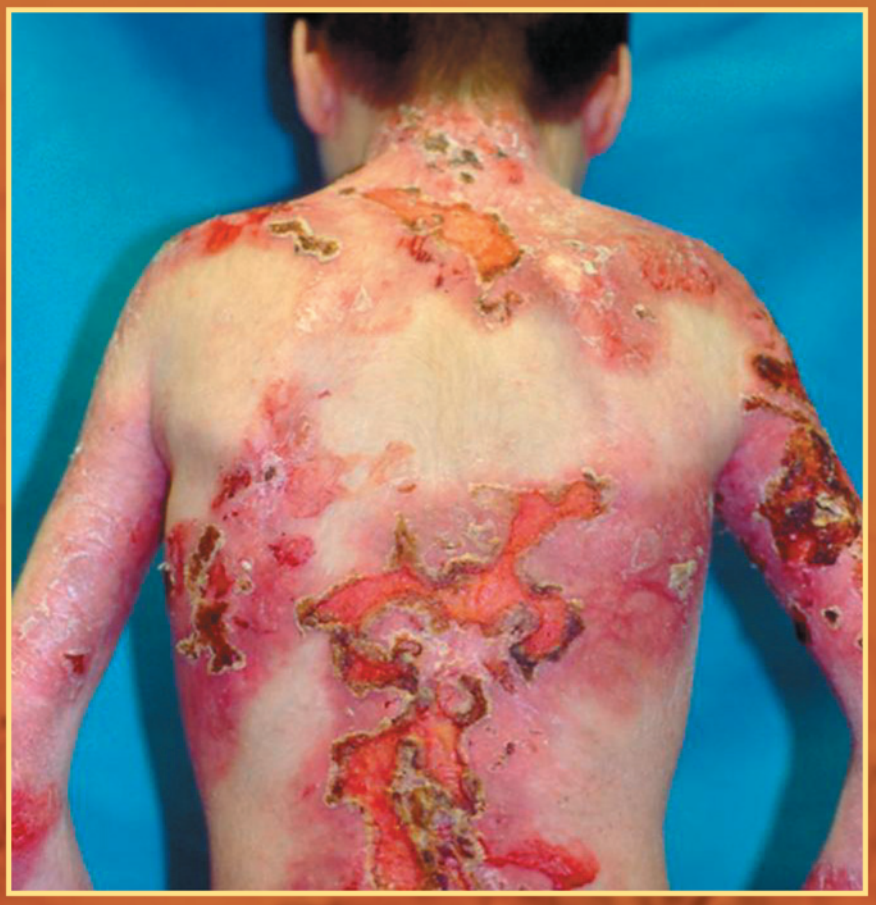
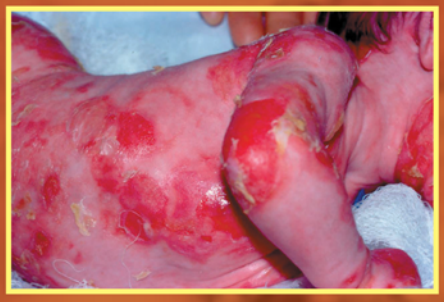
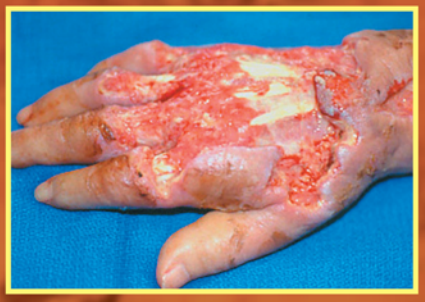
Wound Healing







EDITED BY

Anna F. Falabella
Robert S. Kirsner

Wound Healing

BASIC AND CLINICAL DERMATOLOGY

Series Editors

Alan R. Shalita, M.D.
Distinguished Teaching Professor and Chairman
Department of Dermatology
SUNY Downstate Medical Center
Brooklyn, New York

David A. Norris, M.D.
Director of Research
Professor of Dermatology
The University of Colorado
Health Sciences Center
Denver, Colorado

1. Cutaneous Investigation in Health and Disease: Noninvasive Methods and Instrumentation*, edited by Jean-Luc Lévêque*
2. Irritant Contact Dermatitis, *edited by Edward M. Jackson and Ronald Goldner*
3. Fundamentals of Dermatology: A Study Guide, *Franklin S. Glickman and Alan R. Shalita*
4. Aging Skin: Properties and Functional Changes, *edited by Jean-Luc Lévêque and Pierre G. Agache*
5. Retinoids: Progress in Research and Clinical Applications, *edited by Maria A. Livrea and Lester Packer*
6. Clinical Photomedicine, *edited by Henry W. Lim and Nicholas A. Soter*
7. Cutaneous Antifungal Agents: Selected Compounds in Clinical Practice and Development, *edited by John W. Rippon and Robert A. Fromtling*
8. Oxidative Stress in Dermatology, *edited by Jürgen Fuchs and Lester Packer*
9. Connective Tissue Diseases of the Skin, *edited by Charles M. Lapière and Thomas Krieg*
10. Epidermal Growth Factors and Cytokines, *edited by Thomas A. Luger and Thomas Schwarz*
11. Skin Changes and Diseases in Pregnancy, *edited by Marwali Harahap and Robert C. Wallach*
12. Fungal Disease: Biology, Immunology, and Diagnosis, *edited by Paul H. Jacobs and Lexie Nall*
13. Immunomodulatory and Cytotoxic Agents in Dermatology, *edited by Charles J. McDonald*
14. Cutaneous Infection and Therapy, *edited by Raza Aly*, *Karl R. Beutner*, *and Howard I. Maibach*

15. Tissue Augmentation in Clinical Practice: Procedures and Techniques, *edited by Arnold William Klein*
16. Psoriasis: Third Edition, Revised and Expanded, *edited by Henry H. Roenigk, Jr., and Howard I. Maibach*
17. Surgical Techniques for Cutaneous Scar Revision, *edited by Marwali Harahap*
18. Drug Therapy in Dermatology, *edited by Larry E. Millikan*
19. Scarless Wound Healing, *edited by Hari G. Garg and Michael T. Longaker*
20. Cosmetic Surgery: An Interdisciplinary Approach, *edited by Rhoda S. Narins*
21. Topical Absorption of Dermatological Products, *edited by Robert L. Bronaugh and Howard I. Maibach*
22. Glycolic Acid Peels, *edited by Ronald Moy, Debra Luftman, and Lenore S. Kakita*
23. Innovative Techniques in Skin Surgery, *edited by Marwali Harahap*
24. Safe Liposuction and Fat Transfer, *edited by Rhoda S. Narins*
25. Pyschocutaneous Medicine, *edited by John Y. M. Koo and Chai Sue Lee*
26. Skin, Hair, and Nails: Structure and Function, *edited Bo Forslind and Magnus Lindberg*
27. Itch: Basic Mechanisms and Therapy, *edited Gil Yosipovitch, Malcolm W. Greaves, Alan B. Fleischer, and Francis McGlone*
28. Photoaging, *edited by Darrell S. Rigel, Robert A. Weiss, Henry W. Lim, and Jeffrey S. Dover*
29. Vitiligo: Problems and Solutions, *edited by Torello Lotti and Jana Hercogova*
30. Photodamaged Skin, *edited by David J. Goldberg*
31. Ambulatory Phlebectomy, Second Edition, *Stefano Ricci, Mihael Georgiev, and Mitchel P. Goldman*
32. Cutaneous Lymphomas, *edited by Gunter Burg and Werner Kempf*
33. Wound Healing, *edited by Anna Falabella and Robert Kirsner*
34. Phototherapy and Photochemotherapy of Skin Disease, Third Edition, *Warwick L. Morison*

Wound Healing

Edited by

Anna F. Falabella
University of Miami School of Medicine
Miami, Florida, U.S.A.

Robert S. Kirsner
University of Miami School of Medicine
Miami, Florida, U.S.A.

Taylor & Francis
Taylor & Francis Group

Boca Raton London New York Singapore

Published in 2005 by
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

Printed in the United States of America on acid-free paper
10 9 8 7 6 5 4 3 2 1

International Standard Book Number-10: 0-8247-5458-1 (Hardcover)
International Standard Book Number-13: 978-0-8247-5458-7 (Hardcover)

Library of Congress Cataloging-in-Publication Data

Catalog record is available from the Library of Congress

T&F informa

Taylor & Francis Group
is the Academic Division of T&F Informa plc.

Visit the Taylor & Francis Web site at
http://www.taylorandfrancis.com

Series Introduction

During the past 25 years, there has been a vast explosion in new information relating to the art and science of dermatology as well as fundamental cutaneous biology. Furthermore, this information is no longer of interest only to the small but growing specialty of dermatology. Scientists from a wide variety of disciplines have come to recognize both the importance of skin in fundamental biological processes and the broad implications of understanding the pathogenesis of skin disease. As a result, there is now a multidisciplinary and worldwide interest in the progress of dermatology.

With these factors in mind, we have undertaken this series of books specifically oriented to dermatology. The scope of the series is purposely broad, with books ranging from pure basic science to practical, applied clinical dermatology. Thus, while there is something for everyone, all volumes in the series will ultimately prove to be valuable additions to the dermatologist's library.

The latest addition to the series, volume 33, edited by Drs. Anna F. Falabella and Robert S. Kirsner, is both timely and pertinent. The editors are well known authorities in the field of wound healing. We trust that this volume will be of broad interest to scientists and clinicians alike.

Alan R. Shalita
SUNY Downstate Medical Center
Brooklyn, New York, U.S.A.

Preface

Some of the oldest known medical texts in existence, written more than 3000 years ago, describe techniques used by ancient healers to treat wounds. Despite this long history, the art of wound healing did not advance to any significant degree until recent times. Over the past 20 years, our knowledge of the wound healing process has increased dramatically. With this knowledge has come the development of new, exciting technologies that accelerate normal wound healing and counter the pathophysiologic processes that lead to chronic wound formation. From growth factors to bioengineered skin substitutes, the future of wound healing holds great promise. The purpose of this book is to provide its readers with a comprehensive review of the field of wound healing, from the basic principles of wound healing, to assessment and treatment, to promising therapies of the future.

From basic concepts to advanced therapies, this book is the most complete guide for learning in this field. The book is divided into three sections. The first focuses on the basic science of wound healing and describes, in great detail, the pathophysiology of wound healing. The next section concentrates on the general clinical aspects of wound healing, focusing on epidemiology, diagnosis and prevention of wounds. The last section provides an in-depth description of general and specific treatments available for wound healing, and discusses current research issues.

The professionals who have contributed to this text are some of the most experienced clinicians and scientists in the field of wound healing. Readers of the text should come away with an excellent understanding of the wound healing process, the appropriate evaluation of acute and chronic wounds, and management strategies. One should also come away with a better understanding of newer treatment modalities and the principles upon which new therapies are being developed.

Whether particular interests in wound healing involve research or clinical practice, this book should prove to be an invaluable resource for all professionals involved in the field of wound healing.

Anna F. Falabella
Robert S. Kirsner

Contents

Contributors

David G. Armstrong Department of Surgery, Doctor William M. Scholl College of Podiatric Medicine, Rosalind Franklin University of Medicine and Science, Chicago, Illinois, U.S.A.

Meggan R. Banta Department of Dermatology and Cutaneous Surgery, University of Miami School of Medicine, Miami, Florida, U.S.A.

Janice M. Beitz La Salle University School of Nursing, Philadelphia, Pennsylvania, U.S.A.

Ysabel M. Bello Department of Dermatology and Cutaneous Surgery, University of Miami School of Medicine, Miami, Florida, U.S.A.

Brian Berman Department of Dermatology and Cutaneous Surgery, University of Miami School of Medicine, Miami, Florida, U.S.A.

Andrew J. M. Boulton Division of Endocrinology, Diabetes and Metabolism, University of Miami School of Medicine, Miami, Florida, U.S.A. and Department of Medicine, University of Manchester, Manchester, U.K.

A. L. Cazzaniga Department of Dermatology and Cutaneous Surgery, University of Miami School of Medicine, Miami, Florida, U.S.A.

Carlos A. Charles Department of Dermatology and Cutaneous Surgery, University of Miami School of Medicine, Miami, Florida, U.S.A.

Gloria A. Chin Department of Surgery, University of Florida, Gainesville, Florida, U.S.A.

Amy Colwell Department of Surgery, Brigham and Women's Hospital, Boston, Massachusetts, U.S.A.

Ganary Dabiri Albany Medical Center, Center for Cell Biology and Cancer Research, Albany, New York, U.S.A.

S. C. Davis Department of Dermatology and Cutaneous Surgery, University of Miami School of Medicine, Miami, Florida, U.S.A.

Robert H. Demling Harvard Medical School and Burn Center, Brigham and Women's Hospital, Boston, Massachusetts, U.S.A.

Robert F. Diegelmann Department of Biochemistry, Medical College of Virginia, Richmond, Virginia, U.S.A.

C. Michael DiPersio Albany Medical Center, Center for Cell Biology and Cancer Research, Albany, New York, U.S.A.

Celia M. Divino Division of General Surgery, The Mount Sinai School of Medicine, New York, New York, U.S.A.

Anna Drosou Department of Dermatology and Cutaneous Surgery, University of Miami School of Medicine, Miami, Florida, U.S.A.

William H. Eaglstein Miller School of Medicine, University of Miami, Miami, Florida, U.S.A.

George W. Elgart Department of Dermatology and Cutaneous Surgery, University of Miami School of Medicine, Miami, Florida, U.S.A.

William J. Ennis Advocate Christ Medical Center Wound Treatment Program, Oak Lawn, Illinois, and Evergreen Healthcare Center, Advanced Wound Care Program, Evergreen Park, Illinois, U.S.A.

Anna F. Falabella Department of Dermatology and Cutaneous Surgery, University of Miami School of Medicine, Miami, Florida, U.S.A.

Daniel G. Federman Department of Medicine, Yale University School of Medicine, West Haven, Connecticut, U.S.A.

Caroline E. Fife Department of Anesthesiology, University of Texas Health Science Center, and Memorial Hermann Center for Wound Healing, Houston, Texas, U.S.A.

David Fivenson Department of Dermatology, Henry Ford Health System, Detroit, Michigan, U.S.A.

Lawrence E. Gibson Department of Dermatology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota, U.S.A.

Lauren Grasso Department of Dermatology, Henry Ford Health System, Detroit, Michigan, U.S.A.

Cathy Thomas Hess Clinical Operations, Wound Care Strategies, Inc., Harrisburg, Pennsylvania, U.S.A.

Mark D. Hoffman Department of Dermatology, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois, U.S.A.

Allen Holloway Department of Surgery, Maricopa Medical Center, Phoenix, Arizona, U.S.A.

Harriet W. Hopf Departments of Anesthesia and Surgery, University of California San Francisco, Wound Healing Laboratory, San Francisco, California, U.S.A.

Shasa Hu Department of Dermatology and Cutaneous Surgery, University of Miami School of Medicine, Miami, Florida, U.S.A.

Thomas K. Hunt Departments of Anesthesia and Surgery, University of California San Francisco, Wound Healing Laboratory, San Francisco, California, U.S.A.

Satoshi Itami Department of Dermatology, Osaka University Graduate School of Medicine, Suita, Osaka-fu, Japan

Sarah L. Jensen Department of Dermatology, St. Louis University Hospital, St. Louis, Missouri, U.S.A.

Jonathan Kantor Departments of Dermatology and Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, U.S.A.

Francisco A. Kerdel Chief of Dermatology and Director of Inpatient Services, Cedars Medical Center, Miami, Florida, U.S.A.

Morris D. Kerstein Department of Surgery, Jefferson Medical College, Philadelphia, Pennsylvania and VA Medical and Regional Office Center, Wilmington, Delaware, U.S.A.

Robert S. Kirsner Department of Dermatology and Cutaneous Surgery, University of Miami School of Medicine, Miami, Florida, U.S.A.

Luther C. Kloth Department of Physical Therapy, College of Health Sciences, Marquette University and Department of Plastic Surgery, The Medical College of Wisconsin, Milwaukee, Wisconsin, U.S.A.

Diane L. Krasner Rest Haven—York, York, Pennsylvania, U.S.A.

Jeffrey D. Kravetz Department of Medicine, Yale University School of Medicine, West Haven, Connecticut, U.S.A.

Lawrence A. Lavery Department of Surgery, Scott & White Memorial Hospital, Texas A&M University College of Medicine, Temple, Texas, U.S.A.

Jie Li Department of Dermatology and Cutaneous Surgery, University of Miami School of Medicine, Miami, Florida, U.S.A.

Peggy Lin Department of Dermatology, Boston University School of Medicine, Boston, Massachusetts, U.S.A.

George Tye Liu Department of Orthopedics, Podiatry Division, The University of Texas Health Science Center, San Antonio, Texas, U.S.A.

Markéta Límová Department of Dermatology, University of California San Francisco, San Francisco, California, U.S.A.

Michael T. Longaker Director of Children's Surgical Research, Stanford University Medical Center, Stanford, California, U.S.A.

H. Peter Lorenz Division of Plastic Surgery, Stanford University Center for Children's Surgical Research, Stanford, California, U.S.A.

John M. MacDonald Department of Dermatology and Cutaneous Surgery, University of Miami School of Medicine, Miami, Florida, U.S.A.

Antonio Magliaro Department of Dermatology, University of Pisa, Pisa, Italy

David J. Margolis Departments of Dermatology and Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, U.S.A.

Lucy K. Martin Department of Dermatology and Cutaneous Surgery, University of Miami School of Medicine, Miami, Florida, U.S.A.

Harvey N. Mayrovitz College of Medical Sciences, Nova Southeastern University, Ft. Lauderdale, Florida, U.S.A.

Joseph McCulloch School of Allied Health Professions, Louisiana State University Health Sciences Center, Shreveport, Louisiana, U.S.A.

Felicia A. Mendelsohn Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut, U.S.A.

Patricia M. Mertz Department of Dermatology and Cutaneous Surgery, University of Miami School of Medicine, Miami, Florida, U.S.A.

Michael J. Morykwas Department of Plastic and Reconstructive Surgery, Wake Forest University School of Medicine, Winston-Salem, North Carolina, U.S.A.

George T. Nahass Department of Dermatology, St. Louis University Hospital, St. Louis, Missouri, U.S.A.

Nicholas Namias Division of Burns and Department of Surgical Infectious Diseases, University of Miami/Jackson Memorial Medical Center, Miami, Florida, U.S.A.

Peter A. Noseworthy Dermatology Daycare and Wound Healing Clinic, Sunnybrook and Women's College Health Sciences Centre, Toronto, Ontario, Canada

R. N. Heather Orsted Dermatology Daycare and Wound Healing Clinic, Sunnybrook and Women's College Health Sciences Centre, Toronto, Ontario, Canada

Liza Ovington Ovington & Associates, Inc., Allentown, Pennsylvania, U.S.A.

Wyatt G. Payne Department of Surgery, University of South Florida, Tampa, Florida, U.S.A.

Tania J. Phillips Department of Dermatology, Boston University School of Medicine, Boston, Massachusetts, U.S.A.

Varee Poochareon Department of Dermatology and Cutaneous Surgery, University of Miami School of Medicine, Miami, Florida, U.S.A.

Martin C. Robson Department of Surgery, University of South Florida, Tampa, Florida, U.S.A.

Georgette Rodriguez Department of Dermatology and Cutaneous Surgery, University of Miami School of Medicine, Miami, Florida, U.S.A.

Marco Romanelli Department of Dermatology, University of Pisa, Pisa, Italy

Paolo Romanelli Department of Dermatology and Cutaneous Surgery, University of Miami School of Medicine, Miami, Florida, U.S.A.

Noah A. Rosen Department of Surgery, Boston University Medical Center, Boston, Massachusetts, U.S.A.

Chris B. Ruser Department of Medicine, Yale University School of Medicine, West Haven, Connecticut, U.S.A.

Lawrence A. Schachner Department of Pediatrics, The University of Miami School of Medicine, Miami, Florida, U.S.A.

Stefanie Schluender Department of Surgery, The Mount Sinai Medical Center, New York, New York, U.S.A.

Gregory S. Schultz Department of Obstetrics and Gynecology, University of Florida, Gainesville, Florida, U.S.A.

R. Gary Sibbald Dermatology Daycare and Wound Healing Clinic, Sunnybrook and Women's College Health Sciences Centre, Toronto, Ontario, Canada

Nancy Sims College of Medical Sciences, Nova Southeastern University, Ft. Lauderdale, Florida, U.S.A.

James Spencer Department of Dermatology and Cutaneous Surgery, The Mount Sinai School of Medicine, New York, New York, U.S.A.

John S. Steinberg Department of Orthopedics, Podiatry Division, The University of Texas Health Science Center, San Antonio, Texas, U.S.A.

Tory P. Sullivan Department of Dermatology and Cutaneous Surgery, University of Miami School of Medicine, Miami, Florida, U.S.A.

Jennifer T. Trent Department of Dermatology and Cutaneous Surgery, University of Miami School of Medicine, Miami, Florida, U.S.A.

Isabel C. Valencia Department of Dermatology and Cutaneous Surgery, The University of Miami School of Medicine, Miami, Florida, U.S.A.

Lia van Rijswijk La Salle University School of Nursing, La Salle Neighborhood Nursing Center, Newtown and Philadelphia, Pennsylvania, U.S.A.

Adriana Villa Department of Dermatology and Cutaneous Surgery, University of Miami School of Medicine, Miami, Florida, U.S.A.

Dot Weir Orlando Regional Healthcare, Lucerne Wound Healing Center, Orlando, Florida, U.S.A.

Esperanza Welsh Department of Dermatology, University of Miami School of Medicine, Miami, Florida, U.S.A.

Yuji Yamaguchi Department of Dermatology, Osaka University Graduate School of Medicine, Suita, Osaka-fu, Japan

Sharam Samson Yashar Department of Dermatology, Henry Ford Health System, Detroit, Michigan, U.S.A.

Kunihiko Yoshikawa Department of Dermatology, Osaka University Graduate School of Medicine, Suita, Osaka-fu, Japan

1
Historical Aspects of Wound Healing

William H. Eaglstein
Miller School of Medicine, University of Miami, Miami, Florida, U.S.A.

1. ACUTE WOUNDS

The recorded history of Western medicine begins with Greek physicians who created a system of understanding disease as an imbalance in natural substances: blood, phlegm, yellow bile, and black bile. The corresponding descriptive terms now applied to personalities, sanguine, phlegmatic, bilious, and melancholic attest to the durability of this and many other Greek medical constructs and philosophies. One of the major problems of understanding ancient medicine, trying to understand the disease at issue, is not a problem when studying the history of wound care, at least with regard to acute wounds. Wounds inflicted with sharp and blunt instruments, burns, bites, and other such injuries are presumably the same throughout history. With regard to making wounds to treat wounds, Indian medicine, which introduced skin grafting and skin flaps especially to repair noses which were cut off as punishment, was far ahead of western medicine.

Among the medical works predating Greek medicine, we learn from the Smith papyrus (transcriptions of an Egyptian document dating from 3000–2500 B.C.E.) that wound edges were brought together with resin-covered linen strips, that the standard wound salve was made of grease, honey, and lint (functioning much as our current occlusive dressings), and that wounds were categorized as diseased or sick wounds and not sick wounds. Hippocrates in 400 B.C.E. is generally credited with this "discovery." The *Illiad* (approximately 1000 B.C.E.) describes 147 wounds. Although the treatments were holistic—the wounded were carried to a tent, given a seat, told stories, given a cup of wine sprinkled with grated goat cheese and given a barley meal served by a beautiful woman who later washed the wounds with warm water—they were not very effective and the mortality rate was 77.6%. Bleeding probably accounted for most deaths since the only treatment mentioned to check bleeding, beyond skillful bandaging mentioned twice by Homer, was recitation of a charm or singing of a song. Although not mentioned, it is likely based on agriculture records and pottery designs in the shape of poppies that opium was available for the wounded.

Hippocrates (460–370 B.C.E.), whose existence is confirmed by the writing of both Plato and Aristotle, is known through a collection of medical works, none thought to be original but many of which describe his efforts. Hippocrates worked

frequently with wounds both at his "office," at home at Kos, and when traveling to treat the ill. Credited with defining first intention healing (i.e., direct healing of closely approximated wound edges without suppuration), he rarely had recourse to this approach. In an era when almost all wounds became infected and in which there was not a distinction between acute wounds, chronic wounds, and ulcers, one of the issues most dealt with by Hippocrates was the issue of pus. The two types of pus he noted would today be described as severe infection and mild infection. The Hippocratic physician was in fact fearful of too little pus believing that: (1) pus which came from liquefaction of dried blood and bruised tissue within the wound produced a needed cleaning of the wound (2); patients unable to swell and produce pus were so sick that they did not survive—thus, no pus = bad, pus = good; (3) good pus prevents bad; and (4) bad humors could be eliminated by ripening and being released as pus.

Greek physicians most often attempted to take the acute wound "rapidly through suppuration," especially if it contained any bruised tissues. Toward this end, the physician deliberately irritated the wound. To prevent suppuration Greek physicians used a class of topicals called Enhemes, which were both dry and wet and usually contained metals such as lead oxide, zinc oxide, copper oxide, and copper sulphate. These are antiseptics but toxic to cells as well as bacteria. Based on Hippocratic teaching, Greek physicians almost always poured wine into wounds and over wound dressings and used sponges with dried wine or vinegar. Studies have indeed demonstrated that wine is bactericidal but the active component is not the 9–12% alcohol (70% is required) but the polyphenol, malvoside. Overall, since Greek physicians chose to induce suppuration we would say that the Greek wound healer found it easier to help infection than to fight it, although infection as we know it was unconceptualized.

Local treatment of the wound was not terribly helpful or harmful. However, the three general treatments of seriously wounded (or ill) patients—bleeding, starving, and purging—were not only harmful but also were long lasting, with bleeding ending only in the eighteenth century.

Bleeding, perhaps the most basic issue in wound care, was as little understood and inadequately dealt with as was infection. The concept of a pump was virtually unknown and blood was not known to circulate. While blood was known to be in veins, arteries were thought to contain air. When a wound was inflamed, it was deemed a problem of excess blood which often was treated by bleeding the patient either from the inflamed wound or from a distant site. Although an occasional wound was sutured to bring the lips together, the idea of tying vessels to stem bleeding was unknown to Hippocrates. However, later Greek physicians, especially the Alexandrians, did discover the value of ligating vessels to stop bleeding. Erasistratos, or his pupils in Alexandria, is credited with the discovery of tying off vessels as well as a faulty but early recognition that blood is pumped peripherally, although circulation was not understood.

The Romans distrusted physicians and Greek physicians in particular. In his compendium of information (and misinformation) known as *Natural History*, Pliny the Elder (23–79 C.E.) states, "Heaven knows, the medical profession is the only one in which anybody professing to be a physician is at once trusted, although nowhere else is an untruth more dangerous. We pay however no attention to the danger, so great for each of us is the seductive sweetness of wishful thinking."

Celsus (14–20 C.E.), who lived in Rome before Pliny, was however a Roman and as Pliny, wrote in Latin rather than Greek. Celsus's book *De Medicina* 1478 C.E.

was the first printed medical book by a medical author. It was "lost" for fourteen centuries, but is the only medical book from Western antiquity to survive in a complete form. Celsus is often credited as the first to differentiate a wound from an ulcer noting that blood comes from a fresh or healing wound while pus comes from an ulcer. Celsus stopped bleeding with compression and if this failed, by ligating the veins, leading to the first description of how to amputate legs. Celsus also described cauterization and cupping a distant site to draw blood as hemostatic methods. For closing acute wounds, he described suturing—a woman's hair was often used—or pins (fibulas). All wounds were to be cleansed with sponges squeezed out of vinegar or wine, while blood, lint, and other foreign materials were to be removed. Neither Celsus nor Pliny was short of topical medical wound treatments. Celsus listed thirty-four ointments and plasters for wounds. All but five contained heavy doses of lead and copper salts, some with mercury and antimony sulfates. The five which did not were meant to induce pus. The carriers were resins, pitch bitumen, wax, oil, and vinegar. Without doubt, Celsus is best known to us as the physician who defined the cardinal signs of acute inflammation—redness, swelling, heat, and pain (rubor, tumor, color, and dolor).

The last great name in medical antiquity, Galen, was born in 13 C.E. in Pergamon. Although he was a Greek who had also studied anatomy in Alexandria, Galen lived most of his adult life in Rome, was the physician to Roman emperors including Marcus Aurelius, wrote hundreds of medical and scientific books and had a wide experience in treating wounds during his three years as a physician to the gladiators. As a scientist, he is credited with opening live arteries to prove that they contained blood, tying the ureters of living animals to prove that urine comes from the kidneys and cutting the spinal cord of animals at various levels to study paralysis. As a wound healer, he pinched, sutured, and twisted vessels to stop bleeding. As an admirer of Hippocrates' works, his local wound care consisted principally of wine- and vinegar-soaked sponges and wound debridement. He famously did not advocate tourniquets, which he believed squeezed and lead to more blood coming out of the wound. Galen strongly advocated the four humors theory of disease, as well as diets we would now call non-nutritious and phlebotomies—bleeding to cure bleeding—as treatment for chronic wounds. Overall, the principal wound healing issues of antiquity seem to have been resolved as follows: bleeding was stopped with compression, vessel ligation, and cautery; inflamed wounds were treated with local or distant bleeding; irritation was used to induce mild suppuration ("laudable pus") and secondary intention healing was favored over primary. These views were expressed in the writings of Galen, who became the ultimate medical authority, and they prevailed throughout the Middle Ages and the Renaissance. However, significant dissent to the doctrine of laudable pus and healing by secondary intention was made by some surgeons, especially by Hugh of Luca the founder of the Bologna School, (1160–1257 C.E.) and his son Theodoric (1205–1296 C.E.). Although Hugh left no written record, through the writings of Theodoric ("Chirurgia, 1267 C.E.) and other followers, including the French surgeon Henri de Mondeville, we know that this group of surgeons advocated primary intention healing; specifically, cleaning the wound, bringing its lips together in the proper anatomical state, and, if necessary, holding them by sutures. They also favored use of an opium-containing soporific sponge applied to the nostrils to induce sleep to allow surgical repair to proceed. Despite such independent thinking, the Galenic view remained dominant through medieval times being followed by the great physicians of the period such as Ambrose Paré. It should be noted that the virtue of open or secondary healing

of contaminated wounds was relearned in the World War II and the Korean and the Vietnam wars.

John Hunter the Scottsman (1728–1793), who was an anatomist-turned surgeon, made observations based on animal experimentation and practical war experience which ran counter to the received surgical truths. He described three methods by which wounds healed: by immediate primary union, by implementation with the flow of a cementing "coagulable lymph" or by secondary union (granulation). Using the microscope, he documented that coagulable lymph contained white and red corpuscles, and in contrast to the conclusions of Hippocrates, was not a corrosive fluid derived from the breakdown of devitalized tissue. Hunter's willingness to be guided by direct observation and experimental fact rather than past authority paved the way for the acceptance into medical practice of the scientific advances of the nineteenth century.

Based on their observations that nerves and vessels branched into smaller and smaller units, Greek physicians had developed a concept of "tissue" being composed of invisible strands of nerves and vessels embedded in a material they named interstitia. Greek thinkers are rightly famous for such reasoning, an example of such being their conceptualization of the atom. This technique has been dubbed "the Greek microscope." Having a real microscope, Rudolph Virchow (1821–1902) demonstrated the cellular events of wound healing, especially the key role of the fibroblast. That tissues were composed of cells was an unknown concept in antiquity. It remained for Julius Cohnagin (1839–1884) to show that pus cells are actually blood cells which are allowed to pass into the wound by alteration of the walls of the blood vessels. In the 1860s, the discovery by Louis Pasteur, while working on problems in the silk worm industry, that bacteria played a pivotal role in disease led to dramatic changes in medical thinking. The English surgeon Joseph Lister (1827–1912), noting that simple fractures healed promptly and without suppuration while suppuration and often systemic signs of inflammation were an almost inevitable complication in compound fractures, came to the conclusion that the difference between the two was that the break in the skin allowed micro-organisms into the wound, causing the suppuration in compound fractures. Lister's intuitive conclusions on the applicability of Pasteur's observations to surgical infections as outlined in his 1868 address on the antiseptic approach to surgery, altered operating room behavior rapidly and permanently. The elegant experiments of Robert Koch in the 1870s definitively characterized the etiology of traumatic infected wounds. The role played by the phagocyte host response to bacterial infections was discovered by Elie Metchnikoff (1845–1916).

In 1910, Nobel Prize winner Alexis Carrel divided the stages of wound healing into four periods: quiescent, granulomatous retraction, epidermalization, and cicatricial, based on a series of animal experiments. Hunter had also constructed a time frame for healing but Carrel's work, based on experimental data, was able to assign more precise time limits, and ultimately his work in collaboration with that of others defined some of the effects of diet, temperature, and other factors on the normal wound repair process. The studies of Edward Howes, Joseph Sooy, and Samuel Harvey using tensile strength allowed the study of wounds beyond the skin and led to definition of the influence of aging and vitamin C depletion on the healing of wounds. The introduction of tissue culture techniques by Alexis Carrel and other associates led to many breakthroughs in understanding, including a better appreciation of epidermalization, which was finalized through the work of Shattuck Hartwell and Theodore Gillman. Hartwell in particular noted the considerable difference in

the subepithelial healing events between human and animal wounds. In particular, Hartwell pointed out that experimental wounds in animals including the dog, guinea pig, and rabbit, while similar to one another, had histologic findings similar to those seen in human wound healing by secondary intention. Only in domestic swine were the subepithelial events similar to healing by first intention seen in human wounds healing primarily.

The works described provided much of the basis for wound healing as we now understand it. The important role of the fibroblast in generating fibrotic healing characteristic of dermal repair and the key part played by the macrophage (Liebovich and Ross in 1975) were among the many advances of the twentieth century. However, in general, few concerned themselves with or even believed it possible to do more than to optimize the natural healing process. J. E. Dunphy, surgeon and scientist, conducted experiments showing that wounds deliberately reopened and resutured 4–6 days after operation had almost the same tensile strength as a fresh primary that had not been opened at the end of 1 week. Dunphy's postulate of a "wound hormone" to explain these findings led to a search for such a wound hormone and suggested the possibility of speeding healing beyond the natural speed. In 1962, George Winter's studies of occlusive film treatment of superficial swine wounds showed that epithelization could be sped by about 30%. This work was repeated in man by Hinman and Maibach in 1963 showing indeed that in man epithelization could be sped. David Rovee's work showing that occlusion improved scar appearance expanded the concept of controlling wound repair to include dermal as well as epidermal events. In work conducted in the 1960s that ultimately led to a Nobel Prize, Stanley Cohen, observed that submaxillary gland extracts injected into new born mice led to earlier epidermal maturation as manisfested by early eyelid opening and precocious eruption of the incisors. He ultimately isolated EGF as the active principle in studies which reignited the search for agents able to act as "wound hormones."

2. ULCERS

2.1. Venous Ulcer

Although skin ulcers have been noted at different points throughout history, their recognition as specific entities, such as the venous, and the diabetic ulcer have a shorter formal history than acute wounds and injuries. The venous ulcer, most common of the leg ulcers today, is thought to not have been the most common leg ulcer in the 1700s and 1800s. Studies of medical records from that period indicate that leg ulcers were more frequent in men of 20–30 rather than in women and older people as is currently the case. The records suggest that this was related to the frequency of syphilitic, scorbutic, and tuberculous ulcers.

Hippocrates himself is said to have had a large ulcer. In 400 B.C.E., he wrote that "in the case of an ulcer, it is not expedient to stand, especially if the ulcer be situated on the leg." Hippocrates was also aware of the relationship between varicose veins and leg ulcers, as was Celsus. By 400 C.E., leg ulcers were treated by removing the veins which carried "rotten blood." Such "knowledge" notwithstanding, the dominant view of ulcers, especially those on the legs, was that they were portals to discharge unhealthy humors. Although it was considered permissible to improve them, healing ulcers were thought to be dangerous lest the humors ascend to other organs causing more serious disease. In ulcers healing too rapidly, especially in

elderly, weak patients were deliberately inflamed with chemicals to stimulate a fresh flow. An alternative was to make a wound elsewhere, most often nearby or on the other leg, and keep it open and flowing with various foreign bodies while allowing the ulcer to heal. The dominance of the humoral theory faded by the early 1800s led by John Bill's teaching. Retardation of circulation and an association with varicose veins was considered an important pathologic factor by the eighteenth century. It was recognized that the valves of varicose veins could not resist high pressure and that their walls were weak. Although vessel ligation and pressure bandages were used by some, at this early date the theory that ulcers were safety valves which should not be compressed as they allowed noxious elements to escape was dominant and precluded widespread use of compression and vessel ligation. Subsequently, medical thought about venous ulcers became dominated by theories and treatment related to retrograde blood flow and stasis of blood flow. Trendelenburg claimed that there was a "private circulatory system" in the varicose veins. Unna believed that there was complete capillary insufficiency. In the mid-1800s, John Gay refuted the relationship between varicose veins and leg ulcers noting varicose ulcers in patients without varicosities and the converse. Hauxhausen's studies of blue dye injected into varicose veins refuted the idea of a private circulatory system and showed considerable flow which was improved with walking. His temperature studies indicated a greater flow in the infected legs. By 1917, Homan recognized the relationship of prior deep vein thrombosis. In the mid-1700s, surgeons recognized the curative effect of bed rest but found that short of constant confinement they recurred. Thomas Brynton of Bristol in 1797 described his method of applying adhesive strips about the limb and over the ulcer to draw the edges together and to support and prevent distention of the veins.

2.2. Diabetic Ulcers

Although Marchal de Cavi clearly described diabetic neuropathy and its relationship to diabetics in 1864 and in 1887, T. Davis Pryce assigned " . . . considerable share [of the blame for a perforating foot ulcer] to diabetes and vascular disease." Until the 1930s, diabetes was only credited with causing the painful, dry, or senile gangrene of the foot. Rose and Carless in 1933 recognized in younger diabetic patients a wet gangrene with hot swollen painful foot ulcers under callosities. The link between neuropathies and the deformities as summarized by Charcot was recognized by Lambrinidi in 1937. D.H. Lawrence, himself a diabetic and among the first to use insulin, requested a wedge resection of his metatarsalphalangeal joint and toe leading to the so-called ray amputation, whose healing confirmed the lack of an arteriosclerotic basis for wet gangrene.

2.3. Pressure Ulcers

Pressure ulcers, known also as decubitus ulcers and bed sores, have been recognized throughout much of recorded medical history—bedsores have even been found by contemporary examinations of Egyptian mummies. The therapy recommended by the surgeon Ambrose Paré in his book, *Of Ulcers, Fistulas and Hemorrhoids*, is well illustrated by his description of the case of the Marquis of Auret in 1569. Sent by the French king, Paré found that the wounded Marquis had developed a "buttock bed sore" from "too long a time lying on it. . . ." His treatment included a "rich meat broth . . . ," " . . . a little pillow of down to keep his buttock (wound) in the air without

his being supported on it . . . ,'' pain killers, a clean, dry, soft bed, and several olive oil-based unguentums for the wound. His approach illustrates a keen appreciation for the role of nutrition, cleanliness, and pressure relief. Although now nearly forgotten, the neurotrophic theory debate was in the mid-1800s centered on the pressure ulcer. Jean-Martin Charcot, whose epinomic foot deformity had also related to a lack of nerve-derived nutritional or trophic factors, supported the idea that both the decubitus acuta, pressure ulcers developing rapidly after paraplegia, and the decubitus chronica, slowly developing pressure ulcers in infirmed and debilitated patients, were strongly if not totally the result of absent neurotrophic factors. He supported his proposal with elaborate drawings of clinical cases and nerve pathways. Ultimately, experimental work in animals by Eduard Brown-Séquard showed that paraplegic animals did not develop ulcers, '' . . . when I took care to prevent any part of their bodies from being in a continued state of compression. . . . '' When he allowed ulcers to develop, he cured them by ''preventing compression.'' He also emphasized washing and cleanliness. The debate between Charcot, who dealt with patients, and Brown-Séquard, who studied animals, was heated, with Charcot inscribing above his door the sentence ''You will not find a clinic for dogs here.'' By 1940 Michael Kosiak's now classic and prize-winning paper, Etiology and Pathology of Ischemic Ulcers, showed the inverse relationship between pressure and time and pressure ulcer development. His studies also demonstrated that redness and edema following release of pressure lasted about half as long as the duration of the pressure and that necrosis never occurred before three days. Microscopic pathology was found with as little as 60 mm of mercury for only one hour. The work by J. M. Milholland et al. in 1943 relating low plasma protein to pressure ulcers and showing the therapeutic effect of high protein diet on pressure ulcer healing added considerably to our understanding and ability to treat this still puzzling entity.

3. CONCLUSION

Looking over the history of wound healing, we can appreciate that many strides have been made in understanding and treatment especially of acute wounds. Bleeding can be controlled and infection is understood and in most cases controlled or overcome. Although we are still unable to sufficiently control and improve upon the natural healing of acute wounds, we are able to speed epithelization demonstrating that natural healing can be improved and making improved healing a goal of wound healers. Although our understanding and treatment abilities in the area of ulcers and chronic wounds is less advanced, many of the concepts which inhibited rational thinking about chronic wounds have been overcome and physicians and scientist have joined nurses in their concern for ulcers and chronic wounds.

2
Fetal Wound Repair

Amy Colwell
Department of Surgery, Brigham and Women's Hospital, Boston, Massachusetts, U.S.A.

Michael T. Longaker
Director of Children's Surgical Research, Stanford University Medical Center, Stanford, California, U.S.A.

H. Peter Lorenz
Division of Plastic Surgery, Stanford University Center for Children's Surgical Research, Stanford, California, U.S.A.

1. INTRODUCTION

Scar and fibrosis are the end result of postnatal tissue injury and disease. Remarkably, fetal full-thickness skin wounds heal with restoration of normal epidermal and dermal architecture and not with scar formation. The biology responsible for scarless wound healing, a paradigm for ideal tissue repair, has been actively researched since this discovery.

Despite extensive investigation, the mechanism of fetal wound healing remains largely unknown. We do know that, early in gestation, fetal skin is developing at a rapid pace and the extracellular matrix (ECM) is a loose network facilitating cellular migration. Wounding in this unique environment triggers a cascade of events culminating in a scarless wound phenotype. Comparison between postnatal and fetal wound healing has revealed differences in inflammatory response, cellular mediators, and ECM modulators. Further investigation may reveal novel genes essential to scarless repair and bring us closer to our ultimate goal: elimination of scar.

2. DEVELOPMENT

2.1. Fetal Skin

Since the transition from scarless to scarring wound repair occurs in the context of fetal skin development, an investigation of normal skin maturation is warranted. Development of the epidermis and dermis involves mutual inductive mechanisms between ectoderm and mesoderm. Epidermal primordial cells derived from ectoderm proliferate at 7 weeks gestation forming a squamous layer of periderm and a basal germinative layer. Periderm cells are keritinized, shed, and eventually replaced by

the stratum corneum at 21 weeks. The basal germinative layer becomes the stratum germinativum, a source of new cells for dermal appendages and the intermediate layers found in mature skin. The dermis is derived from mesoderm. Mesenchymal cells produce collagen and elastic connective tissue fibers by 11 weeks. Skin maturation with dermal thickening continues into the postnatal period (1).

2.2. Fetal Extracellular Matrix

The fetal ECM is a dynamic layer of collagen, proteoglycans, and glycosaminoglycans which undergoes a series of changes during development. In the past, the ECM was regarded as an inert scaffolding. We now know that it has an important role in cell adhesion, migration, differentiation, and proliferation (2). Fetal ECM differs from adult ECM in collagen composition, hyaluronic acid (HA) content, and proteoglycan ECM modulators. This may have implications in scarless repair.

Type I collagen is the principal component of both adult and fetal ECM. However, fetal skin has a higher ratio of type III to type I collagen than adult skin (3). With maturation, the relative amount of type III collagen in fetal skin diminishes, although the adult phenotype is not seen until the postnatal period (4). Fetal skin contains more HA, the principal glycosaminoglycan of the ECM, than adult skin (5). The net negative charges of HA attract water molecules, thus tissues rich in HA are more "fluid" and facilitate cellular movement (2). Proteoglycan ECM modulators serve a role in collagen synthesis, maturation, and degradation. Decorin, lysyl oxidase, and matrix metalloproteinases (MMPs) increase during fetal skin development while fibromodulin, another modulator of collagen fibrillogenesis, decreases with maturation (6–9).

3. SCARLESS FETAL WOUND REPAIR SPECIFICITY

3.1. Scarless Fetal Wound Phenotype

The developing fetus has the unique ability to heal wounds by regenerating normal epidermis and dermis in contrast to scarring observed in the adult. Fetal wounds are distinguished from adult wounds by differences in collagen deposition and cross-linking patterns, HA content, and differential expression of proteoglycan ECM modulators (6–11).

In scarless fetal wounds, collagen is rapidly deposited in a fine reticular pattern indistinguishable from uninjured skin. In contrast, adult scarring wounds have disorganized thick collagen bundles with more collagen cross-linking (10–12). The HA content of scarless fetal wounds increases more rapidly, is more sustained, and is overall greater than that of adult wounds (5). Fetal wounds have greater HA-stimulating activity and fewer proinflammatory cytokines, such as IL-1 and TNF alpha, that downregulate HA expression (13).

The ECM architecture is influenced by regulators of collagen organization and degradation. Decorin, a modulator of collagen fibrillogenesis, is downregulated in fetal wounds while fibromodulin is upregulated in the fetus (6,9,14). This may prove useful as a marker of wound phenotype—if exogenous factors decrease scarring, they may decrease decorin and increase fibromodulin. Matrix metalloproteinases and tissue-derived inhibitors (TIMPs) function in ECM turnover. Overall, scarless wounds have a higher ratio of MMP to TIMP expression favoring remodeling and less accumulation of collagen (8).

3.2. Scarless Repair Is Intrinsic to Fetal Skin

The capacity for scarless repair was initially attributed to the sterile intrauterine environment. Amniotic fluid is rich in HA and growth factors but devoid of bacteria and inflammatory stimulators. However, early studies demonstrated that the intrauterine environment is neither essential nor sufficient for scarless repair. Fetal marsupials develop outside the uterus in a maternal pouch and heal cutaneous wounds without scar (15). Adult sheep skin transplanted onto the backs of fetal sheep bathed in the amniotic fluid of the intrauterine environment heal incisional wounds with scar (16).

Fetal scarless repair is also organ-specific. At time points early in gestation where fetal skin heals without scar, fetal stomach, intestine, and diaphragm heal with scar formation (17,18). This suggests that certain subpopulations of cells in skin modulate the local wound healing response. Further evidence implicates the fetal fibroblast as the effector cell responsible for scarless repair. Lorenz et al. (19) transplanted human fetal skin from 15–22 weeks gestation subcutaneously and cutaneously onto the backs of athymic adult mice. In this adult system, wounds created in the subcutaneous fetal grafts healed scarlessly with human collagen from fetal fibroblasts. Conversely, wounds made in the gestationally equivalent cutaneous fetal grafts healed with scar composed of mouse collagen from adult fibroblasts.

3.3. Scarless Repair Depends on Gestational Age and Wound Size

Fetal wounds pass from scarless repair to healing with scar formation during gestation. The ontogenetic transition of rat skin has been defined in an organ culture system and confirmed in vivo with confocal microscopic analysis (12,20). This transition point lies between days 16.5 and 18.5 of gestation (Term = 21.5 days). In a human fetal skin model, the transition point occurs after 24 weeks of gestation (19). Wound size modulates the transition point. In fetal lambs, increasing wound size increased the frequency of scarring at a gestational age when smaller wounds healed scarlessly (21). In nonhuman primates, the transition from scarless to scarring repair has been shown to proceed through an intermediate wound phenotype. Fetal monkey lip incisional wounds heal with restoration of normal epidermal appendage and dermal collagen architecture in midgestation. At the start of the third trimester, these wounds do not restore epidermal appendage (hair follicle and sebaceous gland) architecture, but still heal with a normal collagen dermal pattern. Thus, a ''transition wound'' phenotype occurs. By the mid-third trimester, the wounds heal with a typical scar pattern—no appendages and collagen scar (22).

4. MECHANISMS OF SCARLESS REPAIR

4.1. Wound Healing and Inflammation

The mechanisms underlying fetal wound specificity are under active investigation. In the postnatal animal, tissue injury disrupts the microvasculature of the skin allowing extravasation of blood elements into the wound. Contact with exposed collagen activates platelets causing discharge of their alpha granules and aggregation to form a platelet plug. Adhesion proteins and cytokines, such as platelet-derived growth factor (PDGF) and transforming growth factor-beta (TGF-β), promote additional platelet adhesion and aggregation. These cascades attract macrophages and

neutrophils to the postnatal wound, which secrete a plethora of cytokines amplifying the inflammatory response and attracting fibroblasts (23). However, scarless wounds are characterized by a relative lack of inflammation. Furthermore, introduction of inflammation into normally scarless wounds produces dose-dependent increases in wound macrophages, neutrophils, collagen deposition, and scarring (24). This suggests an important role of inflammation in scar formation.

4.2. Cellular Inflammatory Mediators

4.2.1. Platelets and Neutrophils

The absence of an acute inflammatory infiltrate in scarless wounds may be partly explained by decreased fetal platelet degranulation and aggregation. Olutoye et al. (25) measured the aggregatory capabilities of adult and fetal porcine platelets after exposure to collagen and ADP. The fetal platelets responded suboptimally to collagen and showed an age-dependent aggregatory response to ADP exposure corresponding with the transition period for cutaneous scarless to scar-forming wounds. An age-dependent defect in the ability of fetal neutrophils to phagocytose pathogenic bacteria has also been demonstrated in fetal sheep (26).

4.2.2. Fibroblasts

Synthesis and remodeling of the ECM by fibroblasts are essential for wound healing. Adult and fetal fibroblasts are recruited to the site of injury by soluble chemoattractants released by macrophages and neutrophils. Fetal wounds characteristically have less inflammatory cells and cytokine expression yet heal more rapidly than adult wounds. This may be partly explained by intrinsic differences between adult and fetal fibroblasts.

Fetal fibroblasts have a greater ability to migrate into collagen gels than adult fibroblasts. A migration stimulation factor secreted by fetal fibroblasts is purported to be responsible for this enhanced migratory ability (27). Fetal fibroblasts have more surface receptors for HA, which also serves to enhance fibroblast migration (28).

Differences in contractile fibroblasts, termed ''myofibroblasts'', have also been reported. Wounds made early in gestation have virtually no myofibroblasts. In contrast, scarring fetal and postnatal wounds have progressively more active myofibroblasts, which correlates with contraction and degree of scarring (29).

4.3. Cytokines

4.3.1. Transforming Growth Factor-Beta (TGF-β)

The transforming growth factors were linked to wound healing shortly after their discovery more than 20 years ago. Isoforms TGF-β1 and TGF-β2 are thought to be profibrotic and to promote scar formation because their expression is increased in adult wounds and their exogenous administration to adult wounds increases collagen, protein, and inflammatory cell accumulation (30).

Evidence implicating TGF-β1 as a proscarring cytokine is well established. Scarless wounds in fetal mice have less TGF-β1 staining than neonatal or adult wounds (31). Insertion of PVA sponges containing TGF-β1 into rabbit wounds causes normally scarless wounds to heal with scar (31). Treatment of adult rat wounds with neutralizing antibodies to TGF-β1 and TGF-β2 reduces scar formation (32,33).

Furthermore, the relative proportion of TGF-β isoforms, and not the absolute amount of any one isoform, may determine the wound phenotype. In scarless fetal wounds, TGF-β3 expression is increased while TGF-β1 expression is unchanged. Conversely, TGF-β1 expression is increased and TGF-β3 decreased in scarring fetal wounds (34,35). This suggests the ratio of TGF-β3 to TGF-β1 may determine whether tissue regenerates or forms scar. Treatment of adult rat wounds with exogenous TGF-β3 reduces scar formation (36).

4.3.2. Other Growth Factors

The PDGF and fibroblast growth factor (FGF) are additional profibrotic cytokines. The PDGF, a potent mitogen and chemoattractant for fibroblasts, has prolonged expression during scar formation but disappears by 24 hr in fetal wounds (37). The FGF family of cytokines, including keritinocyte growth factors 1 and 2, has greater expression with increasing gestational age in fetal skin and during adult wounding (38). In contrast, vascular endothelial growth factor (VEGF) increases twofold in scarless wounds while its expression remains unchanged in scarring fetal wounds (39). Thus, an increased stimulus for angiogenesis and vascular permeability may assist in the rapid healing of fetal wounds.

4.3.3. Interleukins

Interleukins are cytokines important in chemotaxis and activation of inflammatory cell mediators. IL-6 stimulates monocyte chemotaxis and macrophage activation while IL-8 attracts neutrophils and stimulates neovascularization. Both IL-6 and IL-8 expression are significantly lower in early fetal fibroblasts at baseline and with PDGF stimulation compared to in adult fibroblasts (40,41). IL-10 has an anti-inflammatory function through decreased production of IL-6 and IL-8. Treating adult mouse wounds with an IL-10 over-expression adenoviral vector reduces inflammation and induces scarless healing (42). This may have potential therapeutic implications in human adult wounds.

4.4. Genetic Controls of Scarless Repair

The mechanistic differences between scarless and scarring repair are likely regulated at the gene expression level. Homeobox genes are transcription factors that are implicated in the patterning and cell type specificiation events during development. Their role in skin embryogenesis and wound healing is being investigated. Human homeobox genes MSX-1, MSX-2, and MOX-1 are differentially expressed in skin development (43). Additionally, human fetal scarless repair is associated with decreased expression of HOXB13 and increased PRX-2 expression (44). Given that scarless repair is inherent to developing skin, it seems likely that coordinated control of groups of genes by transcription factors, such as homeobox genes, has a crucial function during the repair process.

5. SUMMARY

Early in gestation, the fetus heals wounds with regeneration of normal epidermal and dermal architecture. Unique characteristics of fetal extracellular matrix, inflammatory cells, fibroblasts, cytokines, and developmental gene regulation may be

responsible for the scarless wound phenotype. The ability to heal scarlessly is independent of the intrauterine environment but dependent upon gestational age and wound size. More research is necessary to unravel the mechanisms underlying scarless repair if we hope to devise more effective therapies for scar reduction and excess fibrosis.

REFERENCES

1. Moore KL. The integumentary system. Moore KL, Persaud TVN, eds. Before We were Born: Essentials of Embryology and Birth Defects. Philadelphia: W.B. Saunders Company, 1998:482–487.
2. Clark RAF. Wound repair: overview and general considerations. Clark RAF, ed. The Molecular and Cellular Biology of Wound Repair. Vol. 23. New York: Plenum Press, 1996:3–50.
3. Merkel JR, DiPaolo BR, Hallock GG, Rice DC. Type I and type III collagen content of healing wounds in fetal and adult rats. Proc Soc Exp Biol Med 1988; 187:493–497.
4. Hallock GG, Merkel JR, Rice DC, DiPaolo BR. The ontogenetic transition of collagen deposition in rat skin. Ann Plastic Surg 1993; 30:239–243.
5. Mast BA, Flood LC, Haynes JH, DePalma RL, Cohen IK, Diegelmann RF, Krummel TM. Hyaluronic acid is a major component of the matrix of fetal rabbit skin and wounds: implications for healing by regeneration. Matrix 1991; 11:63–68.
6. Beanes SR, Dang C, Soo C, Wang Y, Urata M, Ting K, Fohkalsrud EW, Benhaim P, Hedrick MH, Atkinson JB, Lorenz HP. Down-regulation of decorin, a transforming growth factor-beta modulator, is associated with scarless fetal wound healing. J Pediatr Surg 2001; 11:1666–1671.
7. Beanes SR, Dang C, Soo C, Lorenz HP. Ontogenetic transition in the fetal wound extracellular matrix correlates with scar formation. Wound Repair Regen 2001; 9:151.
8. Lorenz V, Soo C, Beanes SR , Dang C, Zhang X, Atkinson JB, Ting K. Differential expression of matrix metalloproteinases and their tissue-derived inhibitors in scarless fetal wound healing. Surg Forum 2001:397–401.
9. Soo C, Hu FY, Zhang X, Wang Y, Beanes SR, Lorenz HP, Hedrick MH, Mackool RF, Plass A, Kim SJ, Longaker MT, Freymiller E, Ting K. Differential expression of fibromodulin, a TGF-β modulator, in fetal skin development and scarless repair. Am J Pathol 2000; 157:423.
10. Longaker MT, Whitby DJ, Adzick NS, Cromblehome TM, Langer JC, Duncan BW, Bradley SM, Stein R, Ferguson MW, Harrison MR. Studies in fetal wound healing. VI. Second and third trimester fetal wounds demonstrate rapid collagen deposition without scar formation. J Pediatr Surg 1990; 25:63–69.
11. Whitby DJ, Ferguson MWJ. The extracellular matrix of lip wounds in fetal, neonatal, and adult mice. Development 1991; 112:651–668.
12. Beanes SR, Hu FY, Soo C, Dang CM, Urata M, Ting K, Atkinson JB, Benhaim P, Hedrick MH, Lorenz HP. Confocal microscopic analysis of scarless repair in the fetal rat: defining the transition. Plast Reconstr Surg 2002; 109:160–170.
13. Kennedy CI, Diegelmann RF, Haynes JH, Yager DR. Proinflammatory cytokines differentially regulate hyaluronan synthase isoforms in fetal and adult fibroblasts. J Pediatr Surg 2000; 35:874–879.
14. Soo C, Beanes S, Dang C, Zhang X, Ting K. Fibromodulin, a TGF-β modulator, promotes scarless fetal repair. Surg Forum 2001; 52:578–581.
15. Armstrong JR, Ferguson MWJ. Ontogeny of the skin and transition from scar free to scarring phenotype during wound healing in the pouch young of *Monodelphis domestica*. Dev Biol 1995; 169:242–260.
16. Longaker MT, Whitby DJ, Ferguson MWJ, Lorenz HP, Harrison MR, Adzick NS. Adult skin wounds in the fetal environment heal with scar formation. Ann Surg 1994; 219:65–72.