Grabb and Smith's

Plastic Surgery

EIGHTH EDITION






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EDITOR

Wolters Kluwer

Grabb and Smith's Plastic Surgery

Eighth Edition

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Dedication

To the memory of Dr. William C. Grabb

To the Faculty, Residents, and Fellows at the University of Michigan

To Chin-Yin and William

Foreword

It is a distinct privilege for me as the Chief of Plastic Surgery at the University of Michigan to write the Foreword for the 8th Edition of *Grabb and Smith's Plastic Surgery*, edited by Kevin C. Chung, MD, MS. What an honor for Dr. Chung to be able to edit this landmark textbook which has its roots at the University of Michigan where William C. Grabb, MD, served as Professor and Chief of the Section of Plastic Surgery. Dr. Grabb was a consummate clinician, surgeon, educator, and innovator whose legacy has lived on through this book. Dr. Grabb, along with his Co-Editor Dr. Smith, has educated a generation of plastic surgeons, helping to prepare plastic surgery residents for the in-service examination, helping to prepare recent graduates for their written examination, and most importantly, helping plastic surgeons care for patients operatively and nonoperatively. Grabb and Smith has always been a great source of information for plastic surgeons during training and many years thereafter.

The 8th Edition of Grabb and Smith has been designed by Dr. Chung to build on this important legacy of education. Reviewing the Table of Contents will quickly demonstrate to you that the list of authors reads like a "Who's Who in Plastic Surgery." At the same time, the best and brightest young minds in plastic surgery have also contributed to the book. It is this mix of authors that provides a healthy diversity of opinion, viewpoint, and presentation style, which will undoubtedly enhance the value of the material to all readers. The topics may be similar to prior editions of Grabb and Smith, but the chapters have all been completely rewritten. In fact, some of the authors who have contributed chapters to Grabb and Smith in the past have been asked to write new chapters, on different topics, to keep the material fresh, interesting, contemporary, and educational. Additionally, there are many new authors who have not previously contributed to this book, ensuring that the content is current, presented in a way that is relevant to the modern day learner, and yet still maintains the high quality of information necessary to be valuable to all plastic surgeons.

The world around us is changing and the only thing that is constant is change. If we are not adapting to this changing world, we will be falling behind. As a result, the 8th Edition has been completely redesigned to optimize its value and to ensure that all of the critical elements of our rapidly changing specialty are captured. The chapters are written in a consistent style to provide the basic knowledge, fundamental principles, and crucial information needed to become a plastic surgeon and to assist those pursuing lifelong learning. The book is formatted in such a way that the information can be gathered quickly through clear and concise writing, visually pleasing full color figures, photographs, expertly crafted decision algorithms, tables, and flowcharts. The days of reading long chapters have gone. The information is provided in a style well suited for in-service examination or written board exam prepara_indentedtion. More importantly, the information is provided in a style that is well suited for plastic surgeons as they provide high-quality, thoughtful, and compassionate care for their patients.

The pedagogy of the book has been specifically designed by Dr. Chung with the needs and interests of the plastic surgery resident, young practicing plastic surgeon, or the plastic surgeon who needs rapid access to information "at point of care" with a patient. Each chapter begins with 5 to 7 key points, which have been carefully selected by the authors to be the most critical elements of the chapter. An in-depth discussion of each of these bullet points is performed in the body of the chapter where the learner can find as much depth and breadth of information as they desire. At the conclusion of each chapter, there are 5 to 10 multiple-choice questions, which have been designed to reinforce the learning that has occurred throughout the chapter. This chapter construction follows a very traditional and highly successful model of learning: (1) Tell them what you are going to teach them; (2) Teach them; (3) Tell them what you taught them; and (4) Test them on their new knowledge. This approach has worked for decades in the classroom and works very nicely here as well. Additionally, each question includes a detailed description of why the correct answer is correct and even more importantly, why the incorrect answer is incorrect. Lastly, for those who wish to collect the classic articles in plastic surgery, each chapter includes 5 to 10 classic articles, which have been appropriately cited, highlighted, and briefly annotated for historical perspective.

It is such a pleasure to have the 8th Edition of *Grabb and Smith's Plastic Surgery* return home to the University of Michigan with Kevin C. Chung, MD, MS, as the Editor, and so many of our faculty as contributing authors. The book has been expertly designed, beautifully executed, and will be an outstanding addition to any library. It is written in a clear and concise way with easy access to all information. At the same time, the book is sufficiently comprehensive to provide lifelong learning from the very infancy of someone's plastic surgery career to their mature practice. Most of all, this book will help to make us all better physicians and surgeons. I credit the 1st Edition of *Grabb and Smith's Plastic Surgery* for teaching me what I needed to know to be a good plastic and reconstructive surgeon. I am sure many will be able to say the same thing about the 8th Edition of this landmark book.

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Preface

I am honored and most excited to present to you the 8th edition of this classic textbook in plastic surgery. With any historic textbook, at a certain time the content needs complete rejuvenation. In celebration of this 8th edition, I took the liberty of inviting new authors to rewrite every chapter to reflect the innovative spirit of plastic surgery. The authors are some of the best in our specialty, who impart knowledge in a clear and succinct style that is the hallmark of this book. I have also included additional content by presenting annotated classic articles so that the reader can refer to these foundation papers to gain even more insight. Furthermore, the authors have shared select questions and discussed the answer choices in an interactive format.

This edition is illustrated richly with artistic drawings to highlight the anatomy and surgical approaches. This para_indentedbook is not meant to be an encyclopedic para_indentedbook, but serves as an essential reference by striving to "get to the facts" in this era of rapid dissemination of information. As I traveled in the United States and around the world, I am struck by how much this para_indentedbook is revered by trainees and senior surgeons during their formative years of becoming a plastic surgeon. The Grabb and Smith para_indentedbook strives to bind the plastic surgery family all over the world, even in remote regions where plastic surgery is not yet recognized as a specialty.

I want to acknowledge all of the authors who understood the gravity and honor of contributing to this classic para_indentedbook. They have done a magnificent job in distilling the essence of plastic surgery, for which I am grateful. I want to recognize Brian Brown, the publisher of Grabb and Smith, for his confidence in me after serving as a section editor for many years. I appreciate my team at the University of Michigan, Jennifer Sterbenz and You Jeong Kim, who toiled intensely to help me and our authors ensure timely delivery of the chapters and a quality product. Finally, I would like to thank Grace Caputo, who was relentless in her attention to detail, and her dedication to deliver this para_indentedbook one year early.

I welcome Grabb and Smith back to the University of Michigan, for Dr. Grabb was the second chairman of plastic surgery at our historic program. Through the legacy of Dr. Grabb and his trainees, they laid the foundation for our current success. Lastly, I should thank all of the readers of this para_indentedbook. Just because one has purchased previous editions does not mean that this edition is no longer worthwhile. This invigorated 8th edition will certainly set the standard in the publishing world for its educational excellence in synthesizing the encyclopedic plastic surgery specialty into a single para_indentedbook. I am grateful and proud to present to you the 8th Edition of *Grabb and Smith's Plastic Surgery*.

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Contents

PART I

Principles, Techniques, and Basic Science

CHAPTER 1

Fundamental Principles of Plastic Surgery

Theodore A. Kung and Kevin C. Chung

Key Points

- Plastic surgery is a diverse surgical specialty and its practice is guided by a set of fundamental principles.
- There is an inexorable connection between cosmetic surgery and reconstruction surgery because every plastic surgery operation aims to restore both form and function.
- Elective surgeries should be pursued only after considering whether the benefits of surgery will outweigh the risks.
- Outcomes in plastic surgery can be enhanced by addressing modifiable patient factors, adequately preparing wounds prior to reconstruction, replacing lost structures with tissues of similar quality, ensuring optimal vascularity, minimizing donor site morbidity, and deliberately protecting the surgical site.
- A plastic surgeon is always prepared to confront complications with a series of surgical backup plans.
- Plastic surgeons must continually innovate new solutions to clinical problems and will remain at the vanguard of surgical innovation.

Plastic surgery is an incredibly diverse specialty that is challenging to define because its scope cannot simply be characterized by patient age, gender, organ system, or pathology. The purview of plastic surgery extends from neonatal to end-of-life care and is inclusive of a myriad of conditions that affect every single area of the human body. Plastic surgeons possess unique and versatile skills for reconstructing defects relating to cancer extirpation, cosmetically enhancing normal anatomy, salvaging limbs after trauma, rehabilitating burn patients, ameliorating childhood deformities, and performing autotransplantation as well as allotransplantation. This expertise is also critical in devising creative solutions to a variety of problems faced by other physicians, and for this reason, plastic surgeons are frequently consulted by their colleagues in other specialties. How is it possible for one surgical specialty to encompass this enormous breadth and depth of practice?

The unifying trait of all plastic surgeons is a comprehensive understanding of a set of important fundamental principles. Every plastic surgeon abides by these principles to successfully execute the many complex assessments, judgment calls, and technical decisions in the daily practice of plastic surgery. Therefore, the specialty of plastic surgery is exceptional because it is distinguished not by its association to a particular patient population or anatomic region, but by a dedication to imperative principles that enable plastic surgeons to provide effective and individualized care. These principles were conceptualized through centuries of plastic surgery evolution and formalized in recent history by Gillies and Millard, who outlined a collection of philosophical yet practical principles in their text *The Principles and Art of Plastic Surgery*. [1] Years later, Millard published an expanded set of tenets in *Principalization of Plastic Surgery*. [2] This chapter modernizes and expounds on 10 of the most essential fundamental principles of plastic surgery and provides relevant examples of how plastic surgeons utilize these principles in a wide range of clinical scenarios.

Principle I: Make an Informed Decision to Operate or Not Operate

Some types of plastic surgery are mandatory. A wound resulting from resection of a sarcoma with exposed bone requires a reconstructive operation that provides soft tissue coverage over the defect durable enough to withstand the infliction of adjuvant radiation therapy. However, in many situations, the plastic surgeon must make an informed decision whether to perform an operation or not based on a thorough evaluation of the potential benefits against the potential risks. Although this is conspicuously germane to cosmetic surgery, the same thought process is necessary for reconstructive surgery. For example, a large but clean traumatic wound on a patient's thigh could be treated reasonably with one of several options, from nonsurgical strategies such as dressing changes to surgical intervention such as local tissue rearrangement. A multitude of factors must be carefully pondered to select the most appropriate treatment. If dressing changes are used, the wound may be healed eventually but at what burden to the patient? Does the patient have the patience or ability to perform satisfactory dressing changes? Would a definitive surgery result in a healed wound more efficiently? How feasible is the surgery, and what is the likelihood of specific complications? Ultimately, the surgeon must decide if the benefits of surgery will outweigh the risks and predict that the expected outcomes of surgery will enhance the patient's overall health status.

This determination is made more difficult because of the inherently subjective nature of plastic surgery outcomes. Success in plastic surgery is not measured solely on binary scales, such as patency versus occlusion or union versus nonunion. Instead, success is also subjectively gauged by patient satisfaction and is influenced by patient expectations. [3] Consider a consultation between a plastic surgeon and a woman interested in postmastectomy breast reconstruction, an elective operation with substantial psychosocial advantages. In a relatively short amount of time, the plastic surgeon needs to educate the patient regarding the available surgical choices for breast reconstruction and provide an individualized assessment of her candidacy for each option. To guide the patient to the most suitable decision for her, the surgeon must shrewdly evaluate the patient's expectations and her level of understanding of the desired reconstructive surgery. Are her expectations consistent with what is possible from a technical standpoint? Does the patient seem ready to make this decision amidst the other stresses associated with a breast cancer diagnosis? Does the patient understand the possible setbacks that may occur with the surgery? The answers to these types of questions will greatly affect the patient's perception of the success of reconstruction and her reported satisfaction with both the surgery and the plastic surgeon.

Principle II: Optimize Modifiable Patient Factors

Deliberate identification and management of patient risk factors will decrease the chances of complications and increase the likelihood of successful surgical outcomes. For example, smoking is a commonly encountered modifiable risk factor. Nearly 20% of Americans are smokers and cigarette smoking remains the leading cause of preventable disease and death in the United States. [4,5] The noxious components of cigarette smoke are known to cause vasoconstriction, induce endothelial injury, cause thrombogenesis, diminish oxygen transport, and hinder cellular repair mechanisms. [6] Together, these detrimental processes work synergistically to impair wound healing and will directly confer additional risk to plastic surgery patients. Other modifiable medical risk factors that also exacerbate poor wound healing include uncontrolled diabetes, obesity, infection, steroid use, certain homeopathic medications, and malnutrition. [7] These treatable comorbidities should be recognized during preoperative screening and sufficiently addressed prior to any operation. Social risk factors should also be carefully considered during the preoperative evaluation. After surgery, patients will frequently need assistance with their activities of daily living and comply with strict restrictions. The plastic surgeon should inquire about the social support available to the patient and ensure that the patient's postoperative safety is entrusted to either family members or a rehabilitation center.

The importance of risk factor optimization is demonstrated in the care of body contouring patients. During the preoperative consultation, a thorough history is taken to solicit all modifiable risk factors that would impair the patient's ability to heal long incisions and wide dissection planes. [8] For a majority of plastic surgeons, smoking is an absolute contraindication to any body contouring operation. Cessation of smoking for at least 4 weeks and confirmation with a urine cotinine test is a common requirement before surgery is scheduled. Frequently, collaboration with the patient's primary care physician is critical in correcting hyperglycemia, anemia, or vitamin deficiencies. Patients who would benefit from additional weight loss may be referred to a nutritionist or a bariatric surgeon. After the operation, the patient will have considerable activity restrictions and will need to care for the wounds; therefore, a detailed preoperative discussion with the patient about postoperative care and limitations will serve to set expectations and to establish a social support system for the patient.

Principle III: Perform Adequate Debridement Prior to Reconstruction

Debridement is performed to physically remove any barriers to tissue growth, such as infection, biofilm, and senescent cells. [9] The plastic surgeon may choose one of many forms of debridement, from dressing changes to operative excision of the wound, but the critical concept is that the debridement must be adequate to remove all elements hindering wound healing. In many instances, this objective is accomplished only after the wound is debrided serially in the operating room. Chronic wounds are often associated with some degree of necrotic tissue that must be sharply and completely debrided away before definitive reconstruction can be performed. Failure of reconstruction is often attributed to inadequate debridement of the wound. Although *adequate debridement* is usually a term associated with the management of chronic wounds, this essential principle also applies to acute wounds. Acute traumatic wounds, such as open fractures of the lower extremity or lacerations from bite injury, are notoriously contaminated, and adequate debridement in this setting is also critical to the success of reconstruction. In fact, this principle of adequate debridement is so relevant to all forms of plastic surgery that it may even be applied to clean surgical wounds. For example, during reduction mammoplasty, there is often a widespread accumulation of devitalized globules of fat and clots scattered throughout the surgical field. Prior to closure, meticulous removal of this biologic debris facilitates wound healing by decreasing the risks of fat necrosis and infection.

Certain situations will complicate the plastic surgeon's ability to perform adequate debridement. For example, in some traumatic wounds, exposed orthopedic hardware cannot be removed because doing so would result in unacceptable fracture instability. [10] In these challenging cases, debridement serves to decrease the microbial burden of the wound, and deep tissue cultures are taken to help guide antimicrobial therapy. However, the persistent presence of contaminated material will be a major risk factor for infection, and therefore the patient may need suppressive antibiotic therapy until the hardware can be removed. This necessary adaptation of the principle of adequate debridement is also exemplified in the treatment of pressure ulcers with underlying osteomyelitis. These chronic wounds exhibit many deleterious factors that impede wound healing. [11] The first step in surgical treatment is completely excising the soft tissue bursa surrounding the wound. If the osteomyelitis is limited to a small focus of bone at the base of the pressure ulcer, it is possible to remove the area of bone infection entirely during debridement. However, if the osteomyelitis is extensive, complete resection of this bone is not feasible, and the patient will often need suppressive antibiotic therapy guided by intraoperative bone cultures. In this situation, aggressive excision of the bursa is still beneficial because this promotes healing of the soft tissues after surgery and results in a smaller, cleaner, and more manageable chronic wound.

Principle IV: If Possible, Replace Like With Like; If Not Possible, Create It

One of the most famous plastic surgery principles is that lost tissues should be replaced in kind. The plastic surgeon examines the defect carefully and determines the best donor tissues necessary to optimally achieve both a durable reconstruction and an optimal aesthetic outcome. For instance, when primary skin closure is not possible after excision of a cutaneous tumor from an upper eyelid, a frequently chosen donor site is full-thickness skin from the opposite upper eyelid. [12] This option is elegant because it replaces the missing tissue with tissue of the same thickness, color match, pliability, and elasticity. In addition, donor site morbidity is acceptably low when relatively excess skin from one eyelid is used to reconstruct the other eyelid. When such an ideal donor site is unavailable, the next most similar tissue substitute is selected; in this example, skin for eyelid reconstruction can be harvested from postauricular skin or supraclavicular skin. This principle can also be applied to substantially more challenging wounds. An extensive mandibular tumor may necessitate the removal of bone, muscle, mucosa, and skin, and successful reconstruction is predicated on the replacement of these tissues with appropriately similar donor tissues. In these complex cases, reconstruction often requires the use of free flaps that are transferred to the defect, such as a fibula bone flap with associated skin based on the peroneal vascular system. [13]

In some cases, no suitable donor sites exist, and innovative strategies must be employed to create sufficient replacement tissues of similar quality. One example of this is the use of tissue expanders to induce growth of tissues through cellular proliferation. [14] Tissue expansion has revolutionized the treatment of various conditions and given plastic surgeons another tool to better replace *like with like* in clinical scenarios that were previously impossible because of the severity of tissue deficiency. Tissue expanders now serve a critical role in the replacement of hair-bearing skin for large scalp defects, the creation of additional abdominal wall tissue for the closure of large hernias, the expansion of mastectomy skin for breast reconstruction, and the resurfacing of skin affected by giant congenital nevi. This concept of cellular response to force is also the mechanism behind distraction osteogenesis in craniofacial surgery. [15] This technique leverages the natural processes of fracture healing to yield outcomes superior to those achievable through other means such as nonvascularized bone grafting or free tissue transfer. For example, distraction osteogenesis is an excellent strategy for treating micrognathia in children with Pierre Robin sequence. [16] Internal or external distractors are placed surgically around the site of mandibular osteotomies, and a tensile force is slowly delivered to gradually elongate the intervening callus. One major advantage of distraction osteogenesis is that during the process of new bone formation, the overlying soft tissue envelope is also expanded incrementally. This reduces the constrictive effects of the soft tissue on the growing bone and consequently results in a stable reconstruction that is less prone to relapse. These powerful techniques to grow living structures outside of the laboratory setting have completely transformed the plastic surgeon’s ability to replace missing tissues and are often principal options for many complex clinical problems.

Principle V: Optimize Vascularity at Every Opportunity

Plastic surgeons are obsessed with blood supply. Vascularity is paramount to tissue viability and therefore to the success of healing. The plastic surgeon must possess an unparalleled comprehension of the blood supply to various types of tissues and methods to preserve this blood supply during surgery. For example, knowledge of the vastness of the subdermal plexus allows a plastic surgeon to reliably raise thin flaps of skin during a facelift operation. In reconstructive surgery, donor tissues must remain well-vascularized to transfer from one location to another. A detailed understanding of the vascular anatomy of these flaps permits their use for definitive closure of any wound. When vascularity to a surgical site is insufficient, the plastic surgeon must strive to improve it. For instance, surgery may be postponed to await smoking cessation or time may be given for other specialists to help optimize blood flow. An illustration of the latter is when a patient with arterial insufficiency and a chronic lower extremity wound is referred to a vascular surgeon for revascularization prior to surgical treatment of the wound. Vascularity of a particular flap may also be enhanced by performing a delay procedure, which is a staged operation whereby the plastic surgeon partially raises the flap and then waits 1 to 2 weeks before fully elevating the flap for reconstruction. A delay period allows choke vessels to physiologically dilate within the flap and results in greater flap reliability. [17]

This respect for blood supply is also evident in many intraoperative decisions that are made by plastic surgeons. Judicious placement of incisions, especially in the context of unfavorable previous incisions, requires a careful consideration of blood supply. Additionally, at many points during an operation, the plastic surgeon will tailor numerous surgical techniques to maximize vascularity. For example, when a local flap such as a V-Y flap or a rotational flap is used for closure of a wound, minimal undermining is performed during flap elevation to reduce disruption of the flap's underlying blood supply. Any sizable perforating vessels that are encountered during dissection of these local flaps are deliberately preserved if possible. During flap inset, pickups and retractors are handled thoughtfully to prevent iatrogenic tissue injury, and undue tension of the closure is avoided to minimize tissue ischemia. Even the selection of sutures and suturing technique is weighed against the effects on vascularity. For instance, placement of too many deep dermal sutures may cause relative ischemia of the edge of a cutaneous flap, and the choice of horizontal mattress suturing may lead to more ischemia compared with vertical mattress suturing. Each of these intraoperative decisions may influence the quality of the blood supply to the closure and may make a meaningful difference in the functional or cosmetic outcome of the surgery.

Principle VI: Preserve Form and Function

Every plastic surgery operation seeks to restore and preserve form and function. In many instances, the goals of surgery are both cosmetic and reconstructive. Patients with excess upper eyelid skin, for example, may describe dissatisfaction with their appearance as well as visual field deficits. During the preoperative consultation, the plastic surgeon must establish that the objectives of upper lid blepharoplasty are to both rejuvenate the upper eyelids and expand the visual field. A more challenging consideration of form and function occurs in children presenting with congenital facial nerve paralysis. In these patients, abnormalities of the facial nerve result in severe facial asymmetry that leads to devastating psychological consequences such as social isolation and difficulties with eating, speech articulation, emotional expression, and control of saliva. Frequently, the optimal solution for these cases is facial reanimation using a microsurgical transfer of an innervated muscle. [18] This reconstruction elevates the corner of the mouth and nasal ala on the paralyzed side to enhance resting facial symmetry and improve the dynamics of mastication, speech, and oral competence. Furthermore, because the muscle is innervated by a functional donor nerve at the recipient site, this operation can achieve animation of the paralyzed face, and in many instances, continued rehabilitation will result in spontaneous smiling. [19]

In some situations, restoration of form and function is accomplished through a surgical solution that replaces multiple tissue deficiencies. An illustrative example of this is reconstruction after pelvic exenteration for advanced colorectal cancer. [20] Removal of organs such as the bladder and rectum will result in a void in the pelvis, and occasionally, the extent of tumor invasion mandates resection of other structures such as the vagina and perianal skin. The goals of reconstruction in these cases are to recreate normal anatomy, obliterate dead spaces within the pelvis, and supply additional vascularity to a surgical site that often is subject to neoadjuvant radiation. One exceptionally suitable choice that fulfills many of these reconstructive needs is the oblique rectus abdominis myocutaneous (ORAM) flap. [21] The ORAM flap has long reach for a pedicled flap, comprises a large amount of soft tissue bulk, and possesses a highly reliable blood supply. Furthermore, the flap is capable of supporting a large skin paddle that can be used for resurfacing vaginal defects as well as perianal skin deficits. With proper surgical planning, the ORAM flap can achieve excellent form and function by filling the pelvic dead space with vascularized tissue after tumor resection, providing sufficient lining for vaginal reconstruction, and decreasing the tension of closure in the perineum to optimize wound healing.

Principle VII: Minimize Donor Site Morbidity

When donor tissues are required, the plastic surgeon must focus on minimizing the functional and cosmetic sacrifices to the patient. Each operation already possesses inherent risks relating to the surgical site, such as hematoma, infection, or abnormal scarring. The donor site adds an additional anatomic area where complications may arise, and the plastic surgeon must weigh the possibility of donor site morbidity against the benefits of the use of that tissue for reconstruction. Often, several suitable donor sites exist, and a surgeon's ultimate decision will be based upon careful consideration of the potential complications with each site. For example, during a rhinoplasty operation, structural support can be augmented by performing autologous cartilage grafting to the nasal framework. [22] Cartilage grafts can be harvested from the nasal septum, from the conchal bowl of the ear, or from the cartilaginous portion of a rib. The nasal septum would be an ideal donor site if septoplasty is also being performed, but use of this cartilage may cause further destabilization of the nasal framework and has a small risk of septal perforation. Harvest of conchal cartilage can provide adequate grafting material but may be complicated by hematoma, keloid formation, or ear asymmetry. The rib donor site offers an abundance of high-quality cartilage, but its indications must warrant the additional scar and added potential for pneumothorax. Ultimately, the plastic surgeon must choose the most appropriate donor site for reconstruction and justify the unique risks associated with that donor site.

To reduce donor site morbidity, plastic surgeons avoid unnecessary sacrifice of important adjacent anatomic structures. This focus on preservation of function during the harvest of donor tissues contributed to the advent of perforator flaps. For example, breast reconstruction using transverse rectus abdominis myocutaneous flaps commonly results in considerable abdominal wall morbidity, including bulges, hernias, and the need for mesh placement. [23] This morbidity is directly related to the removal of one or both rectus abdominis muscles from their native position, which weakens core strength and the integrity of the anterior abdominal wall. In contrast, the use of deep inferior epigastric perforator flaps for breast reconstruction is associated with lower morbidity to the abdominal donor site. During harvest of a deep inferior epigastric perforator flap, the perforating vessels supplying the skin and fat overlying the abdominal wall are meticulously dissected out of the rectus abdominis muscle, and every effort is made to maintain the continuity of the muscle. Segmental nerves are identified and protected whenever possible to preserve innervation to the rectus abdominis muscle, and a minimal amount of fascia is taken to reduce the tension of fascial closure. A continued ambition to limit donor site morbidity and extensive recent experience with perforator flap techniques have now led to the widespread use of many other workhorse perforator flaps for reconstruction, such as the anterolateral thigh (ALT) flap, the superior gluteal artery perforator flap, the thoracodorsal artery perforator flap, and the internal mammary artery perforator flap. [24]

Principle VIII: Protect the Surgical Site Postoperatively

In plastic surgery, an operation cannot be deemed fully successful at the time of its completion; instead, this evaluation can only be made several weeks to months after the operation. This interval allows for preliminary healing to occur, subsidence of postsurgical swelling, initiation of rehabilitation therapy, and management of any complications. During this critical time, the surgical site must be protected diligently to facilitate recovery and to prevent injury to the healing tissues. The plastic surgeon must actively counsel patients to follow strict activity restrictions and help patients understand the rationale behind the necessary postoperative protocols. Strenuous activity, for example, may increase the likelihood of bleeding, seroma, or wound dehiscence and should be avoided for a period of time that commensurates with the magnitude of the operation and its associated risks. Clear postoperative instructions are provided to patients and may include customized information on various relevant issues such as wound care, splinting, compression garments, weight-bearing status, or limb elevation. Regular follow-up visits are also necessary to ensure that wounds are healing appropriately and to recognize the development of any complications. All of these efforts are directed at protecting the surgical site. Failure to do so may jeopardize the final outcome.

Complex lower extremity reconstruction exemplifies the importance of this principle. [25] An open tibial fracture with a large soft-tissue defect can be reconstructed with a free muscle flap and skin grafting to provide durable coverage of the underlying bone and orthopedic hardware. However, postoperative protection of the surgical site is as influential to successful salvage of the limb as the reconstructive surgery itself. [26] After surgery, the free flap is safeguarded from compression, especially when the muscle extends posteriorly where it would be crushed by the weight of the limb without proper elevation. This can be done using pillows, blankets, or foam; alternatively, if the patient has an external fixator in place, attachments can be added to prop up the leg much like the kickstand of a bicycle. Limb elevation also opposes venous congestion and facilitates the resolution of postsurgical edema. Immobilization is also a critical component of the postoperative protocol because it safeguards the reconstruction from any shearing forces that might disrupt either the muscle or the skin graft. Plaster or plastic splints are useful adjuncts to aid in immobilization of joints after surgery. Although each clinical scenario is unique, soft tissues generally require several weeks of protected healing time before being able to sustain any significant challenges. Therefore, once this initial healing period has occurred, a gradual and supervised release of these restrictions is commenced until complete return to normal activities is possible.

Principle IX: Have a Backup Plan (and a Backup Plan for THAT Backup Plan)

Complications will always arise, and the prepared plastic surgeon will be ready with multiple contingency plans. Most commonly, complications such as wound infection, marginal flap necrosis, or dehiscence can be successfully managed with straightforward and standardized treatment protocols. However, occasionally, the first operative plan fails to adequately address the goals of surgery, and a new plan is necessary. In reconstructive surgery, an old paradigm known as the *reconstructive ladder* advocates for a linear, stepwise approach to surgical problems whereby less-complicated surgical techniques are initially attempted, and progression up the ladder to more complex strategies is pursued only when needed. More recently, significant advancements in the field of plastic surgery have led to a shift away from this paradigm in favor of a treatment algorithm that encourages selection of the most definitive method for reconstruction even if it means picking a more complex one first. [27] If a backup plan is necessary, the plastic surgeon may either choose an alternative surgical plan from another rung of the reconstructive ladder or decide to try the previous plan again. Despite the antiquated adage in plastic surgery that instructs: "Make sure that plan B is not the same as plan A," the same approach may in fact be attempted if careful consideration is given to the reasons why the prior surgery resulted in a failed reconstruction. If these factors can be readily identified and appropriately corrected, the same operative strategy may be performed another time and a successful outcome can be expected.

Reconstruction of upper extremity defects frequently exemplifies this fundamental principle. For example, a dorsal hand wound from a full-thickness burn injury with several exposed extensor tendons and metacarpal bones can be reconstructed by numerous techniques. [28] Although less-sophisticated approaches such as dermal substitutes and skin grafting may ultimately result in a closed wound, these options would not provide sufficiently durable soft tissue coverage over gliding tendons and therefore would result in unacceptable hand stiffness. A superior first choice for reconstruction might be a reverse radial forearm flap from the ipsilateral extremity or another regional flap. Should the plastic surgeon encounter insurmountable complications with the reverse radial forearm flap, a reasonable backup plan might entail the use of a free gracilis muscle flap. If the free flap reconstruction fails, the next backup option might be another free tissue transfer as long as the problems that led to loss of the previous flap are elucidated and the surgeon is confident that these issues can be sufficiently overcome prior to performing another free flap. Alternatively, the plastic surgeon might choose to reconstruct the dorsal hand wound with a pedicled groin flap. This fundamental principle of having a series of sensible backup plans guides the plastic surgeon to prepare for any number of potential setbacks during the reconstructive process and serves to optimize the chances of successful surgical outcomes.

Principle X: Innovate New Solutions to Old Problems

Innovation drives the practice and progress of plastic surgery. Plastic surgeons possess an inherent ambition to improve surgical approaches to existing clinical problems. For this reason, rarely is the exact same operation ever performed twice. Each surgery is individualized according to the clinical situation and specific patient needs. Thus, the plastic surgeon must strive to tailor every operation and often makes numerous adjustments to the accepted *standard techniques*. For example, a cleft lip repair for one child is never precisely the same as that for another child. [29] Although the basic tenets are constant, such as restoring continuity of the orbicularis oris and re-establishing labial subunits, the surgeon must remain flexible during the operation and modify the repair technique to account for the unique abnormalities present in each patient.

This spirit of adaptation and creative problem-solving is a large part of what distinguishes plastic surgery from other surgical disciplines and contributes to the constant evolution of the specialty. Over the course of the last century, plastic surgery has undergone enormous cycles of change that has resulted in significant paradigm shifts in patient care. One of the most profound examples is the advent of microsurgery. Previously, wounds resulting from tumor extirpation, infection, or trauma were reconstructed with either devascularized grafts that were often too thin to provide reliable soft tissue coverage or pedicle flaps that were frequently limited in reach or size. With the development of the operating microscope in the 1960s and a concomitant surge in our understanding of the vascular anatomy of muscle and myocutaneous flaps, [30-33] plastic surgery experienced an explosion of innovation and growth. The ability to raise and transfer a variety of tissue types as free flaps opened an entire realm of reconstructive solutions for problems that were once deemed impossible. For instance, distal third injuries of the lower extremity that commonly resulted in amputation could now be reconstructed with a free flap. Free tissue transfer quickly became the primary reconstructive choice after head and neck cancer resection. Hand surgery was completely revolutionized by the ability to replant amputated parts and reconstruct challenging defects of the upper extremity through the use of free flaps consisting of a variety of tissues including skin, muscle, fascia, and bone. More recently, microsurgical techniques have made vascularized composite allotransplantation a reality, and replacement of an entire complex anatomic structure such as a face, hand, or abdominal wall is now being performed at multiple centers around the world. [34-36]

Plastic surgery will no doubt continue to be at the vanguard of innovating solutions to surgical problems. Plastic surgeons are spearheading ongoing research and development in a variety of emerging fields that are gaining increasing momentum, including tissue engineering, [37] transplant immunosuppression, [38] supermicrosurgery, [39] prosthetic interfaces, [40] perforator flap surgery, [41] and robotic surgery. [42] The ensuing chapters of this textbook will illustrate the persistent evolution of plastic surgery and demonstrate how numerous critical innovations in the field have completely transformed the care of our patients. Additionally, while each chapter will focus on a different aspect of plastic surgery, the reader will appreciate frequent allusions to the themes presented in this introduction and understand that plastic surgery is truly a specialty characterized by a devotion to a set of fundamental principles that guides its practice.

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Questions

1. A 55-year-old woman with long-standing bilateral symptomatic macromastia presents to the office to discuss breast reduction surgery. Her medical history is significant for hypertension and obesity with a body mass index of 39. During the consultation, the plastic surgeon notices a faint smell of cigarette smoke in the room. The patient states she quit smoking 6 months ago but her husband still smokes in the house. What course of action will result in the most favorable patient outcomes?
    a. Perform the surgery after thoroughly discussing the risks of the operation.
    b. Refer the patient to another plastic surgeon.
    c. Defer the operation until modifiable risk factors are addressed.
    d. Refuse to perform the operation because it will not benefit the patient.
    e. Perform the surgery but remove as little breast tissue as possible.

2. A 45-year-old man with vascular disease presents with a nonhealing wound on the medial ankle. Workup is negative for underlying infection, and a reverse sural artery flap is planned for reconstruction to provide durable soft tissue coverage over the wound. The plastic surgeon is concerned about the blood supply to this flap. What can be done to optimize vascularity?
    a. Keep the foot in a dependent position after reconstruction.
    b. Perform a delay operation first and then the definitive operation 2 weeks later.
    c. Apply nitroglycerin ointment to the proximal lower extremity to dilate the vasculature.
    d. Apply compression wraps to the lower extremity after the flap is inset.
    e. Place the patient on a high-protein diet to improve preoperative nutrition.

3. A 65-year-old woman undergoes abdominoperineal resection followed by reconstruction using a pedicled ORAM flap. On postoperative day 1, the plastic surgeon examines the skin paddle of the ORAM flap within the perineum and notes that the flap is mottled with several areas of blistering. It is noted that the patient has been in an upright sitting position since she arrived to the floor after her operation. Which fundamental plastic surgery principle was most likely not heeded?
    a. Make an informed decision to operate or not operate.
    b. Perform adequate debridement prior to reconstruction.
    c. If possible, replace like with like.
    d. Protect the surgical site postoperatively.
    e. Have a backup plan.

4. An 8-year-old boy presents with a 5 cm × 4 cm full-thickness burn of the plantar foot. After adequate debridement and dressing changes, the wound is now ready for reconstruction. There is healthy granulation tissue throughout, and there are no exposed critical structures such as bone or tendon. Which of the following reconstructive options is the best choice for this patient?
    a. Letting the wound heal secondarily with dressing changes
    b. Free ALT flap
    c. Applying a negative pressure device to expedite secondary healing
    d. Split-thickness skin from the thigh
    e. Full-thickness skin from the lower abdomen

5. A 50-year-old woman undergoes excision of a large squamous cell carcinoma from the scalp. The resultant defect is approximately 40% of the total area of the hair-bearing scalp. A temporary dressing is placed on the wound until final negative margins are confirmed by pathology. The open wound is now ready for reconstruction. There is no exposed calvarium, and the wound consists of healthy granulation tissue and galea aponeurotica. The patient desires a reconstruction that will optimize the appearance of the scalp. Which of the following reconstructive options is the best choice

for this patient?

a. Elevate multiple rotation-advancement flaps from the remaining scalp to close the wound with one operation.

b. Apply a negative pressure device now and then perform split-thickness skin grafting in a separate operation.

c. Perform a free latissimus dorsi muscle flap with split-thickness skin grafting.

d. Close the wound with a split-thickness skin graft now and then place tissue expanders in a separate operation to expand the remaining hair-bearing scalp.

e. Apply a dermal substitute now, and then perform full-thickness skin grafting in a separate operation.

1. **Answer: c.** The plastic surgeon should make an informed decision to defer the operation until a later date. This patient has several modifiable risk factors that significantly increase the likelihood of postoperative complications. Patients who are obese have a higher risk of wound healing complications after breast reduction surgery. In addition, she is living with an active smoker, and therefore the second-hand smoke will further contribute to wound healing difficulties. Preoperative interventions such as weight loss, smoking cessation, and control of hypertension will reduce her risks of experiencing complications.

2. **Answer: b.** During a delay operation, the plastic surgeon partially raises a flap and then waits 1 to 2 weeks before fully elevating the flap. This results in opening of choke vessels within the tissues and enhances the vascularity of the flap. The other answers do not directly improve the inherent vascularity of a flap.

3. **Answer: d.** Postoperative protection of the surgical site can be as important as the reconstruction itself. The patient has been sitting immediately after perineal reconstruction, and this is causing vascular compromise of the ORAM flap. Once this problem is identified, safeguards must be in place to offload the flap to avoid further tissue injury or else the entire reconstruction may be jeopardized. The other fundamental principles that are listed may very well have been followed during the patient's perineal reconstruction.

4. **Answer: e.** When selecting a donor site to close a wound, the plastic surgeon must choose the most reliable tissue for reconstruction while minimizing donor site morbidity. Plantar wounds that demonstrate healthy granulation tissue without exposure of critical structures can be resurfaced with a skin graft. In this location, a full-thickness skin graft is preferable to a split-thickness skin graft because it results in a more durable reconstruction on the weight-bearing surface of the foot. Letting the wound heal secondarily (choices a and c) would result in more scarring and possibly contractures of the toes. A free ALT flap may be considered for more complex wounds with exposed critical structures.

5. **Answer: d.** The primary goals in this case are to close the wound and to optimize the appearance of the scalp. The best tissue to replace lost hair-bearing scalp is the patient's own hair-bearing scalp, but in this case the size of the wound precludes the success of local flap options (choice a). Because the base of the wound consists of healthy granulation tissue and galea aponeurotica, a split-thickness skin graft is an appropriate choice to close the wound. Subsequently, after the skin graft is well healed, tissue expanders are placed to slowly grow the hair-bearing scalp. When sufficient growth has been achieved, an operation is performed to remove the implants and excise the split-thickness skin graft, and then the expanded hair-bearing scalp is used to resurface the wound. Scalp defects up to approximately 50% of the hair-bearing scalp can be reconstructed in this manner. A free flap operation (choice c) is not indicated in this scenario because there are no exposed critical structures and because it does not provide hair-bearing tissue. Choices b and e are incorrect because there is no need to delay skin grafting because the wound already consists of healthy vascularized tissue.

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CHAPTER 2

Basic Science of Wound Healing and Management of Chronic Wounds

Buket Gundogan and Dennis P. Orgill

Key Points

- Wounds present with a discontinuity of tissue and rely on complex processes for healing to occur. Most wound healing research focuses on molecular and cellular pathways, but we now appreciate the importance of the extracellular matrix (ECM) and mechanical forces. Classically, wound healing has been summarized into four phases: (1) hemostasis, (2) inflammation, (3), proliferation, and (4) remodeling.
- Aberrant wound healing occurs when normal pathways are disrupted, most commonly in the inflammatory or proliferative phases leading to chronic wounds.
- The most common chronic wounds are arterial ulcers, pressure injuries, venous stasis ulceration, and diabetic foot ulcers.
- Other factors that adversely affect wound healing include radiation therapy, nutrition, and microorganisms.
- Healing strategies involve keeping the wound moist, platelet-derived wound healing techniques, biological skin equivalents, topical growth factors, stem cells, scaffolds, and the application of biophysical forces.

Basic Science of Wound Healing

Wound healing is a complex and highly coordinated biological process. A sound understanding of the traditional stages of wound repair underpins many aspects of wound healing research. The four phases of wound healing—hemostasis, inflammation, proliferation, and remodeling—do not follow a simple and linear chronological order but overlap in time and are densely interconnected. Importantly, increasing research has demonstrated the importance of mechanical forces and the extracellular matrix (ECM) in wound healing biology (Figure 2.1).

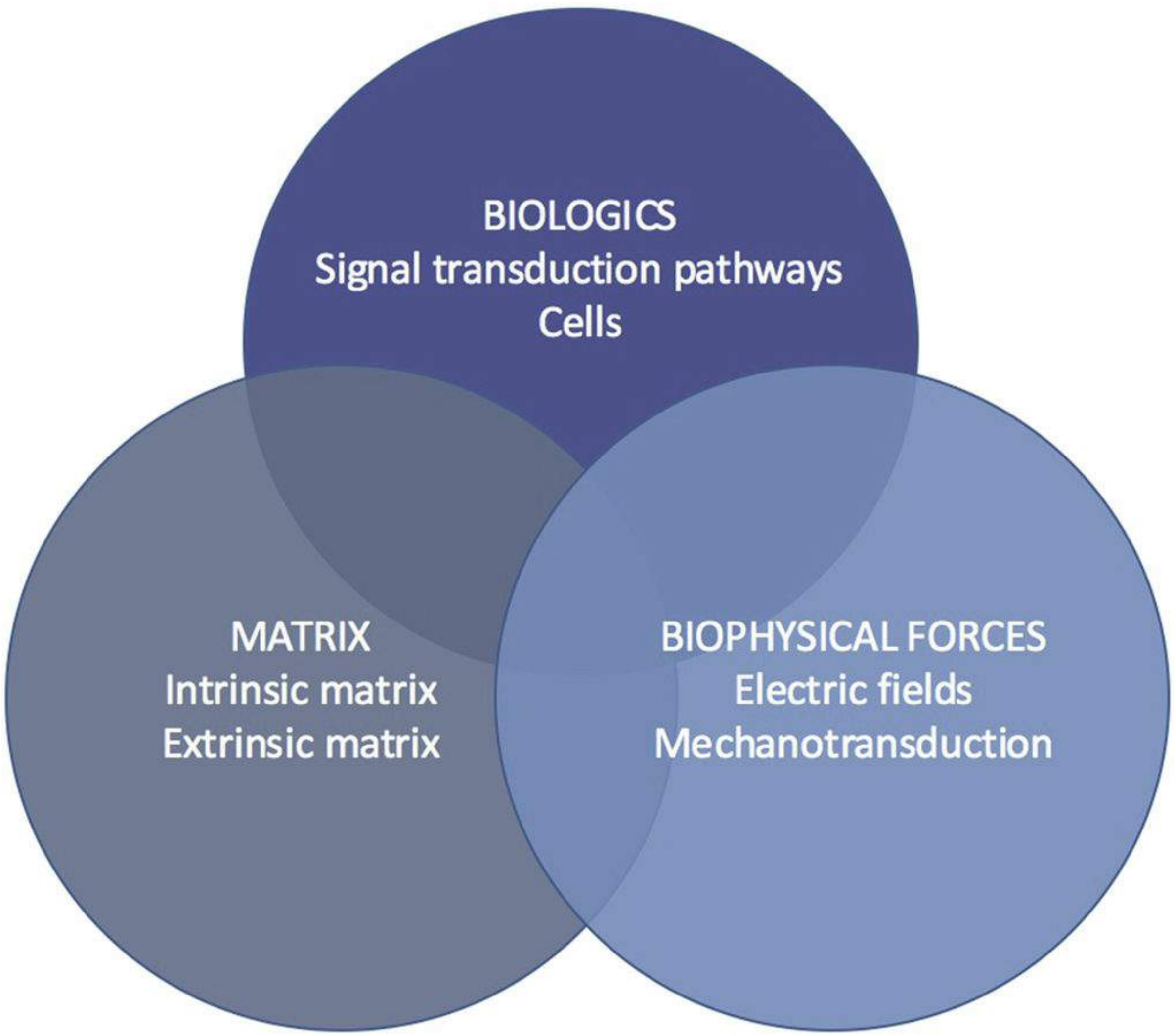

FIGURE 2.1 Factors involved in wound healing. Wound healing strategies involve the use of biologics (in particular cells and signal transduction pathways influenced by growth factors), matrix (intrinsic extracellular matrix proteins and extrinsic mechanical forces), and biophysical forces (electric fields and mechanotransduction). These domains have considerable overlap.

Classic Stages of Wound Healing

Hemostasis

Tissue injury and the consequent damage to capillary blood vessels initiates the coagulation cascade through the activation of fibrinogen. This activation results in the formation of platelet aggregation and fibrin scaffold that stems blood loss and allows for the migration of cells. Platelets play a critical role in the stages of wound healing and in particular are the chief effector cells during hemostasis. In addition to contributing to the hemostatic plug, their cytoplasm contains α-granules that release several growth factors and cytokines, such as platelet-derived growth factor (PDGF) and transforming growth factor-β (TGF-β), which facilitate wound healing by attracting neutrophils, macrophages, and fibroblasts. [1,2] Platelets are also responsible for releasing several proangiogenic and antiangiogenic growth factors that are critical for revascularization of wounds, such as vascular endothelial growth factor (VEGF) and platelet-derived stromal cell–derived factor 1 (SDF-1).

Inflammation

The coagulation cascade, the activation of complement, and bacterial degradation facilitate and trigger the inflammatory phase, which typically lasts 48 hours. [3] These pathways produce various chemotactic factors (such as TGF-β) and complement components (such as C3a and C5a) to attract inflammatory cells to the scaffold. Neutrophils invade the wound and phagocytose foreign debris, followed by monocytes that eventually differentiate into macrophages and further consume debris in their paths. [2] Macrophages are responsible for releasing a whole host of mediators primarily through binding to integrin receptors on the ECM, such as tumor necrosis factor α and interleukin-1 (IL-1) [4] (Figure 2.2). These proinflammatory cytokines stimulate fibroblast infiltration from the surrounding healthy ECM. It is important to note that macrophage invasion is critical to the inflammatory phase because macrophage-defective or macrophage-depleted animals undergo abnormal wound healing. [5]

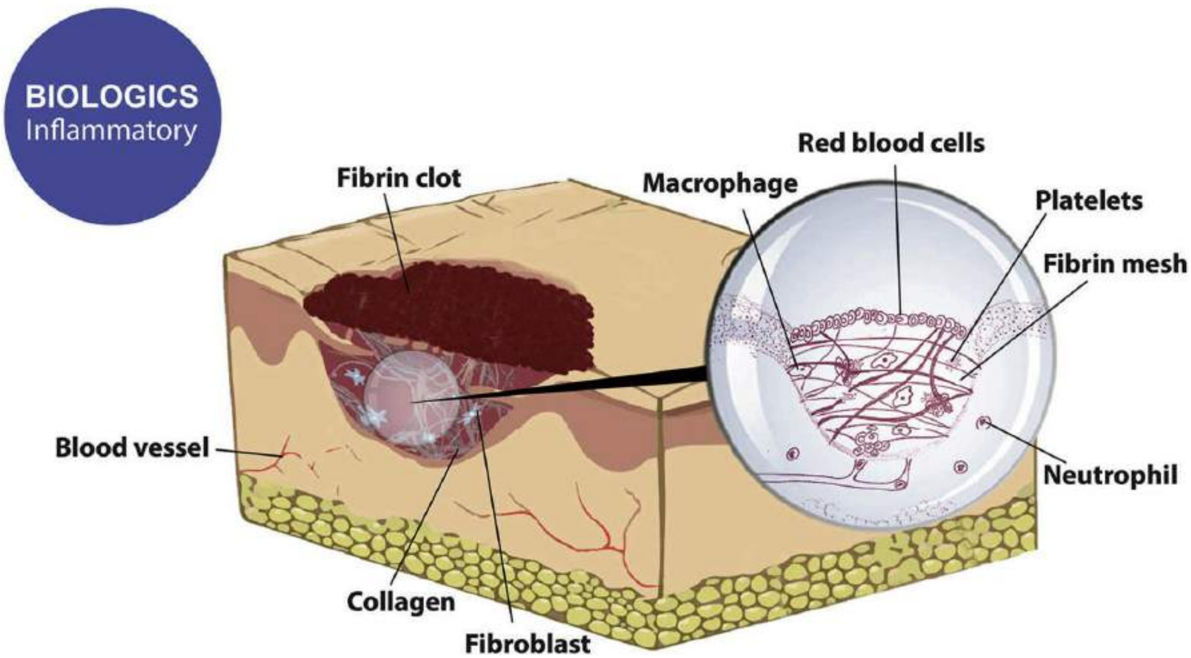

FIGURE 2.2 Inflammatory phase of wound healing. The inflammatory phase typically lasts 48 hours. Neutrophils invade the wound and phagocytose foreign debris, followed by monocytes that eventually differentiate into macrophages, which further consume debris in their paths.

Proliferation

From approximately 48 hours to 10 days after tissue injury, healing enters the proliferation phase (Figure 2.3). Keratinocytes migrate to eventually proliferating enough to create an epithelial layer that covers the wound. This is directly stimulated by epidermal growth factors, heparin-binding epidermal growth factor (HB-EGF), and transforming growth factor-alpha (TGF-α), which are the main members of the epidermal growth factor family involved in wound healing. [6] Fibroblasts are also critical to this stage of wound healing, as they produce collagen that acts as a scaffold for a vascular network. The hypoxic environment increases expression of hypoxia-inducible factor 1 (HIF-1α) protein to serve as the primary stimulus of angiogenesis. [7] HIF-1α activates several target genes such as VEGF and SDF-1 to induce neovascularization. [7] Fibroblasts and macrophages replace the fibrin mesh to form granulation tissue. Granulation tissue, also known as new stroma, consists of new connective tissue (specifically hyaluronic acid, procollagen, elastin, and proteoglycan) and blood vessels. It owes its granular appearance to the new capillary network. [1] The formation of blood vessel networks increases oxygen supply to the wound surface. Finally, fibroblasts that have differentiated into myofibroblasts have contractile ability to assist in bringing the wound edges together in a process known as wound contraction. [8]

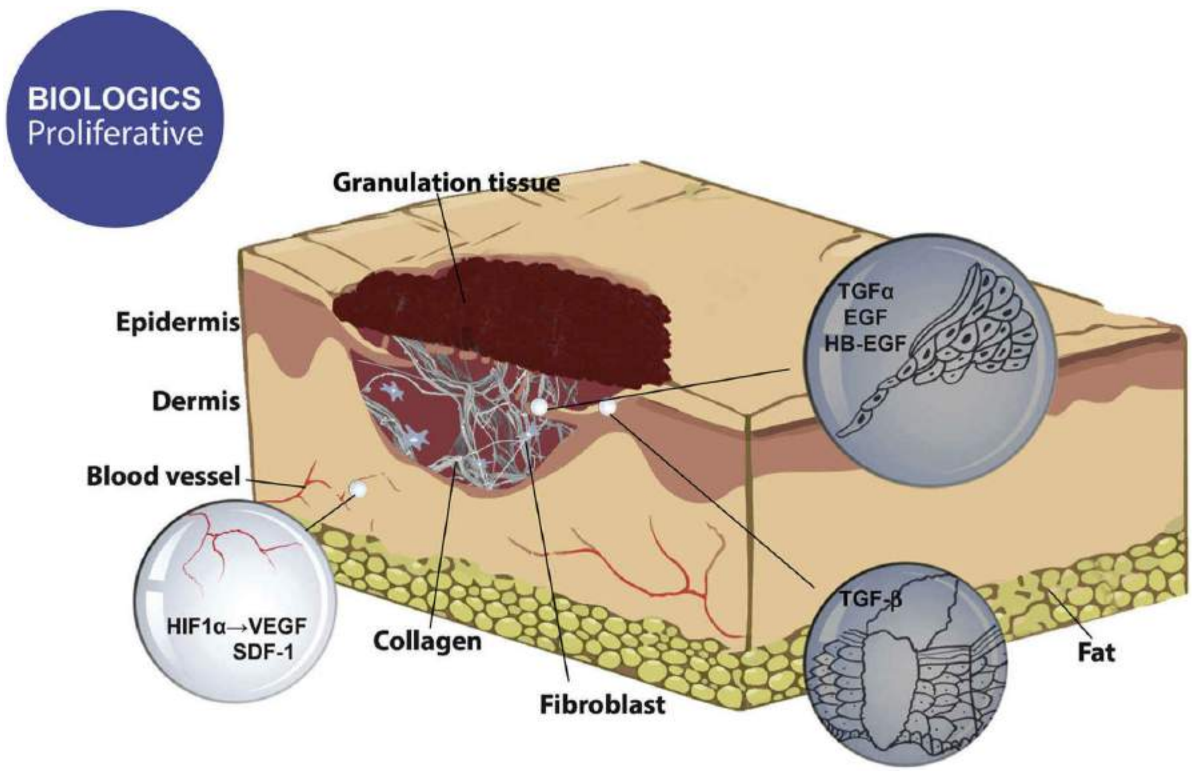

FIGURE 2.3 Proliferative phase of wound healing. During the proliferative phase, the hypoxic environment increases expression of hypoxia-inducible factor 1 (HIF-1α) protein, which is the primary stimulus of angiogenesis. Further downstream growth factors influencing the vascular network include vascular endothelial growth factor (VEGF) and platelet-derived stromal cell–derived factor 1 (SDF-1). Keratinocytes also migrate eventually proliferating enough to create an epithelial layer that covers the wound. This is directly stimulated by epidermal growth factors (EGFs), heparin-binding epidermal growth factor (HB-EGF), and transforming growth factor-alpha (TGF-α), which are the main members of the EGF family involved in wound healing. Factors such as transforming growth factor-β (TGF-β) facilitate wound healing by attracting neutrophils, macrophages, and fibroblasts.

Remodeling

The fourth and final stage of wound healing is the remodeling phase, which starts at approximately 2 weeks and can last for years. Throughout this stage, many of the cells contained in the wound undergo apoptosis or exit the wound, to eventually leave collagen and ECM proteins. This entire matrix is remodeled and strengthened from type III collagen into mainly type I collagen by matrix metalloproteinases (MMPs). MMPs are produced by fibroblasts as well as other cell types. The wound eventually forms scar tissue and never fully regains complete strength comparable to undamaged skin, at approximately 80% normal strength. [9] The ECM is also implicated in the formation of scarring. Cutaneous scar tissue is composed of the same ECM macromolecules as normal tissue but contains different ratios of these macromolecules and typically an absence of hair follicles or fat. [10] Increased levels of TGF-β1 have been implicated in hypertrophic adult scars. [11]

Mechanical Forces in Wound Healing

Human cells and tissues are subjected to many biophysical forces such as electrical, magnetic, and mechanical forces. These forces have various biological effects, and here we specifically discuss mechanical forces. Mechanical forces on cells include but are not limited to tension, shear force, gravity, and osmosis. [12] It is now clear that all phases of wound healing are affected by mechanical forces. In a process known as mechanotransduction, cells have the ability to detect mechanical stimuli in its microenvironment and respond by activating specific cellular pathways. These pathways can modulate cell functions such as proliferation, migration, and differentiation.

Focal adhesion (FA) complexes that are transmembrane proteins to anchor the cell cytoskeleton to other cells or the ECM are key to understanding mechanotransduction. FA complexes contain integrins, which act as primary receptors for the ECM. [13] This process of anchorage generates intracellular mechanical tension and serves not only to sense the wound microenvironment but also to modify its behavior and the surrounding ECM.

Cell migration is of critical importance in wound healing and mechanical forces are key to this. Tension generated by the cytoskeleton-integrin connections pulls the cell cytoplasm of the leading edge forward in a process known as protrusion. At the same time protein complexes of the trailing edge must disconnect from the ECM, resulting in the entire cell body moving forward and the cell producing traction forces. [13] Fibroblasts are thought to generate cell traction forces that are much greater than needed for cell migration, and this excess force deforms the ECM contributing to collagen reorganization in wound healing. [14] Similarly, mechanical forces involved in cellular migration also occur during epithelial repair and restoration.

It is also known that cell proliferation is influenced by mechanical stress, which can be defined as the force per unit area. Keratinocytes respond to mechanical stress by changing morphology, such as stretching, and these mechanotransduction pathways regulate cell proliferation. For example, cells without mechanical stress or stimuli adopt a spherical shape and enter cell-cycle arrest and apoptosis. [15]

Electric fields also play an important role in wound healing. Transepithelial electric potentials are created by the movement of ions across pumps in the epithelium, termed the *skin battery*. Damage to the continuous epithelium generates a current of injury whereby electric potential is directed toward the wound to signal cell migration, termed *electrotaxis*. [16] Studies have demonstrated that influencing such electric fields can alter wound healing in vivo. [16]

The effect of mechanical stimuli on the wound microenvironment is utilized by treatments, such as negative-pressure wound therapy (NPWT) and extracorporeal shock wave therapy (ESWT), which are explained in later sections.

Extracellular Matrix in Wound Healing

The ECM is a meshlike dynamic structure composed of different macromolecules and proteolytic enzymes. These macromolecules include collagen, elastin, glycosaminoglycans, glycoproteins, and proteoglycans. The ECM plays an important role in wound healing. Its function includes providing organization for cells as a physical scaffold, storage for growth factors, controlling cell shape, cell metabolism, and influences many cell behaviors such as migration, proliferation, and differentiation (Figure 2.4).

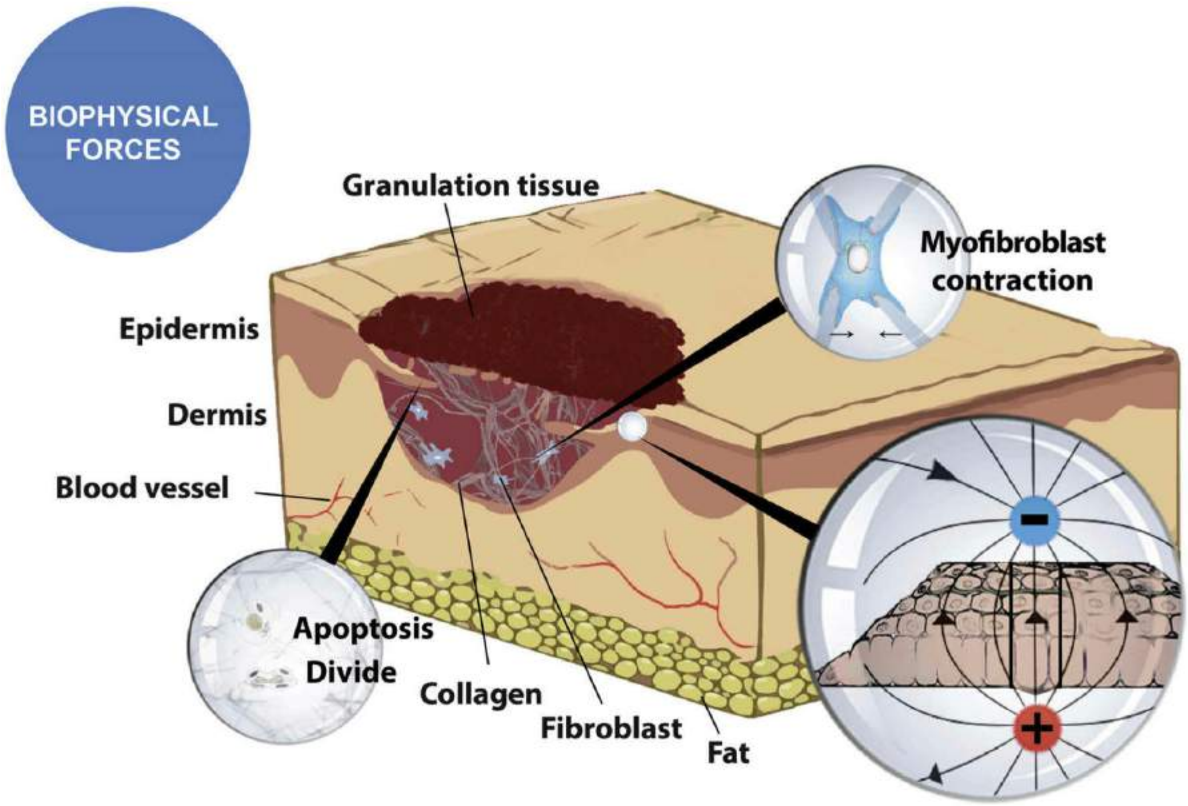

FIGURE 2.4 Biophysical forces in wound healing. Several biophysical forces influence wound healing. In a process known as mechanotransduction, cells have the ability to detect mechanical stimuli in its microenvironment and respond by activating specific cellular pathways. For example, cells without mechanical stress or stimuli adopt a spherical shape and enter cell-cycle arrest and apoptosis. Myofibroblasts also contract and exert tension on the extracellular matrix. Damage to the continuous epithelium generates a current of injury whereby electric potential is directed toward the wound, which has been shown to signal cell migration, termed *electrotaxis*.

The composition, density, and stiffness of the ECM influence the wound microenvironment. In newly injured tissue, ECM is soft and fibrin-rich and this change initiates a repair process of fibroblast differentiation into myofibroblasts that contract and exert tension on the surrounding ECM.

After cutaneous tissue injury, mechanical forces activate the focal adhesion kinase pathway. This pathway is known to be the main regulator of FAs. The focal adhesion kinase pathway has been shown to potentiate the secretion collagen, as well as monocyte chemoattractant protein-1, which has been linked to human fibrosis. [17,18]

The most prominent glycosaminoglycan, hyaluronic acid (hyaluronan) is known to interact with cell surface receptors, mainly CD-44 and RHAMM (*r*eceptor for *h*yaluron*a*n-*m*ediated *m*obilit*y*) to trigger a cascade of processes involved in wound healing, such as modulation of inflammation, chemotaxis, cell migration, collagen secretion, and angiogenesis. [19]

Aberrant Wound Healing

Chronic Wounds

Chronic wounds can be defined as a loss of continuity of the skin secondary to injury that persist for longer than 6 weeks. Chronic wounds are classified into vascular ulcers (arterial and venous), diabetic ulcers, and pressure ulcers. Despite each type of wound having different underlying pathologies, they all share common features such as an excessive and persistent inflammatory phase, impaired cell proliferation, abnormal cell migration, microbial colonization, the presence of biofilms, and ultimately an inability to complete all four phases of wound healing within the normal timeframe. However, they each have distinct pathophysiologies, which are further discussed in this section.

Vascular Ulcers

Vascular ulcers include venous, arterial, or mixed etiology. It has been reported that ulcers related to venous insufficiency constitute 70%, arterial disease 10%, and ulcers of mixed etiology 15% of leg ulcer presentations. The remaining 5% of leg ulcers result from less common pathophysiological causes.

Venous Ulcers

Chronic venous leg ulceration is common and is thought to occur in up to 5% of the population older than 65 years. [20] Venous ulcers are classically distributed in the *gaiter area* on the medial aspect between the knee and ankle. They occur secondary to venous insufficiency where there is valvular incompetence in veins, and the resulting backflow of blood results in increased venous pressure. This leads to capillary leakage of plasma constituents into the surrounding perivascular area, such as fibrin, which is known to decrease collagen production. [21]

The primary pathological events leading to venous disease and therefore venous ulceration are changes in the vein wall and vein valve environment. Elevated venous pressures change shear stress and mechanical forces, which are then detected by endothelial cell intercellular adhesion molecule-1 (ICAM-1, CD54) and the mechanosensitive transient receptor potential vanilloid channels. The endothelial cells respond by secreting vasoactive molecules to begin an inflammatory cascade, ultimately leading to the progression of venous disease. [22]

Arterial Ulcers

Arterial ulcers occur because of arterial insufficiency where there is narrowing of the arterial lumen most commonly secondary to atherosclerosis. They are classically located over bony prominences including the toes, heels, and ankles. Apart from atherosclerosis, other conditions that cause arterial obstruction include embolism, diabetes mellitus, vasculitis, pyoderma gangrenosum, and hematological disorders of sickle cell disease and thalassemia.

Diabetic Foot Ulcers

The prevalence of diabetic foot ulcers in individuals with diabetes mellitus is common and occurs in approximately 15% of patients over their lifetime. [23] There are several pathophysiological factors that contribute to aberrant healing in diabetic individuals. These include abnormal and chronic inflammatory response, hyperglycemia, microvascular abnormalities, hypoxia, and changes of the ECM scaffold. Peripheral neuropathy, peripheral arterial disease, and trauma also contribute to diabetic ulceration.

Chronic inflammation and an impaired inflammatory response is also the hallmark of diabetic wounds. Studies have demonstrated persistent and raised levels of proinflammatory cytokines, such as IL-1, IL-6, and tumor necrosis factor α. [24] Wounds also typically have imbalances in protease production and their inhibitors, which stop normal matrix synthesis and remodeling. [25]

Hyperglycemia leads to nonenzymatic binding of sugar residues to proteins through free amino acid groups, and further alterations lead to advanced glycation end-products. Advanced glycation end-products are known to decrease the solubility of the ECM and exacerbate the inflammatory changes. [26] Glycation of the ECM is linked to cell apoptosis and disruption of normal wound healing processes such as angiogenesis, cell migration, and proliferation. [27] High levels of glucose induce expression of MMP by fibroblasts, endothelial cells, and macrophages to break down the matrix.

Oxygen supply to a wound is also essential for healing, and hypoxic environments adversely affect wound healing. Chronic hyperglycemia prolongs inflammation and delays wound healing by increasing the levels of free radicals. [26]

Pressure Injuries

The pathophysiology underlying pressure injury is a combination of pressure, friction, shearing forces between tissue planes, and moisture. Pressure exceeding arteriolar pressure results in tissue hypoxia, the creation of free radicals, an ischemic reperfusion injury, and consequent tissue necrosis. [28] Factors contributing to the development of pressure ulcers include prolonged immobility, patient position, neuropathy, and existing arterial or venous insufficiency. [28] The National Pressure Ulcer Advisory Panel (NPUAP) staging system defines four stages of severity to pressure injuries: stage 1 pressure injury is nonblanchable erythema of intact skin (Figure 2.5A), stage 2 pressure injury is a partial-thickness skin loss with exposed dermis (Figure 2.5B), stage 3 pressure injury involves full-thickness skin loss (Figure 2.5C), and stage 4 pressure injury involves full-thickness skin and tissue loss (Figure 2.5D). [29]

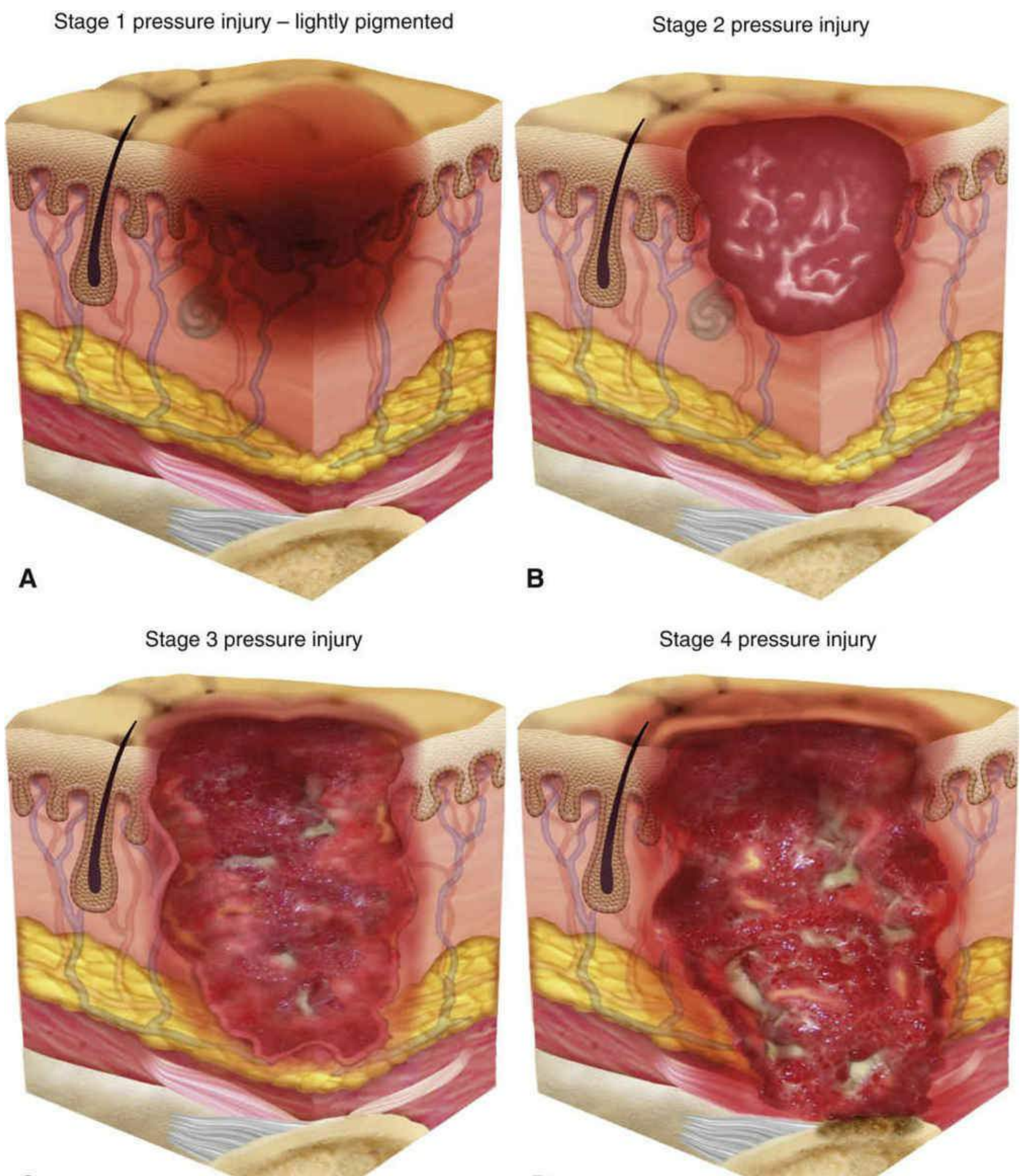

FIGURE 2.5 Pressure injury staging. **A.** Stage 1 is the least severe according to NPUAP staging system. It is defined as nonblanchable erythema of intact skin. **B.** Stage 2 is defined as a partial-thickness skin loss with exposed dermis. **C.** Stage 3 involves full-thickness skin loss. **D.** Stage 4 is the most severe stage of pressure injury. It involves full-thickness skin and tissue loss.

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Factors That Adversely Affect Wound Healing

Radiation Therapy

Radiation therapy such as those used as part of oncologic therapies disrupts the complex pathways of wound healing. Ionizing radiation produces both acute and late effects on tissues. Acutely, basement membrane is damaged, and increased vascular permeability introduces edema to reduce neovascularization of wounds. [30] During the inflammatory phase, there is excess expression of several growth factors, leading to tissue fibrosis. Fibroblasts are also injured and contribute to the late effects of radiation injury such as fibrosis and contraction. [30]

Nutrition

Nutrition has long been known to affect wound healing and chronic wounds. This includes a general malnutrition state, inadequate caloric intake, and deficiencies in vitamins, micronutrients, and macronutrients. Malnutrition is known to prolong the inflammatory phase of wound healing through reducing the proliferation of fibroblasts and the formation of collagen. [31] It can also increase the risk of infection of wounds by altering the function of immune cells, such as reducing phagocytosis and decreasing complement levels. [31] Micronutrients such as copper, zinc, and magnesium are elements and minerals that are essential to bodily chemical processes and, in particular, in wound healing. Deficiencies in these micronutrients can adversely affect wound healing, for example, in copper deficiency.

Macronutrients include protein, amino acids, carbohydrates, fiber, water, and fats. These are required at sufficient levels to promote optimal wound healing. Significantly reduced protein intake is associated with increased rates of wound infection and wound strength. [31] Similarly, lipid deficiencies are associated with altered wound healing. [31]

Microorganisms

Microorganisms have long been known to influence the healing of chronic wounds, and all open wounds contain microbes. Bacteria predominantly exist in biofilms in clinical and natural settings, as opposed to planktonic states (single organisms/free-floating). Biofilms describe adherent populations of microbes that form three-dimensional populations and are organized on extracellular polymers. Over time, chronic wounds are known to develop biofilms, as complex interactions between the host wound microenvironment and heterogeneous bacterial populations mean they are able to proliferate unchecked.

Biofilm bacterial populations delay and inhibit wound healing by not only producing toxins and damaging enzymes, but also promoting the complex chronic inflammatory pathways. [32] Proteases released from bacteria impede growth factors and wound healing proteins. Large levels of microbial exudate have also been shown to affect cell proliferation and wound healing. [32]

Biofilm-infected chronic wounds are clinically challenging to manage and are resistant to elimination by antimicrobials and by the immune system. The current mainstay management of dealing with microorganism-related complications in chronic wounds includes pressure off-loading, appropriate dressings, systemic antibiotics, tissue debridement, and the instillation of NPWTs such as vacuum-assisted closure devices.

Similarly, antiseptic dressings such as those containing chlorhexidine, silver, or iodine and topical antimicrobials (e.g., fusidic acid creams) have been developed over the years to a limited degree of success. Topical antimicrobials have promoted bacterial resistance, and several studies concluded that antiseptic dressings are not significantly better than saline gauze alone. [33] However, there are special situations when topical antimicrobials are proven beneficial. They are particularly useful in burn injuries (especially second-degree burn injuries) to treat infection and therefore prevent sepsis. [34]

Systemic antibiotics are beneficial in infected chronic wounds but are not indicated for most chronic wounds that are merely colonized with bacteria. Antibiotics should have high tissue bioavailability and should be targeted to the specific organisms from deep wound cultures. Studies demonstrate that superficial cultures do not represent the diverse populations of bacteria of the biofilm. [33]

Debridement involves the removal of necrotic tissue and debris at the wound edges and is often surgical, although other mechanical modes and enzymatic and autolytic methods are also utilized. The current theory is that debridement reduces biofilm. It is thought to promote wound healing and decrease the biofilm load. Recolonization of the wound after debridement is common, and often sequential debridements are required for successful healing.

NPWTs, such as vacuum-assisted closure devices, are known to aid wound healing. Several studies have investigated their effect on the microorganisms within chronic wounds, and observational data of NPWT with adjunctive topical dressings have demonstrated decreased biofilm load. [33] A recent small randomized trial (n = 20) of NPWT with instillation and adjunctive sodium hypochlorite solution was effective at reducing both planktonic and nonplanktonic (biofilm) microorganisms. [35]

Obesity and Metabolic Syndromes

Obesity is correlated with increased rates of wound complications such as wound infection, impaired wound healing, pressure injuries, venous ulcers, hematoma, and seroma formation. Hypovascularity, difficulty in repositioning, and friction between skin-to-skin contact points in skin folds are all known to contribute to the formation of pressure injuries in obese individuals.

On a molecular level, obesity is related to lower levels of lymphocyte proliferate, altered cytokine levels and peripheral immune function which improves upon weight loss. [23]

Advanced Wound Healing Strategies

Nonsurgical, advanced would healing strategies can briefly be categorized into those that employ biological therapeutics, use or enhance the matrix, and exploit biophysical forces (see Figure 2.1). Although these modalities are important, basic and simple strategies still form the foundation of wound care. These measures are manifold and include optimizing the management of primary pathological conditions that lead to wound formation, such as optimal lifestyle measures (e.g., nutrition), medication, and patient education. Other measures include debridement of necrotic tissue, local ulcer care, mechanical off-loading, mechanical compression (for venous ulcers), and infection control.

Biological Therapies

Biological therapies have been of great interest in wound healing therapies, and we specifically discuss the use of cadaveric skin and xenografts, placental constructs, growth factors, hyperbaric oxygen therapy (HBOT), biological skin equivalents, and stem cells (see Figure 2.1).

Growth Factors

Growth factor–related wound repair has been of immense interest in wound healing science. Commercially marketed growth factors currently available include recombinant human fibroblast growth factor, recombinant human platelet-derived growth factor, and recombinant human epidermal growth factor. Several other growth factors are also being developed.

Recombinant human epidermal growth factor is a well-known growth factor that can be applied topically or injected and has been shown to improve wound healing in small clinical trials worldwide. [36] Fibroblast growth factor has also shown promising results, in particular an isoform known as recombinant human keratinocyte growth factor-2 to be applied as a topical spray. The trial showed significantly increased wound healing compared with placebo. [37]

Platelet-Derived Growth Factors and Platelet-Rich Plasma

Several studies shown the efficacy of platelet-rich plasma (PRP) and PDGFs obtained from centrifugation of blood. [38]

PDGF has been demonstrated to be effective when compared with placebo, with 7 studies totaling 685 patients that showed a statistically significant percentage of ulcers healed compared with sham therapy. [39]

The first commercially available topical PDGF in the United States is becaplermin gel (Regranex®), which was studied in chronic diabetic foot ulcers. It is important to note that becaplermin gel contains the US Food and Drug Administration (FDA) black box warning, whereby consumers are cautioned to the increased risk of rate of mortality secondary to malignancy if several tubes are used. [40]

Conversely, the evidence for PRP has been scant, with randomized controlled trial (RCT) data showing no significant difference in the percentage of ulcers healed when compared with placebo or platelet-poor plasma therapy. [39]

Stem Cells

There has been significant interest in the use of stem cells to address the defective pathways in aberrant wound healing. Stem cells are undifferentiated cells that possess the ability to mature into differentiated cells of either one embryonic germ layer (multipotent) or all three embryonic germ layers (pluripotent). [41]
Perhaps one of the most widely studied multipotent adult stem cells in wound healing research has been mesenchymal stem cells (MSCs). In several animal-based studies, MSCs have demonstrated the ability to migrate to areas of cutaneous injury, secrete angiogenic and immune-mediating factors, and differentiate into skin cells. [41] There are now several ongoing and published clinical trials using MSCs in wound healing as well as a few commercial products. [41] Multiple clinical trials have shown promising outcomes with regard to wound closure rates; however, they have been limited by small sample sizes and lack of controls. [41] At the time of writing, several clinical trials in the United States are recruiting patients to study the use of MSCs in healing cutaneous wounds. [41]
However, challenges remain with stem cell technologies. Firstly, there are numerous ethical concerns surrounding its use, in particular, pluripotent stem cells; hence, much of the research has focused on multipotent stem cells. [41] Secondly, there are still many questions that need to be answered in the field. Two important questions posited by Sorice et al are which population of stem cells are the most effective in healing wounds and what is the best method to deliver stem cells into a wound? [41] These are important considerations if stem cells are to move into clinical translation.

Hyperbaric Oxygen Therapy

HBOT utilizes compression chambers to deliver high levels of oxygen concentration at raised atmospheric pressures. HBOT aims to promote oxygen-dependent wound healing pathways and has particularly been a treatment strategy when revascularization in vascular insufficiency has been unsuccessful. [42] Systematic review evidence of four long-term studies totaling 233 patients concluded that there was a significant difference in percentage of healed ulcers compared with sham therapy when HBOT was used adjunctively, with one short-term study finding no significant difference. However, strength of evidence was deemed low for all studies. One study of poor quality found HBOT less effective compared with ESWT (n = 84). [39]

Cell Cultured Products

Cell cultured products, also known as tissue-engineered constructs, include Apligraf, Epicel, and Dermagraft. Apligraf (Organogenesis, Canton, MA) utilizes a bovine collagen matrix incorporated with human neonatal fibroblasts and neonatal keratinocytes to act as a scaffold as well as providing cells that produce growth factors and ECM components. Similarly, Dermagraft (Organogenesis, Canton, MA) comprises a polyglactin scaffold with dermal neonatal fibroblasts. A large Apligraf RCT (n = 309) found a significant increase in the number of healed ulcers and a reduced length of time to complete healing compared with standard therapy with compression. [39] Furthermore, cultured epithelial autografts using patients' own keratinocytes, such as Epicel, have been utilized to treat large burns and take 2 to 3 weeks in culture to grow. [43] Genetic manipulation of keratinocytes has recently been reported to regenerate an entire fully functional epidermal layer in junctional epidermolysis bullosa. [44]

Scaffolds

Scaffolds act as a platform for cell migration and angiogenesis and are a key therapeutic modality. Scaffolds can be of human origin (donated tissue or cadaveric) and nonhuman origin (porcine or synthesized through extraction and cross-linking). Several such scaffolds are commercially available. Integra™ (Integra LifeSciences) is a bilayer matrix of bovine collagen and glycosaminoglycan derived from shark skin that is lyophilized to form a highly porous scaffold. Integra™ has been used with considerable success in burns, and clinical trial data have attested its use in the healing of chronic wounds, specifically decreasing time to wound closure in diabetic foot ulcers. [45] Allopatch®, which is a decellularized scaffold derived from human cadaveric tissue, has demonstrated efficacy in closure of nonhealing diabetic foot ulcers. [46] Placental constructs, such as Grafix, which is a cryopreserved placental membrane, have shown to significantly improve diabetic foot ulcer healing and reduce related complications. [47]

Biophysical Forces

Negative-Pressure Wound Therapy

NPWT effectively ensures wound drainage, aids granulation tissue development, and expedites wound contraction. [48] RCT data have shown improved healing of ulcers as well as reduced second amputations. [39]

Extracorporeal Shock Wave Therapy

ESWT delivers high-energy acoustic pulses to tissues and is the standard of care in treating nephrolithiasis and various musculoskeletal conditions. It has been reported to improve cutaneous wound healing through increasing cell proliferation and stimulating angiogenesis. [49]

Electromagnetic Therapies

Electromagnetic therapies, such as pulsed electromagnetic field therapy, have effectively been used in orthopedic practice, and numerous in vitro and animal studies have demonstrated improved cutaneous wound healing. These therapies are thought to interact with endogenous electric fields in the skin to increase expression of growth factors and nitric oxide and also promote angiogenesis [50] (see Figure 2.4). However, RCT data showed mixed results, with one showing no difference between placebo and electromagnetic therapy and another reporting a significant increase in the percentage of healed ulcers between the two groups. [39]

Knowledge Gaps

There has been an explosion in therapeutic options for wound healing in the last 30 years, as the number of wounds has increased because of our aging population, increases in the incidence of type 2 diabetes, and increases in obesity. Currently, there is a lack of clinical data in well-controlled prospective studies to document the clinical efficacy of several of the modalities now used clinically including HBOT, PRP, antimicrobial dressings, topical oxygen therapy, and pulsed electromagnetic stimulation. There is also almost a complete lack of comparative studies on advanced wound healing modalities. Prospective RCTs are challenging in wound healing because of the difficulty in binding both the patient and practitioner as well as the desire by both to achieve a healed wound. Registry studies may provide a powerful method to look at comparative advanced healing modalities and also allow us to better assess the cost-effectiveness of these therapies.

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Questions

1. A 65-year-old woman with diabetes mellitus presents with a heel ulceration not involving the calcaneus. She has palpable pulses. Which therapy has the best published efficacy for healing?
   a. HBOT
   b. Silver alginate dressings
   c. NPWT
   d. Pulsed electromagnetic therapy
2. A 25-year-old man with paraplegia presents with a large ulcer over his right ischium that probes to bone. What stage of pressure injury would this be considered?
   a. Stage 1
   b. Stage 2
   c. Stage 3
   d. Stage 4
   e. Unstageable
3. A patient presents with a heavy scar 3 weeks following a stab wound to the back. What phase of wound healing would this be considered?
   a. Hemostasis
   b. Inflammatory
   c. Proliferation
   d. Remodeling
4. Which of the following wound care modalities would mechanical forces be considered a major factor in the mechanism of action?
   a. Platelet-derived growth factor
   b. Placental-derived constructs
   c. Negative-pressure wound therapy
   d. Saline wash
5. Which of the following would be considered a chronic wound?
   a. A 67-year-old man with a 2-cm heel ulceration for 1 month who just completed external iliac angioplasty
   b. A 75-year-old woman with a prosthetic heart valve on Coumadin who presents with severe bruising of her anterior tibial area 3 weeks after injury
   c. A 30-year-old man with Crohn disease on steroids presents with a dehisced laparotomy wound 1 month following surgery
   d. A 45-year-old woman with breast cancer who has severe desquamation of her skin at the end of her radiation therapy
   e. A 24-year-old man paraplegic with an ischial stage 4 pressure injury for 3 months

1. **Answer: c.** Although all of these modalities have been proposed for use in this patient population, NPWT has the most published high-level studies in wounds.
2. **Answer: d.** Pressure injuries that go to bone are considered stage 4.
3. **Answer: d.** Although there are components of inflammation and proliferation that are still occurring, 3 weeks after an injury, the wound is being actively remodeled and would generally be considered to be in the remodeling phase.
4. **Answer: c.** Negative-pressure wound therapy. This therapy is commonly used by placing an open-pore polyurethane sponge directly over the wound and connecting this to suction. This induces deformations to the wound surface and draws the wound together.

5. **Answer: e.** Wounds should be present for 6 weeks to be considered chronic. Although the severe bruising and the radiation injury cases could turn into chronic wounds, at this point these patients do not have an actual wound.

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