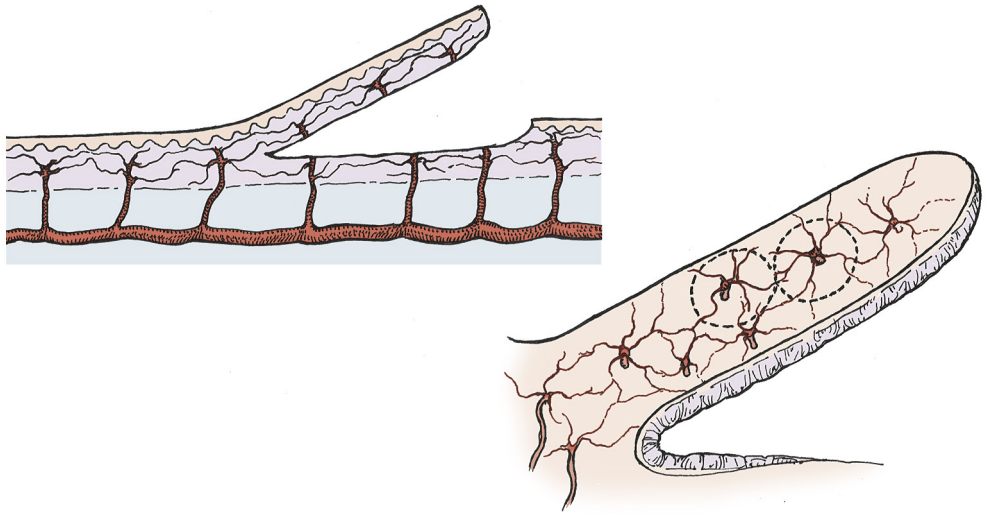

FIG. 2.4 ■ Vascular territories in skin flap. Multiple perforating vessels exist and are interconnected at the periphery of their vascular territory. When vessels are cut, blood supply can be replaced from nearby perforating vessels and tissue necrosis does not occur.

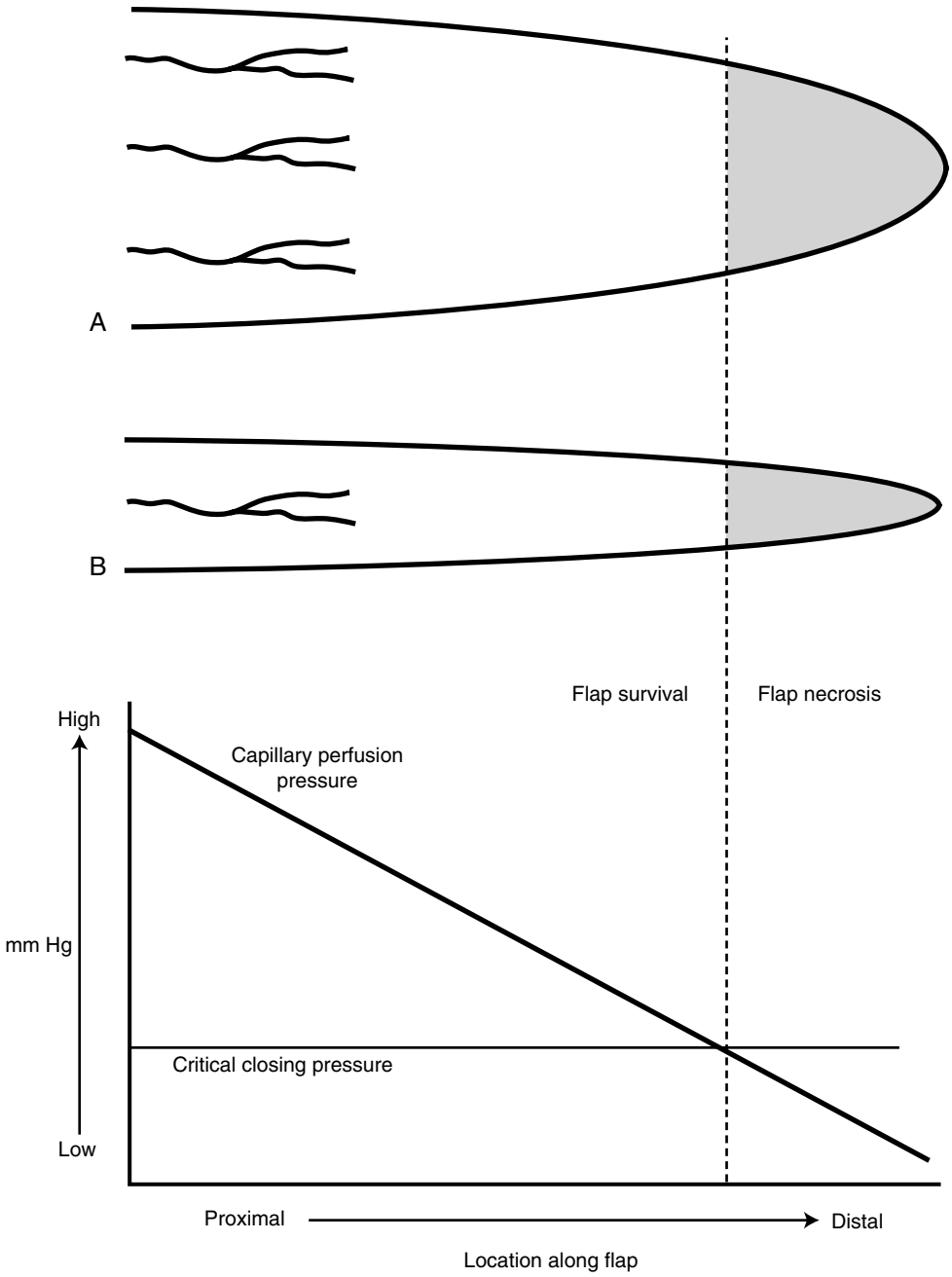

FIG. 2.5 ■ Fallacy of length-to-width ratio. Slope of decreasing perfusion pressure versus flap length does not change with incorporation of additional vessels (flap **A** versus flap **B**) with the same perfusion pressure. Flap necrosis occurs when perfusion pressure falls below the critical closing pressure of capillary bed.

cells can dramatically proliferate. This normally occurs only under certain conditions, such as wound healing and ovulation.

Beginning with an angiogenic stimulus, the angiogenic process involves a number of discrete yet overlying steps (Fig. 2.6). Initially, the vessels become dilated and permeable with retraction of the endothelial cells and a decrease in endothelial junctions. The basement membrane is then dissolved by proteases, and the endothelial cells migrate from the vascular wall toward the angiogenic stimulus. Behind the leading front of migrating endothelial cells, endothelial cell replication begins, forming a capillary sprout that elongates toward the angiogenic source. The nearby capillary sprouts then anastomose to each other, forming capillary loops. As capillary loops and sprouts continue, the loops become patent, forming newly formed blood vessels. These blood vessels differentiate and lay down basement membrane consisting of type IV collagen, laminin, and proteoglycans. Pericytes and fibroblasts then migrate to the capillary loop sites.[17]

With the continued presence or absence of the angiogenic stimulus, substantial remodeling, regression, and rearrangement of the new capillaries occur.[17] Some capillaries join pre-existing flap vessels (inosculation), but the majority of revascularization appears to involve direct ingrowth of recipient vessels into the flap[18] (Fig. 2.7). New capillaries can grow toward an angiogenic source at a mean rate of 0.2 mm/day. When the angiogenic stimulus is discontinued, the capillary vessels regress and

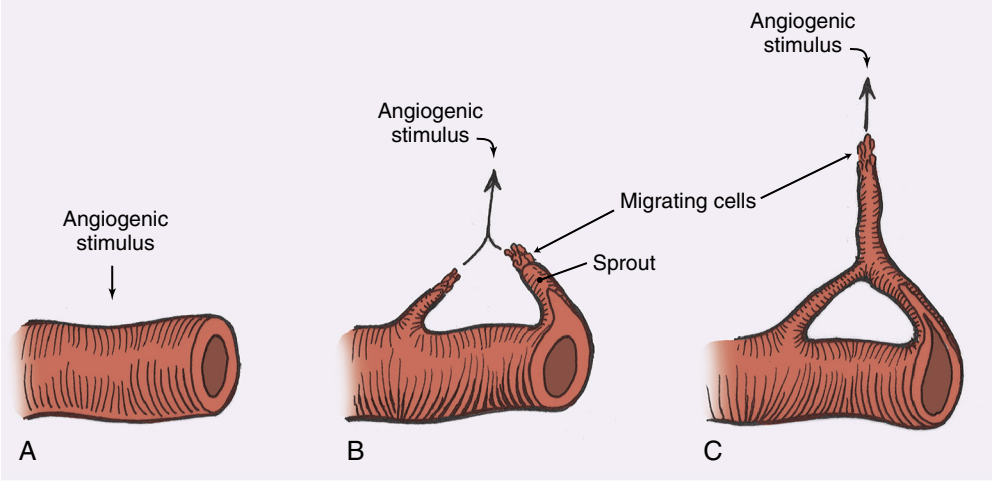

FIG. 2.6 ■ Steps in angiogenesis. **A**, Initial stimulus with retraction of endothelial cells and thinning of basement membrane. **B**, Migration of endothelial cells and formation of capillary sprout. **C**, Formation of capillary loops, which become patent to form new blood vessels.

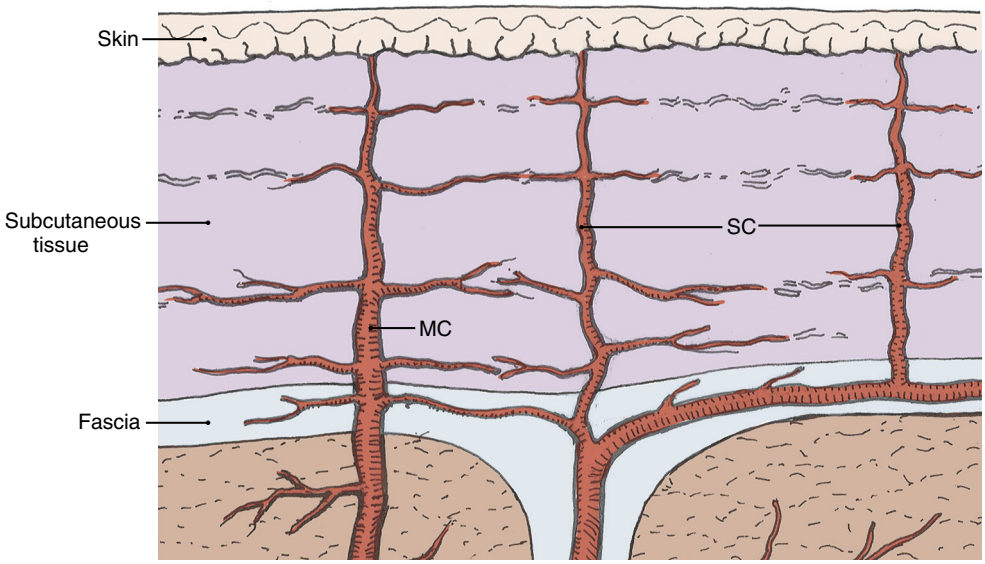

FIG. 2.7 ■ Cross section of flap demonstrating direct ingrowth (**A**) versus inosculation (**B**).

eventually disappear during a period of weeks. Angiogenic growth factors can stimulate capillary growth over distances of 2 to 5 mm.[19]

To prevent an uncontrollable cascade of neovascularization, mechanisms to inhibit angiogenesis are believed to exist. Evidence suggests that pericytes can suppress endothelial growth by direct contact.[20] Thus the physiologic response of angiogenesis may be analogous to the blood coagulation pathway that must be maintained at a constant steady state of control. In soft tissue wound repair, macrophages, lymphocytes, mast cells, and platelets are involved in releasing various factors that modulate angiogenesis.

The venous outflow from the skin is also impaired with flap elevation. Venous flow can occur through the subdermal plexus or by venous channels that accompany the feeding artery in the pedicle. Complete venous occlusion in the early period after elevation may be more damaging to flap survival than inadequate arterial supply.[21] Fortunately, the subdermal plexus alone is often adequate to provide sufficient venous outflow. Care must be taken, however, to preserve venous outflow in flaps pedicled solely on the feeding vessels.

Impairment of lymphatic drainage with flap elevation also occurs. Reduction of the cutaneous lymphatic drainage results in an increase in interstitial fluid pressure that is compounded by increased leakage of intravascular protein associated with inflammation. The resulting edema can decrease capillary perfusion by increasing the intravascular resistance.

Nerve Section

Both cutaneous and sympathetic nerves are severed in the process of flap elevation. Denervation of a skin flap postpones neovascularization of the skin flap. Whereas loss of sensation may limit the usefulness of the flap after transfer, adrenergic denervation has implications for flap survival. When a sympathetic nerve is divided, catecholamines are released from the nerve terminal and the mechanism for catecholamine reuptake is eliminated.[22] A local "hyperadrenergic state" develops that produces

vasoconstriction mediated by alpha-adrenergic receptors in the cutaneous vasculature. In addition, severe sympathetic denervation contributes to the production of oxygen free radicals, which may exert their inhibitory effects on neovascularization.[23]

The vasoconstricting effect of sympathectomy further reduces the total flap blood flow[24] that has already been diminished by division of supplying vessels. This negatively affects the ratio of perfusion pressure to the critical closing pressure of the arterioles in the subdermal plexus. A greater proportion of the distal flap is excluded from the blood supply and necrosis becomes more likely. The stored transmitter is depleted within 24 to 48 hours,[25] and blood flow increases as the concentration of norepinephrine declines. In critical areas of the flap, however, the time to recovery of nutrient blood flow may be delayed sufficiently to produce additional necrosis.

Inflammation and Prostaglandins

The surgical trauma associated with an acutely raised flap results in an inflammatory response. Histamine, serotonin, and kinins are released into the extracellular compartment after flap elevation, increasing the permeability of the microcirculation. The result is an increase in the concentration of proteins and cells within the extracellular space. The presence of nonbacterial inflammation beginning a few days before flap elevation has been shown to improve flap survival.[26,27] This is presumably the result of an increase in local blood flow. The inflammation created during flap elevation, however, may have deleterious effects because of the resultant edema formation.

The action of the primary mediators of the inflammatory response (histamine, serotonin, and kinins) is short-lived. After kinin formation and in the presence of complement, prostaglandins are synthesized by injured cells. Prostaglandins play an important role in the later stages of the inflammatory reaction and also initiate the early phases of injury repair.

Prostaglandins are derived from essential fatty acids that are incorporated in membrane phospholipids (Fig. 2.8). Activation of phospholipases results in the production of prostaglandin H_2 (PGH_2) by cyclooxygenase. Prostaglandin E_1 (PGE_1) and prostaglandin E_2 (PGE_2) can be synthesized from PGH_2 by isomerases in the vascular endothelium. Both PGE_1 and PGE_2 produce vasodilation. Prostaglandin D_2 (PGD_2) is also formed by an isomerase reaction and is the principal cyclooxygenase product of the mast cell. Its effects on the cutaneous microvasculature are similar to those of PGE_1. Prostacyclin (PGI_2) is

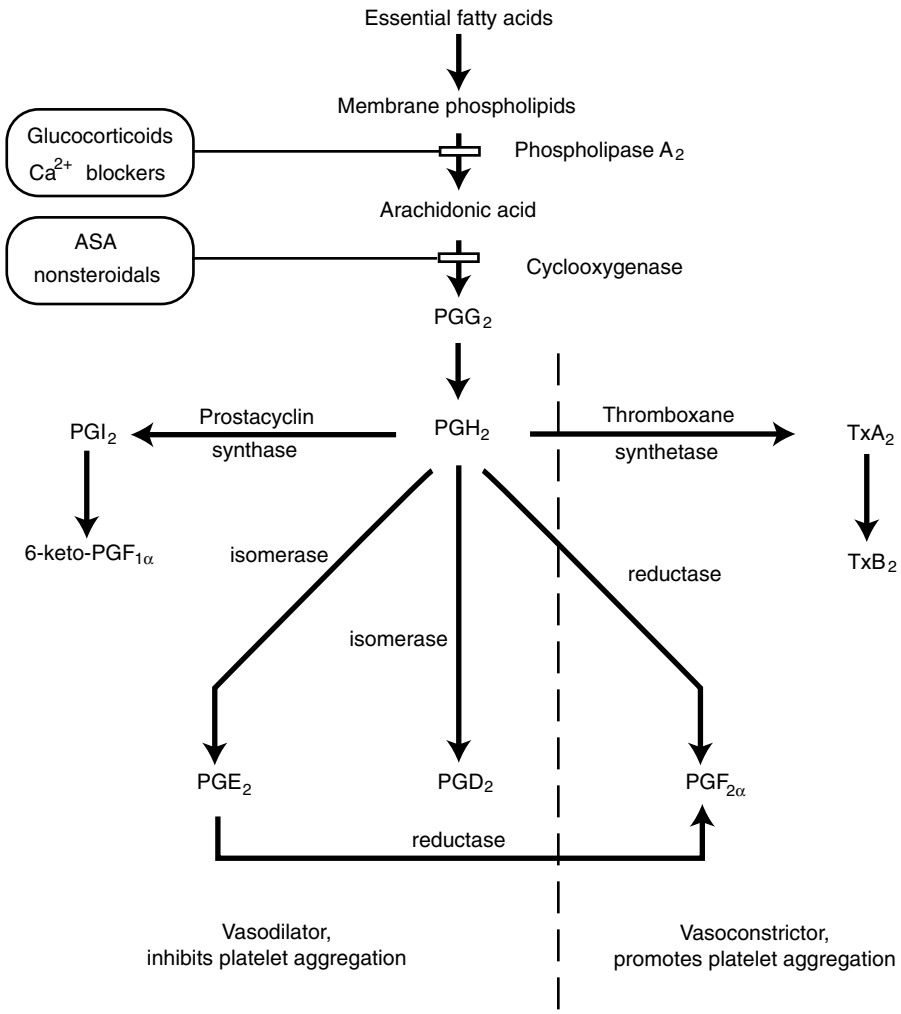

FIG. 2.8 ■ Synthesis of prostaglandins and thromboxanes and their general effects in cutaneous circulation.

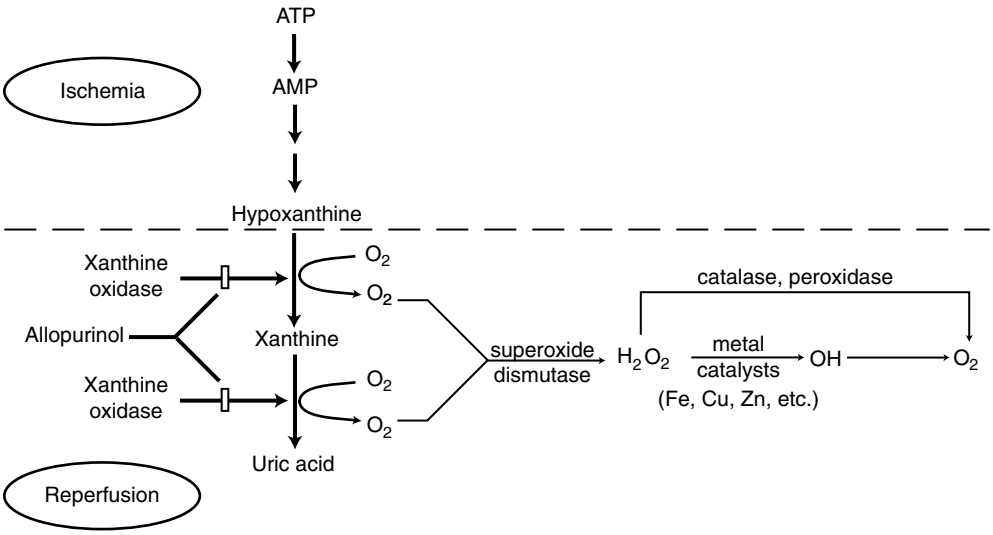

FIG. 2.9 Possible mechanism for formation of oxygen free radicals during reperfusion after ischemia and subsequent reduction of superoxide radical.

a vasodilating agent and inhibitor of platelet aggregation that is derived from PGH_2 through the action of prostacyclin synthase. In the skin, PGI_2 is primarily produced in the endothelial cells of blood vessels.[1,28]

Thromboxane synthetase converts PGH_2 into thromboxane A_2 (TxA_2) and is primarily located in the platelets. Its effects include vessel constriction and promotion of platelet aggregation. Prostaglandin $F_2\alpha$ ($PGF_2\alpha$) is derived from PGH_2 by a reductase reaction. A marked increase in resistance is seen in cutaneous arteries, arterioles, and venules in the presence of $PGF_{2\alpha}$.[29]

The synthesis of prostaglandins and thromboxane can be altered by pharmacologic manipulation. The action of phospholipase A_2 can be inhibited by drugs that reduce the availability of calcium. Glucocorticoids also affect phospholipase A_2 activity by inducing the synthesis of a protein that inhibits the enzyme.[30] Aspirin and other nonsteroidal anti-inflammatory medications interfere with the cyclooxygenase enzyme, inhibiting the synthesis of PGH_2.

Prostacyclin levels were found to peak 7 days after elevation of a porcine flank flap.[1] Elevation of a bipedicled rat dorsal flap resulted in elevated levels of PGE_2, $PGF_2\alpha$, and TxB_2, with a return to nearly normal levels by day 7. Conversion to a single pedicle flap ("delay") resulted in a blunted production of thromboxane and an elevated PGE_2 level. Elevation of an acute flap in the same model showed an elevation of PGE_2, $PGF_2\alpha$, and TxB_2 that was greater and more prolonged than with surgical delay.[31] Prostaglandins clearly play a role in the inflammatory response after flap surgery. Whether these changes in prostaglandin levels represent a cause or a side effect of the observed phenomenon remains to be demonstrated.

Reperfusion (Free Radicals)

Return of blood flow to a flap that is ischemic as a result of excessive release of norepinephrine occurs in approximately 12 hours. With norepinephrine depletion and continued inflammatory response, blood flow can reach a maximum at 24 hours.[24] When oxygen becomes available with reperfusion, an additional menace to flap survival is produced, the free radical. This byproduct of reperfusion can cause damage at both the cellular and subcellular levels,[32] contributing to post ischemic tissue necrosis.

Free radicals are extremely reactive compounds because of an unpaired electron in their outer orbitals. Oxygen free radicals are formed by the sequential univalent reduction of molecular oxygen. The superoxide anion radical (O_2^-) is formed by the addition of a single electron to molecular oxygen. Superoxide is a byproduct of adenosine triphosphate production in the mitochondria and other oxidation reduction reactions.[32] Polymorphonuclear cells are a second source of superoxide radicals that are released in response to bacterial inflammation.

A major source of free radicals in ischemic tissue is the enzyme xanthine oxidase[33] (Fig. 2.9). With ischemia, high-energy phosphate compounds are converted to hypoxanthine that accumulates in the tissues. When oxygen becomes available with reperfusion, xanthine oxidase catalyzes the conversion of hypoxanthine into uric acid, producing superoxide in the process. This reaction is an important mechanism in ischemic tissue injury in skin flaps.[34] The administration of exogenous vascular endothelial growth factor (VEGF) could protect flaps from ischemia-reperfusion injury through the regulation of proinflammatory cytokines and the inhibition of cytotoxic nitric oxide production.[35]

WOUND HEALING

The acute physiologic consequences of flap creation affecting blood flow are of primary importance in determining early flap viability. Other mechanisms, however, play an equally important role in proper flap wound healing and determine the fate of the flap. These additional mechanisms include the four cascades (clotting, complement, kinin, and plasminogen), collagen formation, and collagen degradation. Optimal flap wound healing involves a well-orchestrated interplay of all of these processes.

Throughout the last decade, the role of peptide growth factors in soft tissue wound healing has been gaining more

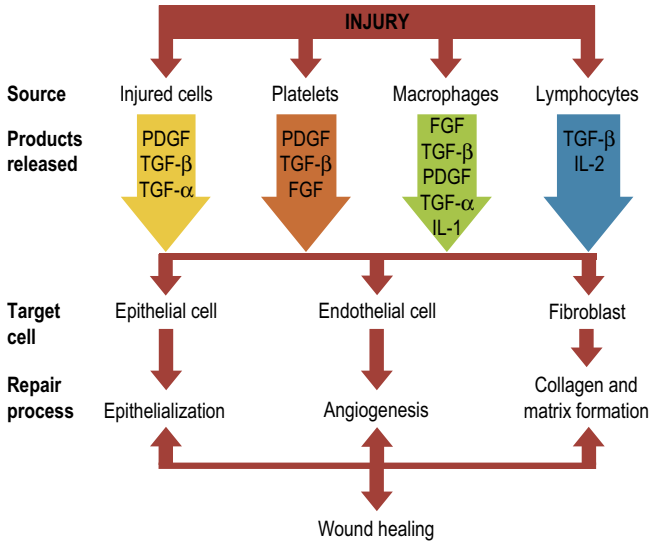

FIG. 2.10 ■ Role of peptide growth factors. FGF, fibroblast growth factor; IL, interleukin; PDGF, platelet-derived growth factor; TGF, transforming growth factor.

attention. These signal proteins contribute to flap wound healing by controlling the recruitment and proliferation of cells (endothelial, epithelial, fibroblast) that modulate the formation of new vessels, collagen, epithelium, and matrix (Fig. 2.10).

ATTEMPTS TO ALTER SKIN FLAP VIABILITY

Kerrigan[36] outlined extrinsic and intrinsic causes of skin flap failure. Extrinsic reasons for flap necrosis are those not resulting from the design of the raised flap. Examples include systemic hypotension, infection, and pedicle compression. These factors can often be overcome in the clinical situation. The primary intrinsic factor affecting flap survival is inadequate blood flow. Numerous experimental attempts have been made to influence flap microcirculation or to decrease the deleterious effects of inadequate flap blood flow (Fig. 2.11). The most successful has been flap delay.

Research Methods

A large amount of literature is available on skin flap physiology. Several studies give conflicting results. Experimental results are often difficult to interpret because of variation in choice of animal model, timing of treatment, route of drug administration, method of data collection, and repeatability of the study.[37] Some standardization of flap research methods would help resolve some of these difficulties.

Two basic experimental designs have been used to investigate the consequences of a vascular insult on a surgical flap. In one design, the blood supply to a flap is interrupted for varying amounts of time by occluding or otherwise interrupting flow through the vascular pedicle. The maximum amount of ischemic time the flap can survive in the experimental and control groups is determined. This design is used to investigate the no-reflow phenomenon and ischemia tolerance. The second design involves flaps with a random extension in which the effect of an experimental manipulation on flap survival or flap blood flow is compared with a control. From this basic framework, a number of animal models and methods to assess blood flow and survival

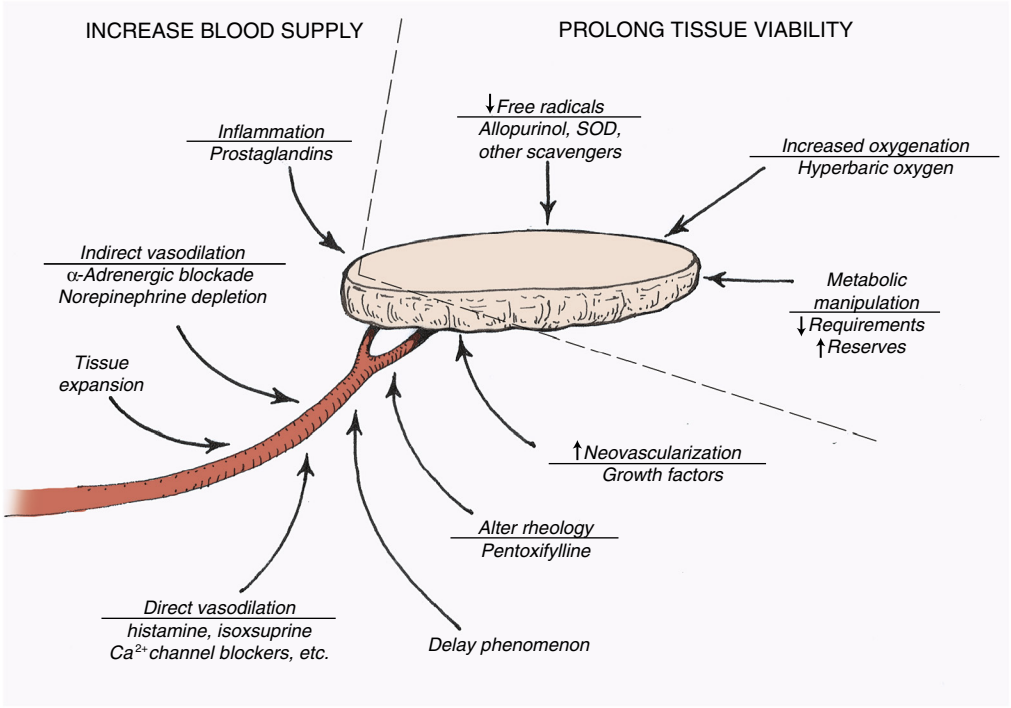

FIG. 2.11 ■ Experimental attempts to affect flap survival. SOD, superoxide dismutase.

have been developed in attempts to alter skin flap viability.

Skin Flap Delay

Four concepts are accepted concerning the delay phenomenon. First, it requires surgical trauma. Second, a large percentage of the neurovascular supply to the flap must be eliminated. Third, delay results in increased flap survival at the time of tissue transfer. Fourth, the beneficial effects can last up to 6 weeks in the human.[38] To explain this phenomenon, three theories regarding the mechanism of delay have been developed: (1) delay improves blood flow, (2) delay conditions tissue to ischemia,[39] and (3) delay closes arteriovenous shunts.[40] Most recent articles support a mechanism resulting in increased circulation to the flap.

Sympathetic denervation causing depletion of norepinephrine within the flap is one mechanism thought to play a role in increasing blood flow to a delayed flap. Degeneration release of norepinephrine occurs soon after flap elevation, and norepinephrine stores are largely depleted in the first 24 to 48 hours.[25] After catecholamine depletion, a relative state of sympathectomy develops, but the vasculature to the flap has an increased sensitivity to the effects of adrenergic drugs (a hyperadrenergic state).[22] Pang et al[24] theorized that a change in the vasoactivity of the small arteries allowed for the delivery of more blood to the distal portion of the flap. During elevation of the bipedicled flap, there is a release of vasoconstrictive substances (norepinephrine, thromboxane, and serotonin). Necrosis is not seen during the first stage of delay because the bipedicled flap has an ample blood supply. During the period of delay, catecholamine depletion occurs and there is a recovery from the hyperadrenergic state. Conversion of the delayed flap to a single pedicle is not accompanied by the same degree of vasoconstriction, resulting in improved blood flow and increased survival.[41]

Another mechanism to increase blood flow to the distal portion of the single pedicle flap is through the development of vascular collaterals and the reorientation of the major vascular channels.[42] Longitudinal flow is also enhanced by vasodilating substances released by inflammation and mild ischemia.[43] Pang et al[43] thought that the depletion of vasoconstricting substances played a role in the early stage of delay, whereas locally released vasodilating substances were involved in the later stages (Table 2.1).

When a flap is delayed, dilation of existing vessels within the flap occurs. The ingrowth of new vessels is not an important mechanism. The maximal anatomic effect on the arterial vessel appears to occur at the level of "choke" vessels during the delay phenomenon. It is believed that the choke vessel dilation during the delay period is a permanent and irreversible event. Specifically, it is an active process associated with both an increase (hyperplasia) and an enlargement (hypertrophy) of the cells in the choke artery wall that increases the caliber of these vessels.[44]

Cytokines may be a mechanism by which surgical delay can increase flap survival. Basic fibroblast growth factor (bFGF) and VEGF expressions increased significantly after delay. In the rat flap model, surgical delay resulted in increased VEGF expression and increased skin paddle survival. These results correlate with previous studies showing that the preoperative injection of VEGF increases skin paddle survival.[45]

TABLE 2.1 **Mechanisms of Improving Blood Flow by the Delay Phenomenon**

Depletion of vasoconstricting substances
Formation of vascular collaterals and reorientation of vascular channels
Stimulation of an inflammatory response
Release of vasodilating substances

Increase of Blood Supply

Indirect Vasodilators

The intense vasoconstriction associated with the release of norepinephrine after flap elevation would seem to hinder flap survival. As previously discussed, one of the benefits of flap delay seems to be the depletion of norepinephrine before the creation of the flap to be transferred. If this vasoconstriction could be blocked or reversed, the duration and severity of distal flap ischemia should be lessened. The result would be increased flap survival without the need for delay.

Several anesthetic agents have vasoactive properties and may influence flap survival. Because general anesthetics are often used during the creation of larger flaps, any potential effects on flap survival are important. Isoflurane (a sympatholytic vasodilator) was found to significantly improve flap survival compared with nitrous oxide, which induces vasoconstriction.[46]

Studies have attempted to produce a "pharmacologic delay" by suppressing the catecholamine-induced vasoconstriction seen after flap elevation. Methods have included the administration of alpha-adrenergic blocking agents and the depletion of norepinephrine stores, but both methods have had mixed results and resulted in systemic toxicity.

Direct Vasodilators

Direct vasodilators such as histamine, hydralazine, and topical dimethyl sulfoxide have shown both a beneficial effect and no effect on skin flap survival.[37] Isoxsuprine is a phenylethylamine derivative of epinephrine, having alpha-adrenergic receptor antagonistic and beta-adrenergic receptor agonistic properties, resulting in relaxation of vascular smooth muscle. Isoxsuprine was found to increase blood flow in the area of the dominant artery in porcine myocutaneous and arterial flaps. Unfortunately, no improvement in blood flow was seen in the distal random portion of the flaps or in flap survival.[47] The smaller vessels in the distal random portion of a flap were theorized to have a sensitivity to vasodilator drugs different from that of muscular or axial arteries. Manipulation of these distal vascular channels appears to be critical to increasing flap survival.

Experiments investigating the effects of other direct vasodilators either have given mixed results or have yet to be confirmed. Studies have attempted to increase skin flap survival with calcitonin gene–related peptide,[48] calcium channel blockers,[49] topical nitroglycerin,[50] and topical dimethyl sulfoxide.[51] The failure of direct vasodilators to reproducibly increase flap survival indicates that mechanisms other than direct arterial dilation are important in survival of the ischemic flap.

Neovascularization

Neovascularization can be potentially accelerated with angiogenic growth factors to improve flap viability. Increased flap survival and vascularity were seen when an endothelial cell growth factor was applied in a sustained-release fashion to accelerate peripheral neovascularization in compromised flaps.[52,53]

Flap Prefabrication

Prefabrication of flaps into desired skin paddle dimensions before flap transposition has gained more attention. Use of angiogenic agents such as bFGF, VEGF, and hyperbaric oxygen to increase vascularity of the skin over the pedicle to enable a larger flap has shown promise. With this concept, it would be possible to tailor the size of a skin paddle of a flap by priming it with angiogenic agents.[54–57] One study showed that a prefabricated skin flap can be created 8 weeks after arteriovenous pedicle implantation underneath the planned tailored skin in a rodent model.[58]

Alteration of Rheology

In a homogeneous fluid that exhibits equal shear stress at different rates of shear, flow (Q) in a vessel can be approximated by the Poiseuille equation:

$$Q = \frac{\Delta P r^4 \pi}{18\eta}$$

where ΔP equals pressure gradient, r^4 is the fourth power of the vessel radius, l is vessel length, and η is viscosity.[4] Although blood is a non-Newtonian fluid, the qualitative relationships in the equation remain. In larger vessels, the radius is a dominant factor; in the capillary microcirculation, however, viscosity becomes more important. By decreasing the viscosity of blood, it may be possible to increase flow to the distal random portion of the acutely raised flap and beneficially affect flap survival. Viscosity is influenced by the hematocrit, serum proteins, temperature, red blood cell deformability, and aggregation, as well as other factors.[59] Each of these factors can be potentially manipulated with a resultant change in viscosity.

Pentoxifylline and low-viscosity whole blood substitutes (Fluosol-DA) will also lower viscosity. Pentoxifylline is a hemorrheologic agent that results in increased red blood cell deformability and decreased platelet aggregability.[59] When it is given 7 to 10 days before flap elevation, pentoxifylline has increased flap survival in porcine dorsal flank flaps[60] and the rat dorsal flap.[59] Beneficial effects with limited preoperative dosing of pentoxifylline, however, have not been uniform.[61] Fluosol-DA administration has also failed to consistently increase flap survival.[62]

Inflammation and Prostaglandins

The surgical trauma associated with an acutely raised or delayed flap results in an inflammatory response. This response results in a local increase in blood flow that could benefit flap survival. Improved flap survival has been shown with different methods of creating an inflammatory response before flap creation.[26,63] These studies demonstrate that the inflammatory response can be a stimulus for "delay" without sympathectomy or vascular division.

The mechanism by which inflammation produces a beneficial effect appears to involve the products of cyclooxygenase metabolism of arachidonic acid. On the other hand, cyclooxygenase inhibitors such as indomethacin and ibuprofen have been shown to increase skin flap viability.[64,65] It has been proposed that the improvement in flap survival with low-level laser energy may be related to a decreased expression of cyclooxygenase 2.[66] Glucocorticoids, which inhibit phospholipase A_2 activity, have also increased flap survival in some studies.[67,68] Administration of prostaglandins that cause vasodilation and decrease platelet aggregation tends to increase survival of experimental flaps.[69,70] Blocking of TxA_2 synthesis has had mixed results.[71,72]

Tissue Expansion

Tissue expansion has been demonstrated to increase the size of a transferred flap in experimental animals and humans. Examination of expanded skin in the guinea pig has shown an increase in the thickness[73] and mitotic activity[74] of the epidermal layer, indicating epidermal proliferation. Blood flow in expanded tissue is greater than in skin overlying a noninflated expander 1 hour after the creation of a pedicled flap in the porcine model.[75] The increased blood flow to expanded skin compared with delay seems to be short-lived.[76] Apart from the acute changes seen with expander manipulation, flap viability and blood flow appear to be similar in expanded skin and in delayed flaps.[77] Irradiation to skin reduces the amount of skin that can safely be expanded. It also reduces the effectiveness of surgical delay and skin flap viability.[78]

Prolonged Viability

Protection Against Harmful Agents

A recent focus of experiments attempting to improve flap survival has been on the formation of free radicals with reperfusion and the return of molecular oxygen to ischemic tissue. This research has focused on decreasing the production of free radicals and employing agents that remove free radicals (free radical scavengers) from the immediate environment.

Administration of allopurinol (a xanthine oxidase inhibitor) preoperatively prevents the increased xanthine oxidase activity seen with acute flap elevation.[79] Improved survival of rat dorsal flaps has been accomplished with

allopurinol when it is given at high doses,[80] with lower doses having no effect. The high doses required have led to concern about the use of allopurinol to increase flap survival in the clinical setting.

Several free radical scavengers are available to protect the tissues from destruction by free radicals. Superoxide dismutase (SOD), an intracellular free radical scavenger, catalyzes the conversion of superoxide to hydrogen peroxide (H_2O_2) and molecular oxygen. When it is given systemically, SOD is an effective scavenger of the superoxide radical regardless of its source. SOD treatment has resulted in improved flap survival[81,82] and increased tolerance to ischemia of rat abdominal flaps.[48] Improved flap survival has also been demonstrated with a number of other naturally occurring compounds with free radical scavenging properties. These include deferoxamine[83]; vitamin E, vitamin A, vitamin C, and glutathione[84]; various amino acids[85]; and amino acid derivatives.[86]

The hydrogen peroxide formed by the dismutation of superoxide is not particularly harmful. In the presence of chelated metal complexes, however, hydrogen peroxide can be converted into a hydroxyl radical (OH) by the Fenton-type or Haber-Weiss reaction. The hydroxyl radical is much more reactive and may be responsible for much of the damage inflicted by oxygen free radicals.[32] The presence of a hematoma under a flap may decrease flap survival by increasing the available iron that acts as a catalyst in the formation of free radicals.[87]

Nitric Oxide

Nitric oxide synthesized by the enzyme nitric oxide synthase has a major physiologic impact on skin flap survival. Nitric oxide is a radical with properties that induce vasodilation and can protect tissues from neutrophil-mediated ischemia-reperfusion injury. With the administration of a nitric oxide precursor, L-arginine, myocutaneous flaps in porcine skin were protected from ischemia-reperfusion injury with reduced flap necrosis, neutrophil accumulation, and edema.[88] It has been proposed that after reperfusion injury, endothelial cell dysfunction leads to disruption of nitric oxide synthase–mediated nitric oxide production and in turn causes the deleterious effects of ischemia-reperfusion injury on flap survival and blood reflow.[89] The role of nitric oxide synthase in promoting skin flap angiogenesis in its early stages after flap transposition has shown promise.[90] Nitric oxide is also believed to be an important contributor to the phenomenon of skin flap delay.[91]

Increased Tolerance of Ischemia

Increased Oxygenation. Improvement in flap survival with hyperbaric oxygen treatment has been documented in the rat model.[92] Hyperbaric oxygen treatment, however, increases blood oxygen-carrying capacity by at most 20%.[93] A greater effect of hyperbaric oxygen treatment may be increasing oxygen diffusion from surrounding perfused tissue to the ischemic portion of the flap.[94] Increased flap survival occurs with treatments using 21% hyperbaric oxygen, implying that increased oxygen could be delivered with an increase in pressure alone.[95] A treatment delay of 24 hours or more after elevation of rat dorsal flaps results in little benefit from hyperbaric oxygen.[96] An experiment using a porcine model was less successful in improving flap survival.[97]

Metabolic Manipulation. Decreasing the metabolic requirements and increasing the metabolic reserves of skin are additional strategies for increasing flap survival. These approaches are based on the idea that flap necrosis occurs when tissue metabolic demand is greater than what the blood supply can deliver. Decreasing temperature is an effective way to reduce metabolic activity and to delay necrotic changes, but improvement in flap survival is not seen.[98]

IMPAIRED FLAPS

Smoking tobacco is associated with an increased chance of flap necrosis in facelift operations.[99] Exposure to tobacco smoke resulted in increased flap necrosis of dorsal flaps in rodents.[100] The deleterious effects of nicotine appear to increase with prolonged exposure.[101] The mechanism whereby tobacco or nicotine lowers flap survival is believed to be direct endothelial damage or vasoconstriction secondary to catecholamine release or local concentrations of prostaglandins. Smoking impairs flap healing by causing vasoconstriction from nicotine and increased levels of carboxyhemoglobin, which limits oxygen delivery. In addition, smoking decreases neutrophilic function and decreases collagen synthesis.[102] Smoking cessation for at least 4 to 6 weeks is recommended before skin flap surgery. Medications such as varenicline (Chantix) and the electronic cigarette (E-cigarette) may assist in cessation.

Venous congestion after skin flap transfer can impair skin flap survival because it can lead to microcirculatory thrombosis and blood stasis. To improve skin flap viability, the use of leeches has been clinically useful to temporarily relieve skin flap congestion several days after skin flap transposition. The goal of leech therapy is to establish temporary venous outflow until further neovascularization has taken place. Leech saliva has the active enzyme hirudin, which is a powerful anticoagulant that allows blood to flow more freely at the bite site. The leeches are applied to the compromised area of the flap every several hours and are removed once they are no longer biting the tissue. Patients need to have antibiotic coverage (such as fluoroquinolones, sulfamethoxazole-trimethoprim, or a second- or third-generation cephalosporin) during leech therapy to reduce the risk for infection (commonly caused by *Aeromonas hydrophilia*). In addition, serial hemoglobin levels should be monitored on a daily basis because leech treatment can lead to sudden anemia requiring blood transfusions.[103]

Some animal studies show that hyperbaric oxygen can improve skin flap survival.[104] Hyperbaric oxygen therapy delivers oxygen concentrations at pressures higher than atmospheric pressures. With a "dive" of 2.4 atmospheres absolute (ATA), tissue wound partial pressure of oxygen would be 800 to 1100 mm Hg. This exposure induces vasoconstriction with increased partial pressures of oxygen in the blood, which subsequently stimulates angiogenesis and fibroblast proliferation.[105] Patient side effects

may include barotrauma and exacerbation of congestive heart failure. More clinical studies are required.

VEGF and nitric oxide cause vasodilation, increase angiogenesis, and improve flap survival. One study showed that a single intra-arterial dose of VEGF or L-arginine, a substrate for nitric oxide production, reduced flap regional necrosis.[106]

VEGF has been consistently implicated as an important factor in increasing skin flap survival. Sustained VEGF release has been associated with increased neovascularization and flap tissue survival with a possible role in the delay phenomena. Modifying VEGF effects may lead to strategies for achieving greater predictability in flap and graft survival.[107]

The administration of VEGF injections to the distal part of a long random skin flap (length to width ratio 5:1) was shown to improve flap survival rate and enhance distal skin flap salvage. The VEGF mechanism was believed to be from increased neovascularization induced by this cytokine.[108] Bone marrow mesenchymal stem cells have also been shown to increase angiogenesis within a rodent model.[109] The use of such stem cells may help reverse the detrimental effects of diabetes in ischemic skin flaps.

Irradiation is deleterious to flap survival in some studies.[110,111] Discrepancies in these studies are probably because of differences in the radiation regimen administered (i.e., radiation dosage, fractionation, and surgical timing in respect to the irradiation). Radiation treatment results in endarteritis obliterans and altered wound healing. In prior irradiated skin, the delay phenomenon does improve flap survival.[112] Flap neovascularization is delayed but not eliminated after irradiation.[113]

The use of angiogenic growth factors has the potential to increase the viability of irradiated skin flaps by means of accelerating revascularization.[53] Use of bFGF has been shown to increase the random skin flap survival of irradiated skin flaps.[114]

In a previously irradiated porcine model, basic FGF increased neovascularization in tissue expanded skin.[115]

When growth factors are administered to influence wound healing and flap survival, it is difficult to determine the best time and mode of delivery to maximize their therapeutic effects. One major factor is that the half-life of growth factors is short. One article described the feasibility of using hollow-fiber catheters to deliver VEGF to porcine random skin flaps at the same time removing edema by ultrafiltration catheters.[116] Other modalities for growth factor delivery continue to be investigated.

Preliminary studies using autologous platelet-rich plasma, which contains a number of growth factors released from platelets, have shown increased skin flap survival.[117] When platelet-rich plasma is administered by subcutaneous injection, platelet-rich skin flaps have an increased blood vessel density and fewer inflammatory cells compared with platelet-poor plasma and control flaps. Furthermore, platelet-rich plasma flaps appear to have an upregulation of genes involved in angiogenesis (elevated mRNA levels of VEGF and platelet-derived growth factor). The use of botulinum toxin A on ischemia-reperfusion injury may provide protection for the musculocutaneous flaps from ischemia-reperfusion injury. This interesting study revealed that local BoTA preconditioning showed significant protection against injury in a rat musculocutaneous flap model.[118]

TISSUE ENGINEERING

Tissue engineering to improve the survival of skin flaps remains in its infancy. In using gene therapy to improve flap survival, various methods have employed plasmids or viruses to transplant genes that code for and produce growth factors in ischemic tissue.[119]

One study showed that liposome-mediated gene transfer could result in useful biologic effects by priming the flap before it is raised. Specifically, cDNA encoding VEGF complexed to commercially available liposomes was injected into rat skin 1 week before the raising of a random flap. Flap survival was enhanced by 14%.[120]

Another study investigated the use of adenovirus-mediated gene therapy with VEGF (Ad-VEGF) delivered into the subdermal space to treat compromised skin flaps. Compared with the control, both local and midline subdermal injections of Ad-VEGF showed improved overall flap survival.[121] In ischemic tissues, flap survival was enhanced by the administration of a cDNA encoding VEGF[122] as well as by the incorporation of the VEGF gene into mesenchymal stem cells.[123] The use of plasmid DNA as a carrier for platelet-derived growth factor B delivered subcutaneously 7 days before flap elevation may also give an effective nonsurgical approach to increase flap survival by increasing vascularity.[124] Other gene therapy delivery methods include a cell-based gene-transfer model of fibroblasts delivering the combination of VEGF165 and basic FGF proteins to ischemic and nonischemic tissues. This gene therapy increased blood vessels and reduced necrosis by 25%.[125]

SUMMARY

Skin flap survival is very dependent on vascular flow of the transferred soft tissue to allow for adequate flap revascularization. The ultimate goal is to allow the skin flap to integrate within the wound bed and peripheral margins. The blood flow required for nutritional support of the skin is significantly less than what is necessary to carry out its thermoregulatory function. This allows the skin to survive a compromise of its blood supply during the creation of local flaps. The surviving length of a particular flap depends on the relationship between the intravascular perfusion pressure and the critical closing pressure of the arterioles in the subdermal plexus. Appropriate flap design is the most critical factor to maintain adequate intravascular perfusion pressure and to avoid tissue necrosis.

During the first 48 hours after a flap is raised, the transferred tissue must survive a number of hazards. The arteriolar closing pressure is increased by catecholamine released from divided sympathetic nerves within the tissue. An inflammatory response begins the process of wound healing but may also impair blood flow with the formation of tissue edema. The increased oxygen available with reperfusion results in the formation of

free radicals, which can further damage tissue. Beyond the first few days, neovascularization and wound healing lessen the surviving flap's dependence on the pedicle.

Attempts to improve flap survival have involved improving flap design, altering the early physiologic impairment of blood flow, and increasing tissue resistance to ischemia. Surgical delay is the most effective intervention. Pharmacologic manipulations designed to improve blood flow or to increase tissue tolerance of ischemia have not achieved the significant and reproducible results required for incorporation into common clinical usage. Research with growth factors and tissue engineering will expand the horizons in tailoring flap reconstruction.

The reference list can be found on the companion Expert Consult website at http://www.expertconsult.inkling.com.

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CHAPTER 3

BIOMECHANICS OF SKIN FLAPS

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INTRODUCTION

Scientific and clinical research in the areas of wound healing and the biomechanics of skin flaps has changed skin flap design from erratic, unsure, and artistic to consistent, scientific, and artistic. Today, skin flap design emphasizes vascular patterns, skin physiology, and the biomechanical characteristics of cutaneous tissue. The unique mechanical properties of skin influence blood flow and flap survival and thus are integral in the design of local skin flaps. The study of soft tissue biomechanics has increased the precision and reliability of local cutaneous flaps, supporting the use of local flaps as the procedure of choice for the reconstruction of small and medium-sized facial defects that cannot be closed primarily.

BIOMECHANICAL PROPERTIES OF CUTANEOUS TISSUE

The mechanical properties of a material are described by the relationship that exists between a force applied to a specimen and the resultant deformation of the specimen as a function of time. In engineering, these mechanical properties are defined by the quantities *stress* (force per unit of original cross section) and *strain* (change in length divided by the original length). The stress/strain ratio thus measures the relationship between force and elongation by said force for a given cross-sectional area. The stress-strain relationship is independent of the dimensions of the specimen and is a property of the material itself. Uniform materials, such as titanium, have a linear stress-strain relationship. Their mechanical properties can be described by the proportionality constant (C = stress/strain). If the stress-strain relationship does not vary as a function of time, the material is said to be *elastic*.[1]

Unlike many engineering materials, skin is a heterogeneous substance composed of a network of dissimilar materials. Skin is a living tissue, capable of proliferation, change, and response to physical stimulus. It is not surprising that the mechanical properties of skin are unique compared with other materials. For simplicity, skin can be said to have three basic mechanical properties: nonlinearity, anisotropy, and viscoelasticity.

Nonlinearity

This mechanical behavior of skin is attributable to its heterogeneous nature. Skin is composed of a series of interrelated networks that are intimately entwined. Structurally important components in the dermis include collagen fibers, elastic fibers, nerve fibers, capillaries, lymphatics, and ground substance. Skin without tension has collagen fibers distributed throughout the dermis in a haphazard, diffuse manner. Collagen is woven in a multidirectional array without preferential orientation of thick and thin bundles. Numerous connections between collagen bundles form a continuous network without visible free ends. There are no restrictive attachments among adjacent collagen bundles that seem free to glide, relative to each other. Elastic fibers loop spirally around collagen and attach at multiple points along each bundle. Elastic fibers function as a type of energy storage device, bringing stretched collagen back to a relaxed position. Structural proteins are found in the interstitial fluid that acts as a lubricant enabling movement on the one hand and acting as a buffer to resist rapid change on the other.

A typical stress-strain curve for isolated skin is shown in Fig. 3.1. The shape of the curve is similar to stress-strain and force-advancement curves obtained from tests on skin flaps and other soft tissues.[1] It is apparent from the graph that skin and skin flaps have nonlinear stress-strain relationships. The mechanical behavior can be divided into three separate regions: (1) an initial flat section in which considerable extension occurs with little force, (2) an intermediate section of rapid transition, and (3) a terminal section where little extension is possible despite great increases in applied force. Histologic examinations of the sequential stages of skin extension provide an explanation for the nonlinear nature of this graph. During initial deformation, randomly oriented collagen and elastic fibers are stretched in the direction of the applied force. Collagen fibers do not bear a significant burden until the bundle is completely straight in the direction of the applied force.[1] As a result, there is little resistance to initial deformation, and the stress-strain relationship is nearly linear and elastic (region 1). As deformation progresses, additional collagen fibers are recruited into the load-carrying role and resistance rises. The low stress required for the high strain inherent in region 1 allows the small movements resulting from flexion and extension at joints, enabling freedom of movement and natural facial expression. Region 2 is the strain at which many collagen fibers transition from non–load carrying to a load-carrying role. At high-stress loads (region 3), virtually all the dermal collagen fibers are aligned in the direction of the applied force. At this point, no further deformation is possible because of the inextensible nature of fully oriented collagen. Wholly oriented collagen (region 3) preserves the structural integrity of skin by limiting deformation during accidental stresses.[1] Raposio and Nordstrom[2] studied the stress-strain curve of human scalp tissue during serial excision of the scalp

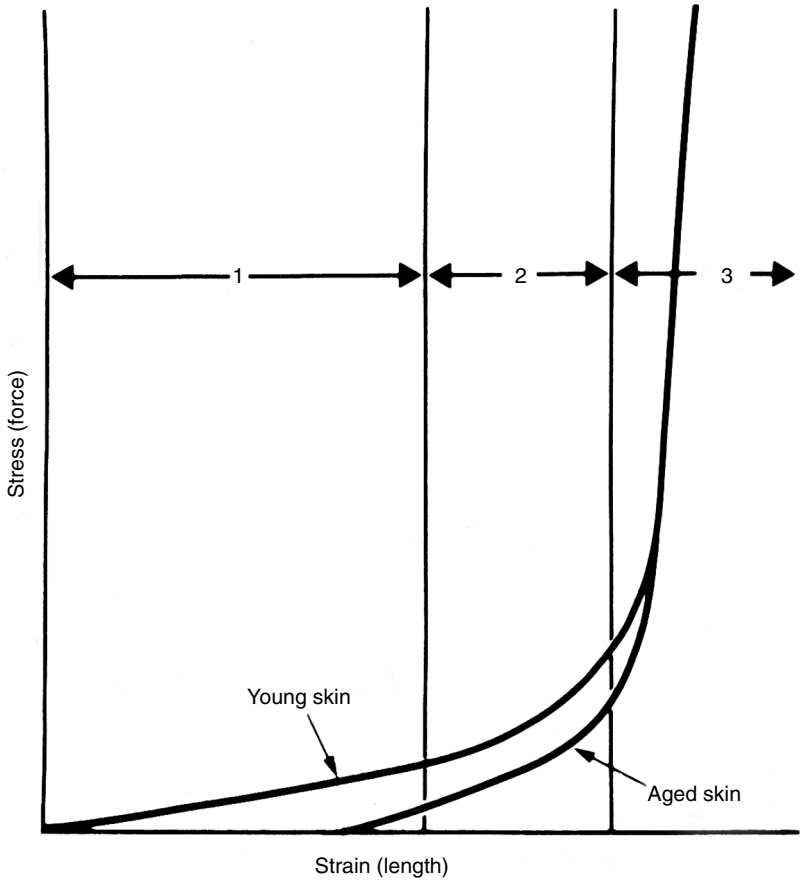

FIG. 3.1 Stress-strain curve for isolated skin can be divided into three separate regions. Aged skin deforms under its own weight, shifting the apparent origin of the curve along x-axis. (From Larrabee WF Jr: Immediate repair of facial defects. *Dermatol Clin.* 1989;7:662.)

and found scalp to be initially linear from 0 to 500 g, gradually reducing in compliance from 500 to 1500 g, and rapidly increasing in stiffness from 1500 to 5000 g.

Anisotropy

There are enormous individual variations in the extensibility of human skin—differences between the slim and obese, young and old, male and female. The shape of the force-advancement curve is further influenced by edema, inflammation, hormonal conditions, and body weight. It is the variation in skin tension within the same individual, however, that is the most interesting to the reconstructive surgeon. On the face, the skin is lax around the eyes and cheek, whereas it is taut on the nose, chin, and forehead. In each of these locations, there are directional (anisotropic) considerations for skin movement. In most regions of the body, there is skin tension in every direction, but the degree of tension is greatest parallel to the relaxed skin tension lines (RSTLs).[3] Pierard and Lapiere[4] showed that the presence of skin tension lines depends on the interaction between elastic fibers and collagen fibers and the anchorage of collagen fibers to each other. An incision made at a right angle to the RSTL will gape widely and is more likely to produce a widened or hypertrophic scar. The lines of maximal extensibility (LME) run perpendicular to the RSTLs and represent the direction in which closure can be performed with the least tension.[5,6] Therefore elliptical excisions should be performed parallel to the RSTLs to place the maximum closure tension parallel to the LME and local skin flaps should be designed so that the donor site closure is parallel to the LME.

RSTLs are not to be confused with Langer's lines. Langer's lines of cutaneous tension correspond to the orientation of forces that cause a circular puncture mark in the skin of a cadaver to distort into a fusiform shape. The orientation of Langer's lines is often distinct from the creases formed in living subjects when the joints are placed in a relaxed position. RSTLs follow the longest and straightest furrows formed when the skin is relaxed and are not visible features of the skin. Rather, RSTLs derive from the act of pinching the skin and observing the furrows and ridges that form.[3] When skin tension is preserved at the time of biopsy, a small number of extracellular collagen and elastin bundles have been demonstrated to run parallel to the RSTLs.[4]

Viscoelasticity

When a material resists shear flow and strain in a linear fashion related to time in response to a force, it is said to be viscous. Elastic materials demonstrate immediate strain when a force is applied but return to their original state when the force is removed. Skin exhibits properties of both viscosity and elasticity (viscoelasticity). Skin behaves like an elastic substance only during initial deformation at low stress level (see Fig. 3.1, region 1). At higher stress loads, skin shows viscoelastic properties, and strain becomes a function of both load and time.

Two time-dependent properties of skin that are routinely exploited by surgeons are *creep* and *stress relaxation*.

Creep refers to the increase in the length of skin compared with the original length when skin is placed under a constant stress (force per unit area). At high-stress loads, a modicum of creep can be achieved in a short time. A small increase in length (strain) occurs as compressed and straightened collagen fibers displace interstitial fluid that is loosely bound to the extracellular matrix (ground substance). When skin is stretched in air, it is possible to see this fluid collect on the undersurface.[7] Time is required for fluid to move from one area to another, which explains the time dependence of the process. This mechanism partially explains the biomechanical and histologic changes that occur during tissue expansion, obesity, and pregnancy.

Stress relaxation and creep are related. *Stress relaxation* refers to a decrease in stress that occurs when skin is held under tension at a constant strain. If a skin flap is closed under excessive tension, a certain amount of relaxation occurs as the tissue creeps. Stress relaxation allows large lesions in inelastic regions to be removed with serial excision. It also accounts for the improved vascularity observed in the first 24 hours of flaps closed under tension. These biomechanical properties may save a questionable flap but should not be an integral part of flap design.

MECHANOTRANSDUCTION AND SKIN

The mechanical properties of skin, including nonlinearity, anisotropy, and viscoelasticity, are readily observed at a macroscopic level and exploited during reconstructive surgery. It stands to reason that the physical forces applied to skin at the macroscopic level would induce changes at the cellular level. Some of the first evidence of this at a cellular level was provided by Folkman and Moscona[8] in 1978. The authors grew cells in culture in varying concentrations of poly(2-hydroxyethyl methacrylate) to control cell shape and, indirectly, cell tension and found that varying shape and tension resulted in differences in DNA synthesis and proliferation. These results suggested that cells sense changes in force and respond accordingly at the molecular level. The mechanism by which these mechanical forces lead to cellular responses came to be called *mechanotransduction*.

Mechanotransduction requires that cells be able to sense a mechanical stimulus, which in turn leads to the activation of biochemical signaling pathways to achieve the desired end result (i.e., apoptosis, proliferation). Mechanotransduction can act on cells directly, in which the cell senses and acts on the mechanical force itself, or indirectly, in which the force is sensed by other cells, such as sensory nerves, leading to the release of chemical mediators that act on nearby cells.

Direct Mechanotransduction

Direct mechanotransduction is the process by which a cell converts mechanical stimuli into biochemical signals. For a cell to convert a mechanical signal to a biochemical signal, it must be able to sense the signal. Ingber[9] proposed the idea of "tensegrity," in which a cell's cytoskeletal framework is coupled to the extracellular matrix as well as to the cytoskeletal framework of nearby cells, creating a homeostasis of tension from which deviations might be recognized.

Cellular adhesion molecules, such as integrins, are key to tensegrity. Integrins couple the extracellular matrix to the actin cytoskeleton. This coupling allows integrins to transduce external mechanical forces into changes within the cell and vice versa. The activation of integrins, which are primarily in an off state in the cellular membrane, can modulate downstream signaling events controlling a wide variety of cellular events including apoptosis, proliferation, and gene expression, among others.[10] Recent studies suggest the involvement of integrin signaling pathways in up or down-regulation of certain ECM components (i.e., collagen I and fibronectin) that play pivotal roles in the proliferation and migration of fibroblasts and keratinocytes in wound healing.[11]

Altered expression of integrins has been implicated in studies of wound healing and chronic wounds. Hakkinen et al[12] used in situ hybridization to investigate the expression of β_6 integrin in chronic wounds, hypertrophic scars, and keloids in humans and found that chronic wounds expressed high levels of β_6 integrin, whereas keloids and hypertrophic scars did not demonstrate any expression. Furthermore, the authors engineered a homozygous transgenic mouse line that constitutively expressed β_6 integrin in skin epithelium and found that a significant percentage (27%) of these mice spontaneously developed chronic wounds, suggesting that altered expression of integrins might be responsible in some cases of poor healing.

Whereas the mechanisms of mechanotransduction by integrins have been the best characterized, cells possess other means by which to translate mechanical forces into biochemical signals. Some cells possess mechanosensitive ion channels that respond to mechanical forces with either the activation or inactivation of an ion flux.[13] One of the most important of these is the mechanosensitive calcium ion channel. Yano et al[14] cultured human keratinocytes on flexible dishes that were stretched 20% and discovered that the stretching induced hyperproliferation as measured by BrdU incorporation secondary to the activation of extracellular signal–regulated kinases (ERK1/2). The possibility of a role for the mechanosensitive calcium-gated ion channel was suggested by the almost complete inhibition of hyperproliferation when a calcium channel inhibitor was cultured with the cells.

Protein deformation is another mechanism of direct mechanotransduction.[15] Protein deformation is the process by which mechanical forces induce conformational changes to a protein, which may unmask new binding motifs or, alternatively, mask previously accessible binding sites. For example, Tamada et al[16] removed the cell membranes and soluble proteins from human embryonic kidney cells and demonstrated that stretching of the remaining cytoskeleton could activate the protein Rap1, which is important for the activation of the p38 mitogen-activated protein kinase cascade. Similarly, transforming

growth factor β1 (TGF-β1) is an important mediator of inflammation and wound healing. TGF-β1 typically remains in an inactive state bound to latency-associated peptide in the large latent complex. The binding of integrins to the large latent complex can cause conformational changes in the large latent complex and dissociation of the latency-associated peptide from TGF-β1, which renders it active.[17] Focal adhesion proteins have become a topic of research in recent years because these proteins (including vinculin, FA kinase, and p130Cas) are critical to the cell's ability to sense, transmit, and respond to mechanical forces and generate cytoskeletal tension. The details behind how they function are still being elucidated.[18]

Indirect Mechanotransduction

Indirect mechanotransduction involves a cell-sensing mechanical force leading to the release of proteins or other chemical messengers, which then act on nearby cells to mediate a variety of effects. One example of indirect mechanotransduction is the peripheral nervous system. The peripheral nervous system contains mechanosensitive and nociceptive sensory nerves that sense mechanical forces and effect changes on surrounding cells. The skin contains low-threshold mechanoreceptors, such as Meissner's corpuscles, as well as high-threshold nociceptors, which sense both pain and mechanical forces. The activation of nociceptors leads to the release of neuropeptides from afferent sensory nerve endings. The neuropeptides released from afferent sensory nerve endings include calcitonin gene–related peptide (CGRP), substance P (SP), somatostatin, and vasoactive intestinal peptide (VIP), among others. For example, Chin et al[19] used a murine model of skin stretching in which skin was exposed to cyclic or continuous stretch for 4 hours and observed increased expression of both SP and CGRP.

The neuropeptides released by sensory nerve endings act on nearby cells, leading to vasodilation, cytokine production, and increased vascular permeability, among others.[20] Keratinocytes possess receptors for SP, VIP, and CGRP.[21] Activation of the receptor for SP on human and murine keratinocytes induces proliferation and promotes migration of fibroblasts.[22,23]

The release of neuropeptides in response to mechanical forces has also been implicated in inflammation and wound healing.[24] SP and CGRP serve to initiate neurogenic inflammation by acting on mast cells.[21] Binding of SP and CGRP to their receptors on mast cells leads to degranulation and histamine release with subsequent erythema, vasodilation, and capillary leakage. Additional effects of SP include stimulation of the release of tumor necrosis factor 1 from mast cells and interleukins 1 and 4 from keratinocytes and upregulation of intercellular adhesion molecules, which lead to increased binding of immune cells to endothelium and subsequent migration into the tissue. SP also induces endothelial cell proliferation, leading to neovascularization and angiogenesis, which are important for wound healing.[25] Deviations of mechanotransduction leading to prolific inflammation have been implicated in the development of keloids and hypertrophic scars.

Mechanotransduction and Fibroblasts

Mechanical force on wound closure is also known to play a key role in hypertrophic scarring, with dermal fibroblasts being the primary skin cell involved in the formation of hypertrophic scars. Fibroblasts in hypertrophic scars have different biochemical and biophysical properties from their normal skin counterparts, such as an increased proliferation ability and production of collagen and growth factors. Mechanotransduction pathways are involved in the transformation from normal to hypertrophic skin fibroblasts and are triggered by mechanical strain. Multiple studies have looked at the influence of stretch/force magnitude and frequency on fibroblasts and have found that a cell's response to mechanical stress is dependent mainly on magnitude rather than frequency of the strain. Additionally, stretched fibroblasts show increased rates of cell proliferation and are found to orient nearly perpendicular to the direction of the applied strain.[26] A recent publication by Kuang et al[27] further investigated the optimal stretch magnitude for this dermal fibroblast transformation. Interestingly, cell proliferation, as well as expression of growth factor TGF-B and collagen, were highest at 10% strain magnitude compared with 15% and 20%. Mechanotransduction signaling factors such as integrin B1 and P130Cas were also optimized at the 10% strain level.[27]

SURGICAL APPLICATIONS OF THE BIOMECHANICS OF SKIN

Tissue Expansion

Physiologic tissue expansion occurs during rapid growth at puberty, during pregnancy, and at times of rapid weight gain. During both pregnancy and rapid growth, the time interval can be relatively short and skin thinning can occur as evidenced by the striae that sometimes form. Obesity causes an overall increase in skin surface area, but the skin maintains a normal thickness in both the epidermis and dermis with a normal collagen content.[28]

The first clinical application of tissue expansion was published by Neumann[29] in 1957 and then improved on by Radovan.[30] Although it is clinically useful, debate has centered on the biomechanical properties of the expanded skin. Preservation of epidermal thickness during tissue expansion has been verified by several authors.[31,32] The underlying mechanism for the overall increase in skin surface area without thinning of the epidermis is increased epidermal mitotic activity and keratinocyte proliferation.[33–35] The long-term effects of tissue expansion on the dermis are more difficult to discern. Unequivocally, dermal thickness is reduced both during tissue expansion and for an undefined period thereafter. What is not clear, however, is whether eventual restoration of the normal dermis occurs and by what mechanism. Johnson et al[33,36] demonstrated in a porcine model that an increase in surface area of skin occurred during and after tissue expansion but that dermal thinning persisted for 36 weeks after completed expansion (Fig. 3.2). Clinical extrapolation of these data is difficult because the tissue expanders were left in place (Fig. 3.3).

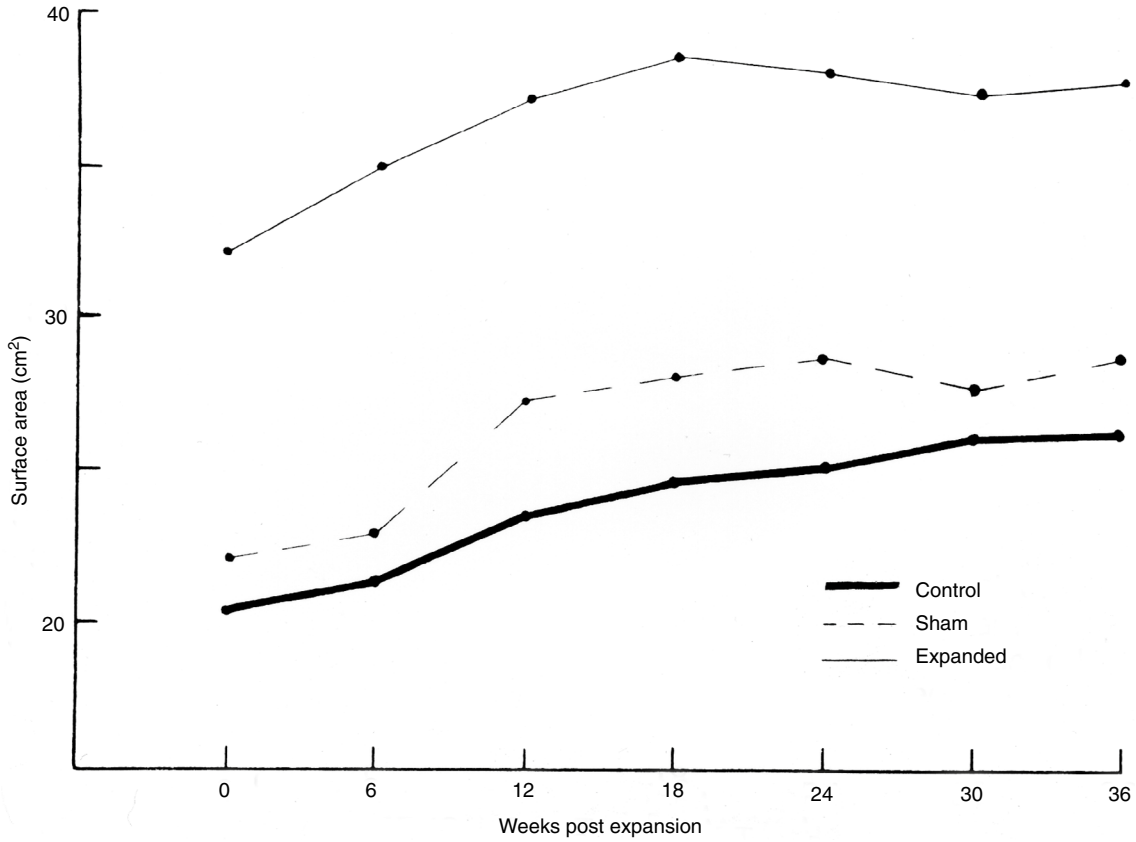

FIG. 3.2 ■ Increase in surface area seen with tissue expansion. Tissue expanders were left implanted during the postexpansion period. (From Johnson PE, Kernahan DA, Bauer BS: Dermal and epidermal response to soft-tissue expansion in the pig. *Plast Reconstr Surg.* 1988;81:391.)

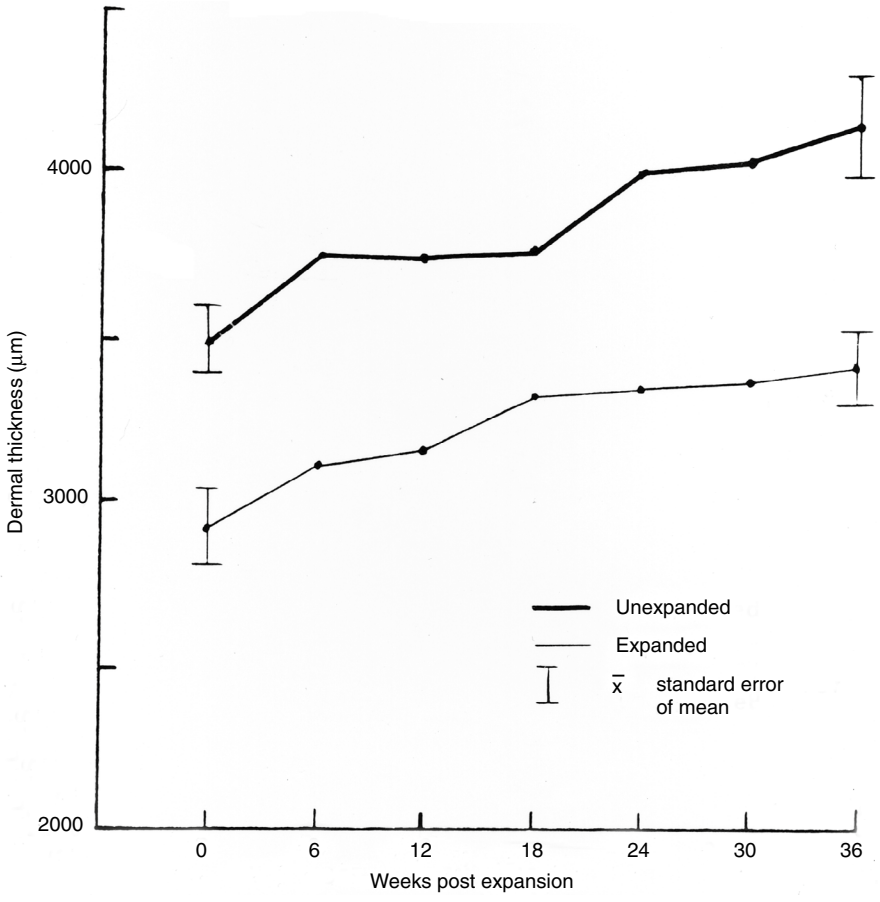

FIG. 3.3 ■ Dermal thickness after tissue expansion. Persistent thinning is noted 36 weeks after expansion. Tissue expanders were left implanted during the postexpansion period. (From Johnson PE, Kernahan DA, Bauer BS: Dermal and epidermal response to soft-tissue expansion in the pig. *Plast Reconstr Surg.* 1988;81:391.)

Dermal compensation in response to tissue expansion appears to be slow compared with the rapid response found in the epidermis. This discrepancy is found during pregnancy but not during chronic obesity, in which both dermal thickness and epidermal thickness are preserved.[28] Expanded skin does demonstrate an increase in vascularity and vasodilation, which is thought to account for the increased mean surviving lengths of expanded skin flaps compared with random skin flaps.[31]

Gibson and Kenedi[7] first suggested that additional tissue for wound closure could be obtained by acutely stretching the skin. The clinical efficacy of intraoperative cyclic loading of skin was thought to derive primarily from the effects of increased undermining.[37] Others, however, have shown that intraoperative tissue expansion increases skin compliance with decreased tension compared with simple undermining.[38]

Wound Tension and Blood Flow

The effect of wound closure tension on blood flow has been studied by comparing tissue survival to wound closure tensions in animal models.[7,39] A quantitative description of the relationship between blood flow and wound closure tension is seen in Fig. 3.4. In this experimental pig model, the investigators created a random skin flap 3 cm wide and 6 cm long. Laser Doppler blood flow measurements were taken at the base of the flap (area 4) and at 2-cm intervals toward the distal tip (area 1). Tension was increased by 50-g increments to maximal tension. This experiment demonstrated that blood flow is inversely proportional to the distance from the base of the flap and that it decreases steadily with increasing tension until a critical value of 200 to 250 g is reached.[40] On the basis of the supporting evidence in Fig. 3.4, it seems

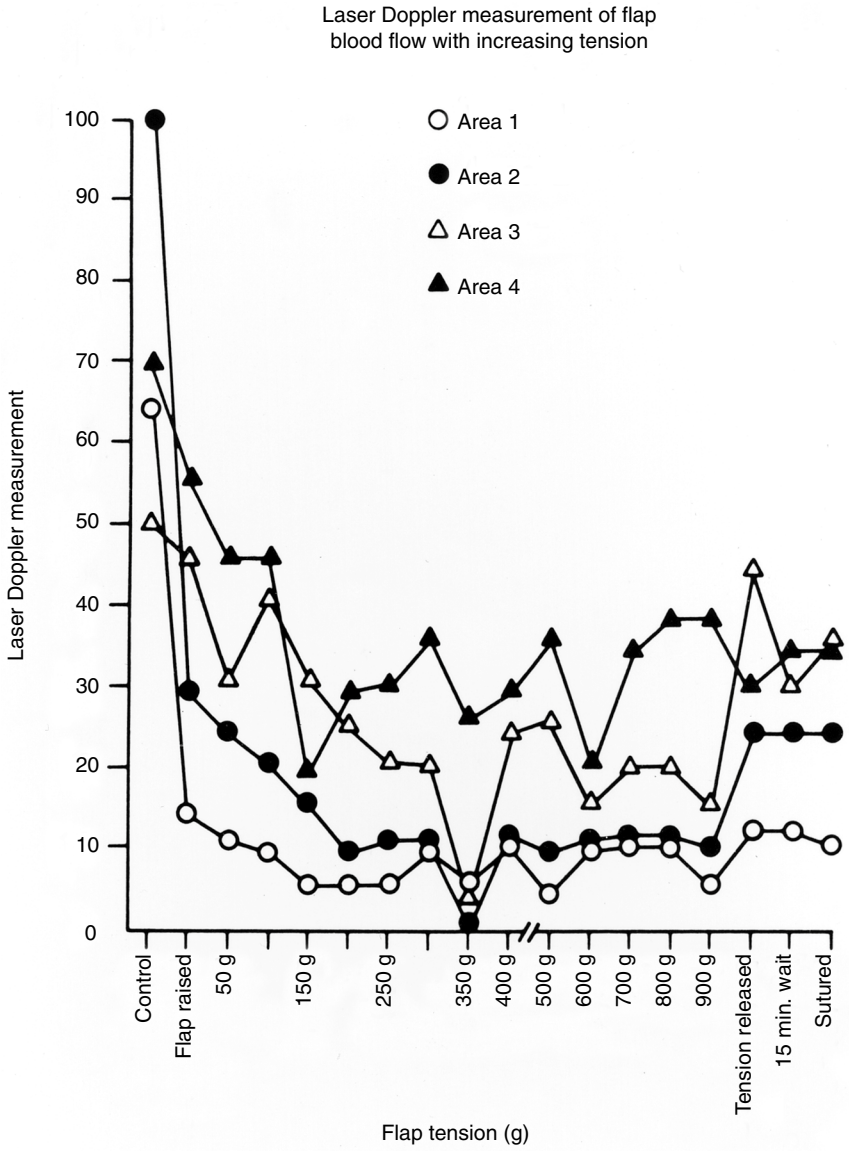

FIG. 3.4 ■ Relationship between tension and blood flow in 3-cm-wide and 6-cm-long random skin flap. Measurements were taken at 2-cm intervals from base of flap (area 4) to distal tip (area 1). Flow decreases steadily until critical value of 200 to 250 g is reached. (From Larrabee WF Jr, Holloway GA Jr, Sutton D: Wound tension and blood flow in skin flaps. *Ann Otol Rhinol Laryngol* 1984;93:114.)