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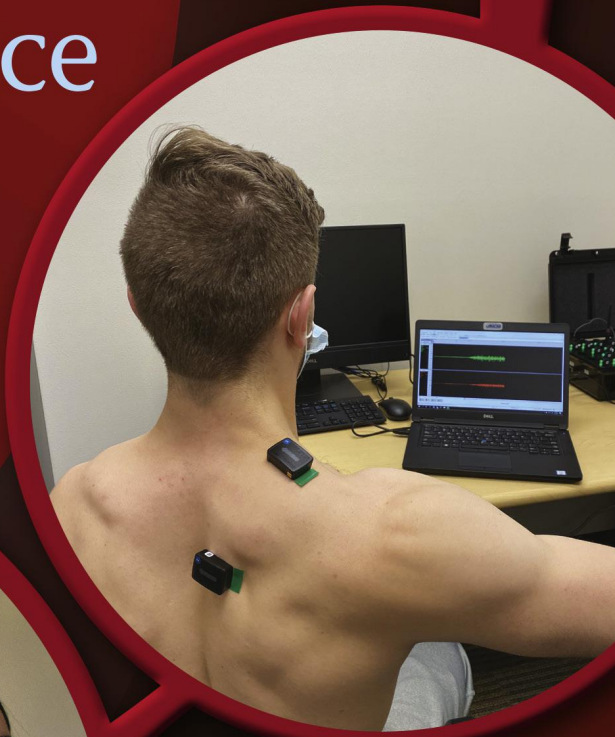
PHYSICAL AGENTS IN REHABILITATION

An Evidence-Based Approach to Practice

Michelle H. Cameron



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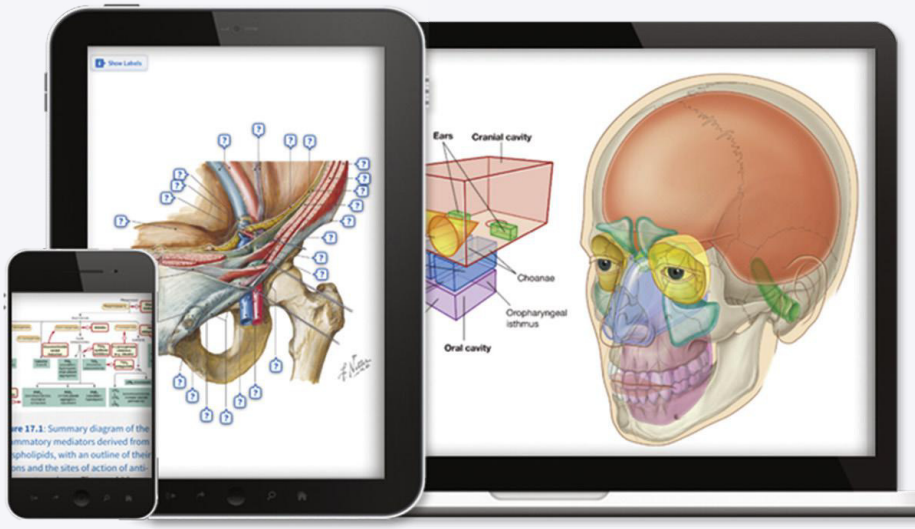

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Physical Agents in Rehabilitation

An Evidence-Based Approach to Practice

Physical Agents in Rehabilitation

An Evidence-Based Approach to Practice

Sixth Edition

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Biography

Michelle H. Cameron, MD, PT, MCR, the primary author of *Physical Agents in Rehabilitation: An Evidence-Based Approach to Practice,* is a physical therapist and a physician as well as an educator, researcher, and author. After 10 years working as a clinical physical therapist and teaching rehabilitation providers about physical agents, Michelle furthered her own education through medical training. She now works as a neurologist, focusing on the clinical care of people with multiple sclerosis and on research to optimize mobility in people with multiple sclerosis, while continuing to write, teach about, and do research on the use of physical agents in rehabilitation. Michelle is the co-editor of the texts *Physical Rehabilitation: Evidence-Based Examination, Evaluation, and Intervention* and *Physical Rehabilitation for the Physical Therapist Assistant* and has written and edited many articles on electrical stimulation, ultrasound and phonophoresis, laser light therapy, and wound management. Michelle's discussions of physical agents bring together current research and practice to provide the decision-making and hands-on tools to support optimal care within today's health care environment.

Acknowledgments

First and foremost, I want to thank the instructors who use this book in the classroom and the readers and purchasers of its previous editions. Without you, this book would not exist. In particular, I would like to thank those readers who took the time to contact me with their comments, thoughts, and suggestions about what worked for them and what could be improved.

I would also like to give special thanks to Cassidy Taylor, editorial research assistant, for her help with updating this edition of the book. Her skills and dedication to precision and organization kept me sane and on track and ensured that all the parts and the people came together to make the whole greater than the sum of its parts. I would also like to thank Melissa Rawe and Laura Klein, senior content development specialists at Elsevier, Sindhuraj Thulasingam, project manager at Elsevier, and Lauren Willis, senior content strategist at Elsevier, for their support throughout this project; Diane Allen, Jason Bennett, Tony Rocklin, Bill Rubine, and Gail Widener, contributing authors to this and previous editions, who updated their respective chapters thoroughly and promptly; David Adelson and Erika Hagstrom for their update of Chapter 3 on inflammation and tissue repair; Kimberly Jones who provided insightful updates to Chapter 4 on pain and pain management; Dana Lindberg who contribute to the update of Chapter 5 on tone abnormalities; and particularly Linda Monroe and Michelle Ocelnik, who not only updated their own chapters but also updated and reviewed all the teaching questions and slides that accompany this book.

Thank you all,
Michelle H. Cameron

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Preface

By writing the first edition of this book, I tried to meet a need that I believed existed—the need for a book on the use of physical agents in rehabilitation that covered the breadth and depth of this material in a readily accessible, systematic, and easily understood manner. I produced a text that leads the reader from the basic scientific and physiological principles underlying the application of physical agents to the research evaluating their clinical use, then to the practical details of selecting and applying each specific physical agent to optimize patient outcomes. The enthusiasm with which the previous editions of this book have been received—including compliments from readers; adoption by many educational programs; translation into multiple languages; and purchase by many clinicians, educators, and students around the world—demonstrates that the need was there and was met.

In all the subsequent editions, I have done my best to keep the most successful aspects from previous editions while bringing the reader new and updated information, further clarifying the presented material, and improving information accessibility. Each edition of this book provides easy-to-follow guidelines for the safe application of all physical agents discussed, as well as the essential scientific rationale and evidence base to select and apply interventions with physical agents safely and effectively. As the quantity of research has increased, along with the quality, this text has become even more important for making clinical decisions. To keep up with the pace of research, new developments in the field of rehabilitation, and technological advances in information delivery, I have added a number of new features to this edition.

The most significant new features in this edition of *Physical Agents in Rehabilitation* are the addition of a chapter on shock wave therapy (Chapter 18); the substantial updating of Chapter 4, on pain; and the reorganization of Chapter 9, on ultrasound, to make it consistent with other chapters, ease access to the information, improve clarity, and maximize comprehension.

In earlier editions, I tried to summarize and reference all the research on the use of each physical agent in rehabilitation. With the exponential growth of research and publication, this became impossible, and with the increased access to information and the growing search skills of clinicians, this has also become unnecessary. This edition focuses on and summarizes only the highest-quality evidence, including the most recent systematic reviews and meta-analyses and subsequent large-scale randomized controlled trials. The case studies then demonstrate how to seek out evidence specific to an individual patient by providing sample MEDLINE search strategies using the Patient, Intervention, Comparison (PICO) framework, followed by summaries of relevant key studies and reviews.

The new chapter on shock wave therapy (Chapter 18) was added in response to consistent feedback and requests from instructors and other readers. Shock wave therapy, which involves the application of brief, high-intensity, focused or radial sound waves, is gaining popularity as a therapeutic agent, particularly in promoting the resolution of chronic tendinopathy and other chronic localized inflammatory conditions. This chapter has the same structure as other chapters in this book and focuses on the use of shock wave therapy for the treatment of chronic musculoskeletal conditions. I am sure you will find it clear and that it meets your needs for a thorough, up-to-date summary of the use of shock wave therapy in rehabilitation.

In addition to the bigger changes, I have also made some smaller but significant changes to this text. I have kept electronic resources for students and practitioners, including PICO charts from the case studies, review questions for each chapter, and the extremely popular *Electrical Stimulation, Ultrasound, and Photobiomodulation (Laser) Handbook*, which has been updated to align with chapter updates and can be printed and used as a clinical quick reference guide. In addition, course instructors have access to PowerPoint slide sets and corresponding Image Collections for each chapter on Evolve (https://evolve.elsevier.com/).

Welcome to the sixth edition of *Physical Agents in Rehabilitation*!

Contents

1

Physical Agents: Essentials

CHAPTER OUTLINE

CHAPTER OBJECTIVES

After reading this chapter, the reader will be able to do the following:

- Maximize learning by understanding how to use all of the resources in this book.
- Define *physical agents.*
- List different categories of physical agents.
- Describe the basic effects physical agents have on various indications.
- List general contraindications and precautions for physical agents.
- Evaluate and plan for the use of physical agents.
- Describe attributes to consider when choosing a physical agent.
- Accurately and completely document treatment with physical agents.

How to Use This Book

This book is intended primarily as a course text for those learning to use **physical agents** in **rehabilitation.** It was written to meet the needs of students learning about the theory and practice of applying physical agents and to help practicing rehabilitation professionals review and update their knowledge. This book describes the effects of physical agents, provides guidelines on when and how physical agents can be most effectively and safely applied and when they should be avoided, and describes the outcomes that can be expected from integrating physical agents within a program of rehabilitation. The book covers the theory underlying the application of each agent and the physiological processes the agent influences, the research concerning its effects, and the rationale for the treatment recommendations. All chapters also include patient case studies with sample online PubMed search strategies used to identify relevant evidence.

After reading this book, the reader should be able to integrate the ideal physical agents and intervention parameters within a complete rehabilitation program to promote optimal patient outcomes. Readers should also feel confident structuring independent search strategies to locate relevant literature in PubMed, a freely accessible, constantly updated search engine that provides access to MEDLINE, a database of biomedical and allied health literature maintained by the U.S. National Library of Medicine.

This book's recommendations regarding the clinical use of physical agents integrate concepts from a variety of sources, including the American Physical Therapy Association's ***Guide to Physical Therapist Practice 3.0* (*Guide 3.0*).**[1] *Guide 3.0* is a normative model of physical therapist professional practice that encompasses the standards for quality assessment; professional conduct; evidence-based practice; and the International Classification of Functioning, Disability and Health (ICF) model of the World Health Organization (WHO). *Guide 3.0* is the most recent edition and is widely used by physical therapists and physical therapist assistants. This book applies the principles of evidence-based practice and the ICF model to guide the selection and application of physical agents. The ICF model (see Fig. 2.1) is used to consider and describe the impact of physical agent interventions on patient outcomes. This model was developed to describe functional abilities and differences and has been adopted globally, particularly among rehabilitation professionals.[2] The specific recommendations presented throughout this book are derived from the best available evidence on the physiological effects and clinical outcomes of physical agents, and the search strategies used to locate the evidence are shared. The book is divided into six parts:

Part I: Introduction to Physical Agents includes this introductory chapter, followed by a chapter introducing the physiological effects of physical agents and their clinical use by various professionals.

Part II: Pathology and Patient Problems starts with a chapter on inflammation and tissue repair, followed by individual chapters on pain, motion restrictions, and tone abnormalities.

Part III: Thermal Agents covers thermal agents, including superficial cold and heat, ultrasound, and diathermy.

Part IV: Electrical Currents starts with a chapter describing the physical properties of electrical currents. This is followed by individual chapters on the use of electrical stimulation for muscle contraction, pain control, and tissue healing and a chapter on electromyographic (EMG) biofeedback.

Part V: Electromagnetic Agents discusses photobiomodulation (previously known as *low-level laser therapy*) and ultraviolet therapy.

Part VI: Mechanical Agents has a new chapter on shock waves, followed by chapters on hydrotherapy, traction, and compression.

The print book includes access to an enhanced eBook with resources for students and practitioners, including PICO charts from the case studies, review questions for each chapter, and the *Electrical Stimulation, Ultrasound, and Photobiomodulation (Laser) Handbook*. In addition, course instructors have access to PowerPoint slide sets and corresponding Image Collections for each chapter on Evolve (https://evolve.elsevier.com/).

What Are Physical Agents?

Physical agents consist of energy and materials applied to patients to assist in their rehabilitation. Physical agents include heat, cold, water, pressure, sound, electromagnetic radiation, and electrical currents. The term *physical agent* can be used to describe the general type of energy, such as electromagnetic radiation or sound; a specific range within the general type, such as **ultraviolet (UV) radiation** or **ultrasound;** and the actual means of applying the energy, such as a UV lamp or an ultrasound transducer. The terms **physical modality,** *biophysical agent, physical agent modality, electrophysical agent,* and **modality** are alternatives for the term *physical agent* and are used interchangeably in this book.

Clinical Pearl

Physical agents are energy and materials applied to patients to assist in their rehabilitation. Physical agents include heat, cold, water, pressure, sound, electromagnetic radiation, and electrical currents.

Categories of Physical Agents

Physical agents can be categorized as thermal, electromagnetic, or mechanical (Table 1.1). **Thermal agents** include superficial-heating agents, deep-heating agents, and superficial-cooling agents. **Electromagnetic agents** include electromagnetic fields and electrical currents. **Mechanical agents** include **sound waves,** water, **traction,** and **compression**. Some physical agents fall into more than one category. Water and ultrasound, for example, can have mechanical and thermal effects.

TABLE 1.1 Categories of Physical Agents

Category	Types	Clinical Examples
Thermal	Superficial heating agents	Hot pack, paraffin
	Deep-heating agents	Ultrasound, diathermy
	Cooling agents	Ice pack
Electromagnetic	Electrical currents	TENS
	Electromagnetic fields	Ultraviolet, laser
Mechanical	Sound	Ultrasound, shock waves
	Water	Whirlpool
	Traction	Mechanical traction
	Compression	Elastic bandage, stockings

TENS, Transcutaneous electrical nerve stimulation.

THERMAL AGENTS

Thermal agents transfer energy to a patient to increase or decrease tissue temperature. Examples of thermal agents are hot packs, ice packs, ultrasound, whirlpools, and **diathermy. Cryotherapy** is the therapeutic application of cold. **Thermotherapy** is the therapeutic application of heat. Depending on the thermal agent and the body part to which it is applied, temperature changes may be superficial or deep and may affect one type of tissue more than another. For example, a hot pack produces the greatest temperature increase in superficial tissues with high thermal conductivity in the area directly below it. In contrast, ultrasound produces heat in deeper tissues and produces the most heat in tissues with high **collagen** content and thus high ultrasound absorption coefficients, such as tendon and bone. Diathermy, which involves applying shortwave or microwave electromagnetic energy, heats deep tissues having high electrical conductivity.

Thermotherapy is used to increase circulation, metabolic rate, and soft tissue extensibility or to decrease **pain.** Cryotherapy is applied to decrease circulation, metabolic rate, or pain. A full discussion of the principles underlying the processes of heat transfer; the methods of heat transfer used in rehabilitation; and the effects, **indications,** and **contraindications** for applying superficial heating and cooling agents is provided in Chapter 8. The principles and practice of applying deep-heating agents are discussed in Chapter 9 in the section on thermal applications of ultrasound and in Chapter 10 in the section on diathermy.

Ultrasound is a physical agent that has both thermal and nonthermal effects. *Ultrasound* is defined as sound with a frequency greater than 20,000 cycles/second (i.e., >20,000 hertz [Hz])—too high to be heard by humans. Ultrasound is a mechanical form of energy composed of alternating compression and rarefaction waves. Thermal effects, including increased deep- and superficial-tissue temperature, are produced by continuous ultrasound waves of sufficient intensity, and nonthermal effects are produced by both continuous and **pulsed ultrasound.** Continuous ultrasound is used to heat deep tissues to increase circulation, metabolic rate, and soft

tissue extensibility and to decrease pain. Pulsed ultrasound is used to facilitate tissue healing or to promote transdermal drug penetration by nonthermal mechanisms. Further information on the theory and practice of applying ultrasound is provided in Chapter 9.

ELECTROMAGNETIC AGENTS

Electromagnetic agents apply energy in the form of an electrical current or electromagnetic radiation. Agents that use electromagnetic radiation include **infrared (IR) radiation,** light (via **photobiomodulation),** UV radiation, and diathermy.

Electrical currents can be used to induce muscle contractions (motor-level **electrical stimulation [ES]**) and changes in sensation (sensory-level ES), reduce edema, or accelerate tissue healing. The effects and clinical applications of electrical currents vary according to the waveform, intensity, duration, and direction of the current flow and according to the type of tissue to which the current is applied. Electrical currents of sufficient intensity and duration can depolarize nerves, causing sensory or motor responses that may be used to control pain or increase muscle strength and control. Electrical currents with an appropriate direction of flow can attract or repel charged particles and alter cell membrane permeability to control the formation of edema, promote tissue healing, and facilitate transdermal drug delivery. Muscle contractions are associated with changes in ionic activity. This activity can be detected by EMG electrodes placed on the skin and can be fed back to the patient to facilitate or inhibit muscle activity. This is known as *EMG biofeedback*. Further information on the theory and practice of electrical current and EMG biofeedback application is provided in Chapters 11–15.

Electromagnetic radiation can be applied at different frequencies and intensities to produce differing effects at different depths of penetration. For example, IR radiation, which has a frequency of 10^{11} to 10^{14} Hz, produces heat in superficial tissues, whereas UV radiation, which has a frequency of 7.5×10^{14} to 10^{15} Hz, produces erythema and tanning of the skin but does not produce heat. **Lasers** output monochromatic, coherent, directional electromagnetic radiation, and therapeutic laser light is generally in the frequency range of visible light or IR radiation. Continuous shortwave diathermy, which has a frequency of 10^5 to 10^6 Hz, produces heat in superficial and deep tissues. When shortwave diathermy is pulsed (pulsed shortwave diathermy [PSWD]) to provide a low average intensity of energy, it does not produce heat and is known as **nonthermal shortwave therapy (SWT).** SWT is thought to modify cell membrane permeability and cell function by nonthermal mechanisms and thereby control pain and edema. Further information on the theory and practice of photobiomodulation using lasers and other forms of light is provided in Chapter 16. UV radiation and diathermy are discussed in Chapters 17 and 10, respectively.

MECHANICAL AGENTS

Mechanical agents apply force to increase or decrease pressure on the body. Examples of mechanical agents are water, traction and compression, and sound. Water can provide resistance, hydrostatic pressure, and buoyancy for exercise or can apply pressure to clean wounds. Traction decreases the pressure between structures, whereas compression increases the pressure on and between structures. Sound may be applied in the form of ultrasound or shock waves. Both ultrasound and shock waves are compression-rarefaction waves. Ultrasound, as discussed in the section on thermal agents, is high-frequency sound, above 20,000 Hz. In contrast, shock waves are low-frequency sound waves, generally at 1 to 10 Hz, with high, asymmetric compression-rarefaction.

The therapeutic use of water is called **hydrotherapy.** Water can be applied with or without immersion. Immersion in water increases pressure around the immersed area; provides buoyancy; and, if there is a difference in temperature between the immersed area and the water, transfers heat to or from that area. Movement of water produces local pressure that can be used as resistance for exercise when an area is immersed and for cleansing or debriding open wounds with or without immersion. Further information on the theory and practice of hydrotherapy, as well as on negative-pressure wound therapy, is provided in Chapter 19.

Traction is the application of a pulling mechanical force. Traction is most commonly used to alleviate pressure on structures, such as nerves or joints, that produce pain or other sensory changes, or that become inflamed, when compressed. Traction can normalize sensation and prevent or reduce damage or **inflammation** of compressed structures. The pressure-relieving effects of traction may be temporary or permanent, depending on the nature of the underlying **pathology** and the force, duration, and means of applying traction. Further information on the theory and practice of applying traction to the spine and the hips is provided in Chapter 20.

Compression is the application of a compressing mechanical force. Compression is used to counteract fluid pressure and to control or reverse edema. The force, duration, and means of applying compression can be varied to control the magnitude of the effect and to accommodate different patient needs. Further information on the theory and practice of applying compression is provided in Chapter 21.

Because ultrasound is used to heat tissues, it is covered in the discussion of thermal agents. Shock waves, also known as *pressure waves,* are asymmetric compression-rarefaction waves with a frequency of between 1 and 10 Hz produced by pneumatic compression. Shock waves alter cell membrane permeability, thereby modifying inflammation and tissue healing. Shock waves are discussed in detail in Chapter 18.

Effects of Physical Agents

Physical agents primarily reduce tissue inflammation, accelerate tissue healing, relieve pain, modify **muscle tone**, or alter collagen extensibility. A brief review of these processes and tables that summarize the physical agents that modify each of these conditions follow. More complete discussions of the physiological processes affected by physical agents are provided in Chapters 3 through 6, and a full discussion of each of the physical agents is provided in Chapters 7 through 21.

TABLE 1.2 Physical Agents for Promoting Tissue Healing

Stage of Tissue Healing	Goals of Treatment	Effective Agents	Contraindicated Agents
Initial injury	Prevent further injury or bleeding	Static compression, cryotherapy	Exercise
			Intermittent traction
			Motor-level ES
			Thermotherapy
	Clean open wound	Hydrotherapy (immersion or nonimmersion)	
Chronic inflammation	Prevent/decrease joint stiffness	Thermotherapy	Cryotherapy
		Motor ES	
		Shock waves	
		Whirlpool	
		Fluidotherapy	
	Control pain	Thermotherapy	Cryotherapy
		ES	
		Shock waves	
		Photobiomodulation	
	Increase circulation	Thermotherapy	
		ES	
		Compression	
		Hydrotherapy (immersion or exercise)	
	Progress to proliferation stage	Pulsed ultrasound	
		ES	
		SWT	
		Shock waves	
Remodeling	Regain or maintain strength	Motor ES	Immobilization
		Water exercise	
		EMG biofeedback	
	Regain or maintain flexibility	Thermotherapy	Immobilization
	Control scar tissue formation	Brief ice massage	
		Compression	

EMG, Electromyographic; *ES,* electrical stimulation; *SWT,* nonthermal shortwave therapy.

INFLAMMATION AND TISSUE HEALING

When tissue is damaged, it usually responds predictably. Inflammation is the first phase of recovery, followed by the proliferation and **maturation phases**. Modifying this healing process can accelerate rehabilitation and reduce adverse effects from prolonged inflammation, pain, and disuse. This in turn leads to improved function and more rapid achievement of therapeutic goals. The stages of tissue healing are described in detail in Chapter 3. The selection of physical agents to optimize tissue healing based on the stage of healing is summarized in Table 1.2.

Thermal agents modify inflammation and healing by changing the rates of circulation and chemical reactions. Mechanical agents control motion and alter fluid flow, and electromagnetic agents alter cell function, particularly membrane permeability and transport. Many physical agents affect inflammation and healing, and when appropriately applied, they can accelerate progress, limit adverse consequences of the healing process, and optimize the final patient outcome. However, when poorly selected or misapplied, physical agents may impair or potentially prevent complete healing.

PAIN

Pain is an unpleasant sensory and emotional experience associated with actual or threatened tissue damage. This text follows the recommendations of the International Association for the Study of Pain, considering pain to be a dynamic and multidimensional experience involving an idiosyncratic interaction of biological, physical, psychological, social, and environmental factors.[3] Because pain is complex and multifactorial, the reasoning behind the application of physical agents to pain management can also be somewhat complex. Different physical agents have specific and often beneficial effects on tissues, but they also have nonspecific sensory, cognitive, and emotional effects on patients that should also be accounted for. The selection of physical agents for managing pain at various stages and of various etiologies is summarized in Table 1.3.

Chapter 4 describes the physiology of pain and makes evidence-based recommendations for acute pain management, for reducing the probability of acute pain becoming chronic, for a mechanism-based approach to evaluating and managing common presentations of chronic pain, and for applying physical agents as part of palliative care.

TABLE 1.3 Physical Agents for the Treatment of Pain

Type of Pain	Goals of Treatment	Effective Agents	Contraindicated Agents
Acute	Control pain	Sensory ES, cryotherapy	
	Control inflammation	Cryotherapy	Thermotherapy
	Prevent aggravation of pain	Immobilization, EMG biofeedback	Local exercise, motor ES
		Low-load static traction	
Referred	Control pain	ES, cryotherapy, thermotherapy	
Spinal radicular	Decrease nerve root compression and inflammation	Traction	
Pain caused by malignancy	Control pain	ES, cryotherapy, superficial thermotherapy	

EMG, Electromyographic; *ES,* electrical stimulation.

MUSCLE TONE

Muscle tone is the underlying tension that serves as the background for the contraction of a muscle. Muscle tone is affected by neural and biomechanical factors and can vary in response to pathology, expected demand, pain, position, and physical agents. Abnormal muscle tone is usually the direct result of nerve pathology or may be a secondary sequela of pain that results from injury to other tissues.

Central nervous system injury, as may occur with head trauma or stroke, can result in increased or decreased muscle tone in the affected area, whereas peripheral motor nerve injury, as may occur with nerve compression, traction, or sectioning, can decrease muscle tone in the affected area. Pain may also increase or decrease muscle tone to protect injured tissue.

Processes underlying changes in muscle tone are discussed fully in Chapter 5.

Clinical Pearl

Physical agents can alter muscle tone directly by altering nerve conduction, nerve sensitivity, or the biomechanical properties of muscle or indirectly by reducing pain or the underlying cause of pain.

Physical agents can alter muscle tone directly by altering nerve conduction, nerve sensitivity, or the biomechanical properties of muscle or indirectly by reducing pain or the underlying cause of pain, as summarized in Table 1.4.

COLLAGEN EXTENSIBILITY AND MOTION RESTRICTIONS

Collagen is the main supportive protein of skin, tendon, bone cartilage, and connective tissue. Tissues that contain collagen can become shortened as a result of being immobilized in a shortened position or being moved through a limited range of motion (ROM). To return soft tissue to its normal functional length and thereby allow full motion without damaging other structures, the collagen must be stretched. Collagen can be stretched most effectively and safely when it is most extensible. Because the extensibility of collagen increases in response to increased temperature, thermal agents are frequently applied before soft tissue stretching to optimize stretching (Fig. 1.1).[4–7] Processes underlying the development and treatment of motion restrictions are discussed in Chapter 6.

Physical agents can be effective adjuncts to the treatment of motion restrictions caused by muscle weakness, pain, soft tissue shortening, or a bony block; however, appropriate interventions for these different sources of motion restriction vary (Table 1.5).

Clinical Pearl

Physical agents can be effective adjuncts to the treatment of motion restrictions caused by muscle weakness, pain, soft tissue shortening, or a bony block.

General Contraindications and Precautions for Physical Agent Use

Restrictions on the use of particular treatment interventions are categorized as contraindications or **precautions.** Contraindications are conditions under which a particular treatment should not be applied, and precautions are conditions under which a particular form of treatment should be applied with special care or limitations. The terms *absolute contraindications* and *relative contraindications*

TABLE 1.4 Physical Agents for the Treatment of Tone Abnormalities

Tone Abnormality	Goals of Treatment	Effective Agents	Contraindicated Agents
Hypertonicity	Decrease tone	Neutral warmth, prolonged cryotherapy, or EMG biofeedback to hypertonic muscles	Quick ice of agonists
		Motor ES or quick ice of antagonists	
Hypotonicity	Increase tone	Quick ice, motor ES, or EMG biofeedback to agonists	Thermotherapy
Fluctuating tone	Normalize tone	Functional ES	

EMG, Electromyographic; *ES,* electrical stimulation.

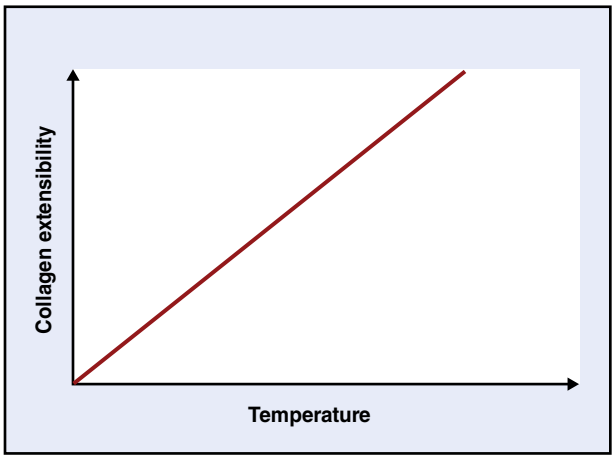

FIGURE 1.1 Changes in collagen extensibility in response to changes in temperature.

can be used in place of *contraindications* and *precautions,* respectively.

Although contraindications and precautions for the application of specific physical agents vary, several conditions are contraindications or precautions for the use of most physical agents. Therefore, caution should be used when applying a physical agent to a patient having any of these conditions. In patients with such conditions, the nature of the restriction, the nature and distribution of the physiological effects of the physical agent, and the distribution of energy produced by the physical agent must be considered.

PREGNANCY

Pregnancy is generally a contraindication or precaution for the application of a physical agent if the energy produced by that agent or its physiological effects may reach the fetus. These restrictions apply because the influences of these types of energy on fetal development usually are unknown and because fetal development is adversely affected by many influences, some of which are subtle.

✶ CONTRAINDICATIONS for Application of a Physical Agent

- Pregnancy
- Malignancy
- Pacemaker or other implanted electronic device
- Impaired sensation
- Impaired mentation

MALIGNANCY

Malignancy is generally a contraindication or precaution for the application of physical agents if the energy produced by the agent or its physiological effects may reach malignant tissue or alter the circulation to such tissue. Some physical agents are known to accelerate the growth, or metastasis, of malignant tissue. These effects are thought to result from increased circulation or altered cellular function. Care must be taken when considering treatment on any area of the body that currently has or previously had cancer cells because malignant tissue can metastasize and therefore may be present in areas where it has not yet been detected.

PACEMAKER OR OTHER IMPLANTED ELECTRONIC DEVICE

The use of a physical agent is generally contraindicated when the energy of the agent can reach a pacemaker or any other implanted electronic device (e.g., deep brain stimulator, spinal cord stimulator, implanted cardioverter defibrillator) because the energy produced by some of these agents may alter the functioning of the device.

IMPAIRED SENSATION AND MENTATION

Impaired sensation and mentation are contraindications or precautions for the use of many physical agents because the limit for application of these agents is the patient's report of how they feel. For example, for most thermal agents, the patient's report of the sensation of heat as comfortable or painful is used to guide the intensity of treatment. If the patient

TABLE 1.5 Physical Agents for the Treatment of Motion Restrictions

Source of Motion Restriction	Goals of Treatment	Effective Agents	Contraindicated Agents
Muscle weakness	Increase muscle strength	Water exercise, motor ES, EMG biofeedback	Immobilization
Pain			
At rest and with motion	Control pain	ES, cryotherapy, thermotherapy, SWT, spinal traction, EMG biofeedback	Exercise
With motion only	Control pain	ES, cryotherapy, thermotherapy, SWT	Exercise into pain
	Promote tissue healing	Ultrasound, ES, SWT, shock waves	
Soft tissue shortening	Increase tissue extensibility	Thermotherapy	Prolonged cryotherapy
	Increase tissue length	Thermotherapy or brief ice massage and stretch	
Bony block	Remove block	None	Stretching blocked joint
	Compensate	Exercise	
		Thermotherapy or brief ice massage and stretch	

EMG, Electromyographic; *ES,* electrical stimulation; *SWT,* nonthermal shortwave therapy.

cannot feel heat or pain because of impaired sensation or cannot report this sensation accurately and consistently because of impaired mentation or other factors affecting their ability to communicate, applying the treatment is not safe and therefore is contraindicated.

Although these conditions indicate the need for caution with the use of most physical agents, the specific contraindications and precautions for the agent being considered and the patient's situation must be evaluated before an intervention may be used or should be rejected. For example, although applying ultrasound to a pregnant patient is contraindicated in any area where the ultrasound may reach the fetus, this physical agent may be applied to the distal extremities of a pregnant patient because ultrasound penetration is shallow and limited to the area close to the applicator. In contrast, it is recommended that diathermy not be applied to any part of a pregnant patient because the electromagnetic radiation it produces reaches areas distant from the applicator. Specific contraindications and precautions, including questions to ask the patient and features to assess before the application of each physical agent, are provided in Parts III through VI of this book.

Evaluation and Planning for the Use of Physical Agents

Physical agents have direct effects primarily at the level of impairment. These effects can improve activity and participation. For example, for a patient with pain that impairs motion, electrical currents can be used to stimulate sensory nerves to control pain and allow the patient to increase motion and thus increase activity, such as lifting objects, and participation, such as returning to work. Physical agents can also increase the effectiveness of other interventions and should generally be used to facilitate an active treatment program.[8] For example, a hot pack may be applied before stretching to increase the extensibility of superficial soft tissues and promote a safer and more effective increase in soft tissue length when the patient stretches.

When considering the application of a physical agent, one should first check the physician's referral, if one is required, for a medical diagnosis of the patient's condition and any necessary precautions. Precautions are conditions under which a particular treatment should be applied with special care or limitations. The therapist's examination should include, but should not be limited to, the patient's history, which would include information about the history of the current complaint, relevant medical history, and information about current and expected levels of activity and participation; a review of systems; and specific tests and measures. Examination findings and a survey of available evidence in the published literature should be considered in tandem to establish a prognosis and select the interventions and a plan of care, including anticipated goals. This plan may be modified as indicated through ongoing reexamination and reevaluation. The process of staying abreast of the latest clinical evidence is discussed in more detail in Chapter 2, and the sequence of examination, evaluation, and intervention follows in the case studies described in Parts II through VI of this book.

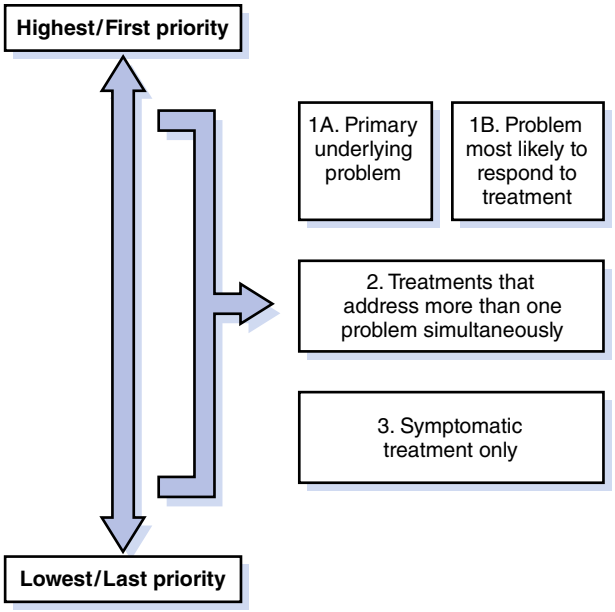

FIGURE 1.2 Prioritizing goals and effects of treatment.

CHOOSING A PHYSICAL AGENT

Physical agents generally assist in rehabilitation by reducing inflammation, pain, and motion restrictions; healing tissue; and improving muscle tone. Guidelines for selecting appropriate interventions based on the direct effects of physical agents are presented here in narrative form and are summarized in Tables 1.2 through 1.5. If the patient presents with more than one problem and so has numerous goals for treatment, only a limited number of goals should be addressed at any one time. It is generally recommended that the primary problems and problems most likely to respond to available interventions should be addressed first; however, the ideal intervention will facilitate progress in a number of areas (Fig. 1.2). For example, if a patient has knee pain caused by acute joint inflammation, treatment should first be directed at resolving the inflammation; however, the ideal intervention would also help to relieve pain. When the primary underlying problem, such as arthritis, cannot benefit directly from intervention with a physical agent, treatment with physical agents may still be used to help alleviate sequelae of these problems, such as pain or swelling.

ATTRIBUTES TO CONSIDER IN THE SELECTION OF PHYSICAL AGENTS

Given the variety of available physical agents and the unique characteristics of each patient, it is helpful to take a systematic approach to selecting the physical agents so that the ideal agent will be applied in each situation (Fig. 1.3).

The first consideration should be the goals of the intervention and the physiological effects required to reach these goals. If the patient has inflammation or delayed tissue healing, pain, problems with muscle tone, or motion restrictions, the use of a physical agent may be appropriate. Looking at the evidence for the effects of a particular physical agent on these conditions is the next step. For example, heat can help during the remodeling phase of healing by promoting increased tissue extensibility and may also temporarily alleviate pain to allow for more activity. Having determined which

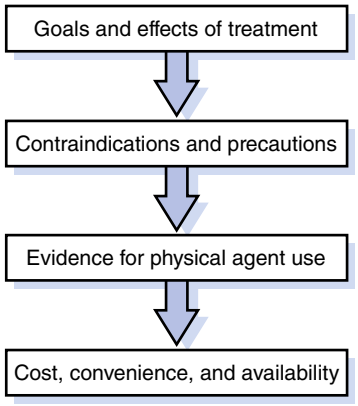

FIGURE 1.3 Attributes to consider when selecting physical agents.

physical agents can promote progress toward determined goals, the clinician should then determine what tissue is affected and then which type of energy is best absorbed by this affected tissue. For example, if a deep tendon is affected, continuous ultrasound would be an appropriate way to provide heat because ultrasound penetrates deeply and is absorbed by tissues with high collagen content. In contrast, if a superficial muscle is affected, a hot pack would be an appropriate way to provide heat because the heat from a hot pack only reaches superficially and is best absorbed by tissues with high water content.

After determining the goals of treatment, physiological effects to achieve these goals, what tissue type is affected, and which type of energy is best absorbed by this type of tissue, the provider should evaluate for contraindications and precautions. Contraindicated interventions should be rejected and all precautions adhered to. If several methods could be effective and applied safely, the ease and cost of application and the availability of resources should also be considered. After selecting physical agents, the clinician should also select the ideal treatment parameters and means of application using the same principles as they used to select the agents. They must then appropriately integrate the chosen agents into a complete rehabilitation program.

USING PHYSICAL AGENTS WITH EACH OTHER AND WITH OTHER INTERVENTIONS

To progress toward the goals of intervention, a number of physical agents may be used simultaneously and/or sequentially. Because physical agents are adjuncts to other therapeutic interventions, they are usually applied in conjunction with or during the same treatment session as other interventions. Interventions are generally combined when they have similar effects or when they address different aspects of a common array of symptoms. For example, splinting, ice, pulsed ultrasound, photobiomodulation, SWT, and phonophoresis or iontophoresis may be used during the acute inflammation phase of healing. Splinting can limit further injury; ice may control pain and limit circulation; pulsed ultrasound, photobiomodulation, and SWT may promote progress toward the proliferation stage of healing; and phonophoresis and iontophoresis may limit the inflammatory response. During the chronic inflammation or proliferation stages of healing, heat, SWT, shock waves, motor-level ES, and exercise may be used, and ice or other inflammation-controlling interventions may continue to be applied after activity to reduce the risk of recurring inflammation.

Rest, ice, compression, and elevation (RICE) are frequently combined for the treatment of inflammation and edema because these interventions can control inflammation and edema. Rest limits and prevents further injury, ice reduces circulation and inflammation, compression elevates hydrostatic pressure outside the blood vessels, and elevation reduces hydrostatic pressure within the blood vessels of the elevated area to decrease capillary filtration pressure at the arterial end and facilitate venous and lymphatic outflow from the limb. ES may be added to this combination to further control inflammation and the formation of edema by repelling negatively charged blood cells and ions associated with inflammation.

When the goal of intervention is to control pain, a number of physical agents may be used to influence different mechanisms of pain control. For example, cryotherapy or thermotherapy may be used to modulate pain transmission at the spinal cord, whereas motor-level ES may be used to modulate pain by stimulating endorphin release. These physical agents may be combined with other pain-controlling interventions, such as medications, and may be used in conjunction with treatments such as joint mobilization and dynamic stabilization exercise, which are intended to address the underlying impairment causing pain.

When the goal of intervention is to alter muscle tone, various tone-modifying physical agents or other interventions may be applied during or before activity to promote more normal movement and to increase the efficacy of other aspects of treatment. For example, ice may be applied for 30 to 40 minutes to the leg of a patient with hypertonicity of the ankle plantar flexors caused by a stroke to temporarily control the hypertonicity of these muscles, thereby promoting a more normal gait pattern during gait training. Because practicing normal movement is thought to facilitate the recovery of more normal movement patterns, such treatment may promote a superior outcome.

When the goal of intervention is to reverse soft tissue shortening, the application of thermal agents before or during stretching or mobilization is recommended to promote relaxation and increase soft tissue extensibility, thereby increasing the efficacy and safety of treatment. For example, hot packs are often applied in conjunction with mechanical traction to help relax the paraspinal muscles and to increase the extensibility of superficial soft tissues in the area to which traction is being applied.

Physical agents are generally used more extensively during the initial rehabilitation sessions when inflammation and pain control are matters of priority, with progression over time to more active or aggressive interventions, such as exercise or passive mobilization. Progression from one physical agent to another or from the use of a physical agent to another intervention should be based on the course of the patient's problem. For example, hydrotherapy may be applied to cleanse and debride an open wound during initial treatment sessions; however, once the wound is clean, this treatment should be stopped, and ES may be initiated to promote collagen deposition.

Documentation

Documentation involves entering information into a patient's medical record. Documentation communicates examination findings, evaluations, interventions, and plans to other health care professionals; serves as a long-term record for oneself and others; and supports reimbursement for provided services.

Clinical Pearl

Good documentation effectively, accurately, and completely communicates examination findings, evaluations, interventions, and plans to other health care professionals; serves as a long-term record; and supports reimbursement.

Documentation of a patient encounter may follow any format but is often done in the SOAP note format that includes the four sequential components of subjective (S), objective (O), assessment (A), and plan (P). Alternative documentation schemes may also be used. The SOAP note format is used in this book for consistency and to demonstrate the reasoning used.

Within each component of the SOAP note, details vary depending on the patient's condition and assessment and the interventions applied. When a physical agent is used, documentation should include what agent was used; what area of the body was treated; and all treatment parameters, including intervention duration, outcomes, progress toward goals, and regressions or complications arising from application of the physical agent. This is an example of a SOAP note written after a hot pack was applied to the lower back:

S: Pt reports low back pain and decreased sitting tolerance, which functionally prohibit writing.

O: Pretreatment: Pain level 7/10. Forward and side-bending ROM restricted 50% by pain and muscle spasm. Pt unable to lean forward for writing tasks.

Intervention: Hot pack to low back, 20 minutes, Pt prone, six layers of towels. Pt performed single knee to chest 2 × 10, double knee to chest 2 × 10.

Posttreatment: Pain level 4/10. Forward-bending increased, restricted 20%.

Pt instructed in home program of heating pad on medium for 10 to 20 minutes followed by SKTC and DKTC 3 × 10 daily.

A: Pain decreased, forward bending ROM.

P: Continue use of hot pack as above before stretching. Progress exercise program.

Specific recommendations for SOAP note documentation and examples are given in the text for all physical agents discussed in this book.

Chapter Review

1. Physical agents consist of materials or energy applied to patients to assist in rehabilitation. Physical agents include heat, cold, water, pressure, sound, electromagnetic radiation, and electrical currents. These agents can be categorized as thermal (e.g., hot packs, cold packs), electromagnetic (e.g., lasers, light, ES, UV radiation, EMG biofeedback), or mechanical (e.g., ultrasound, shock waves, water, compression, traction). Some physical agents fall into more than one category. For example, water and ultrasound are both thermal and mechanical agents.
2. Physical agents are components of a complete rehabilitation program. They are rarely the sole intervention.
3. Physical agents are commonly used with each other and with other interventions.
4. The selection of a physical agent is based on integrating findings from the patient examination with evidence of the effects (both positive and negative) of available agents.
5. Physical agents primarily affect inflammation and healing, pain, motion restrictions, and tone abnormalities. Knowledge of normal and abnormal physiology in each area can help in the selection of a physical agent for a patient. These are discussed in Chapters 3 through 6. The specific effects of particular physical agents are discussed in Chapters 7 through 21.
6. Contraindications are circumstances in which a physical agent should not be used. Precautions are circumstances in which a physical agent should be used with caution. General contraindications and precautions, such as pregnancy, malignancy, pacemakers, and impaired sensation and mentation, pertain to the application of all physical agents. Specific contraindications and precautions for each physical agent are discussed in Chapters 7 through 21.

Glossary

Collagen: The protein in the fibers of skin, tendon, bone, cartilage, and all other connective tissue. Collagen is made up of individual polypeptide molecules combined in triplets forming helical tropocollagen molecules that then associate to form collagen fibrils.

Compression: The application of a mechanical force that increases external pressure on a body part to reduce swelling, improve circulation, or modify scar tissue formation.

Contraindications: Conditions in which a particular treatment should not be applied; also called *absolute contraindications*.

Cryotherapy: The therapeutic use of cold.

Diathermy: The application of shortwave or microwave electromagnetic energy to produce heat within tissues, particularly deep tissues.

Electrical stimulation (ES): The use of electrical current to induce muscle contraction (motor level) or changes in sensation (sensory level).

Electromagnetic agents: Physical agents that apply energy to the patient in the form of electromagnetic radiation or electrical current.

Guide to Physical Therapist Practice 3.0 (Guide 3.0): A book used by physical therapists to categorize patients according to preferred practice patterns that include typical findings and descriptive norms of types and ranges of interventions for patients in each pattern.

Hydrotherapy: The therapeutic use of water.

Indications: Conditions under which a particular treatment should be applied.

Inflammation: The body's first response to tissue damage, characterized by heat, redness, swelling, pain, and often loss of function.

Inflammation phase: The first phase of healing after tissue damage.

Infrared (IR) radiation: Electromagnetic radiation in the IR range (wavelength range, approximately 750 to 1300 nm) that can be absorbed by matter and, if of sufficient intensity, can cause an increase in temperature.

Iontophoresis: The delivery of ions through the skin for therapeutic purposes using an electrical current.

Laser: Acronym for *l*ight *a*mplification by stimulated *e*mission of *r*adiation. Laser light has the unique properties of being monochromatic, coherent, and directional.

Maturation phase: The final phase of tissue healing, in which scar tissue is modified into its mature form.

Mechanical agents: Physical agents that apply force to increase or decrease pressure on the body.

Modality: Other term for *physical agent*.

Muscle tone: The underlying tension in a muscle that serves as a background for contraction.

Nonthermal shortwave therapy (SWT): The therapeutic use of intermittent shortwave radiation in which heat is not the mechanism of action (previously called *pulsed shortwave diathermy [PSWD]*).

Pain: An unpleasant sensory and emotional experience associated with actual or threatened tissue damage or described in terms of such damage.

Pathology: Alteration of anatomy or physiology as a result of disease or injury.

Phonophoresis: The application of ultrasound with a topical drug to facilitate transdermal drug delivery. Also known as *sonophoresis*.

Photobiomodulation: Light therapy with lasers, light-emitting diodes (LEDs), superluminous diodes (SLDs), or broadband light.

Physical agents: Energy and materials applied to patients to assist in rehabilitation.

Physical modality: Other term for *physical agent*.

Precautions: Conditions in which a particular treatment should be applied with special care or limitations; also called *relative contraindications*.

Pulsed ultrasound: Intermittent delivery of ultrasound during the treatment period.

Rehabilitation: Goal-oriented intervention designed to maximize independence in individuals who have compromised function.

Sound waves: Alternating compression and rarefaction waves that move through a compressible medium.

Thermal agents: Physical agents that increase or decrease tissue temperature.

Thermotherapy: The therapeutic application of heat.

Traction: A mechanical force applied to the body in a way that separates, or attempts to separate, joint surfaces and elongates soft tissues surrounding a joint.

Ultrasound: Sound with a frequency greater than 20,000 cycles per second (Hz) that is used as a physical agent to produce thermal and nonthermal effects.

Ultraviolet (UV) radiation: Electromagnetic radiation with a wavelength from less than 290 to 400 nm, which lies between x-rays and visible light.

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2

Physical Agents in Clinical Practice

Michelle H. Cameron | Ashley L. Shea

CHAPTER OUTLINE

CHAPTER OBJECTIVES

After reading this chapter, the reader will be able to do the following:

- Describe the history of the use of physical agents in medicine and rehabilitation.
- Explain the role of physical agents as components of rehabilitation intervention.
- Use evidence to guide the integration of physical agents within rehabilitation.
- Use physical agents in rehabilitation within different health care delivery systems.

History of Physical Agents in Medicine and Rehabilitation

Physical agents have been a component of medical and rehabilitative treatment for many centuries and are used across a wide variety of cultures. Ancient Romans and Greeks used heat and water to maintain health and to treat various musculoskeletal and respiratory problems, as evidenced by the remains of ancient bathhouses with steam rooms and pools of hot and cold water still present in many major Roman and Greek cities.[1] The benefits from soaking and exercising in hot water regained popularity in the late 19th century with the advent of health spas in Europe in areas of natural hot springs. Today, the practices of soaking and exercising in water continue to be popular throughout the world because water provides resistance and buoyancy, allowing the development of strength and endurance while reducing weight bearing on compression-sensitive joints.

Other historical applications of physical agents include the use of electrical torpedo fish in approximately 400 BCE to treat headaches and arthritis by applying electrical shocks to the head and feet. Amber was used in the 17th century to generate static electricity to treat skin diseases, inflammation, and hemorrhage.[2] Reports from the 17th century describe the use of charged gold leaf to prevent scarring from smallpox lesions.[3]

Before the widespread availability of antibiotics and effective analgesic and antiinflammatory drugs, physical agents were commonly used to treat infection, pain, and inflammation. Sunlight was used for the treatment of tuberculosis, bone and joint diseases, and dermatological disorders and infections. Warm Epsom salt baths were used to treat sore or swollen limbs.

Although physical agents have been used for their therapeutic benefits throughout history, over time, new uses, applications, and agents have been developed, and certain agents and applications have fallen out of favor. New uses of physical agents have been discovered as a result of increased understanding of the biological processes underlying disease, dysfunction, and recovery and in response to the availability of advanced technology. For example, **transcutaneous electrical nerve stimulation (TENS)** for the treatment of pain was developed on the basis of the **gate control theory of pain modulation,** as proposed by Melzack and Wall.[4] The gate control theory states that nonpainful stimuli can inhibit the transmission of pain at the spinal cord level. Various available modes of TENS application are primarily the result of the development of electrical current generators that allow fine control of the applied electrical current.

A physical agent usually falls out of favor because the intervention is found to be ineffective or because more effective interventions are developed. For example, the superficial heat that infrared (IR) lamps produce was commonly used to dry out open wounds, but IR lamps are no longer used for this application because we now know that wounds heal more rapidly when kept moist.[5,6] During the early years of the 20th century, sunlight was used to treat tuberculosis; however, since the advent of antibiotics to eliminate bacterial infections, physical agents are rarely used to treat tuberculosis or other infectious diseases.

Most recently, the use of a number of physical agents has fallen out of favor. The first of five recommendations in the American Physical Therapy Association (APTA) Choosing Wisely initiative, most recently updated in 2015, is "don't use (superficial or deep) heat to obtain clinically important, long-term outcomes in musculoskeletal conditions."[7] The APTA clarifies this recommendation with the following statement:

There is limited evidence for use of superficial or deep heat to obtain clinically important long-term outcomes for musculoskeletal conditions. While there is some evidence of short-term pain relief for heat, the addition of heat should be

supported by evidence and used to facilitate an active treatment program. A carefully designed active treatment plan has a greater impact on pain, mobility, function and quality of life. There is emerging evidence that passive treatment strategies can harm patients by exacerbating fears and anxiety about being physically active when in pain, which can prolong recovery, increase costs and increase the risk of exposure to invasive and costly interventions such as injections or surgery.

Looking at this statement carefully, it does imply that heat can be used to facilitate an active treatment program, as recommended in this book.

In addition, the fifth recommendation of the APTA Choosing Wisely initiative is "don't use whirlpools for wound management." The APTA clarifies this recommendation with the following statement:

Whirlpools are a non-selective form of mechanical debridement. Utilizing whirlpools to treat wounds predisposes the patient to risks of bacterial cross-contamination, damage to fragile tissue from high turbine forces, and complications in extremity edema when arms and legs are treated in a dependent position in warm water. Other more selective forms of hydrotherapy should be utilized, such as directed wound irrigation or a pulsed lavage with suction.

Based on the evidence and this recommendation, the use of whirlpools for wound management was deleted from the fifth and subsequent editions of this book, and details on directed wound irrigation and pulsed lavage with suction are provided.

Furthermore, spinal traction, particularly for the lumbar spine, has come into question in recent years because evidence from randomized controlled trials (RCTs) has failed to prove its benefits and because of concerns that this passive form of treatment may increase the risk of illness behavior and chronicity.[8] Spinal traction is still covered in this book because, as recently as 2015, over 75% of physical therapists reported using lumbar traction[9] for managing low back pain, because there is substantial evidence of traction being associated with effects that may be beneficial in certain patients, and because the evidence for the efficacy of cervical spine traction is more positive.

Physical agents also sometimes wane in popularity because they are cumbersome, have excessive associated risks, interfere with other aspects of treatment, or have just fallen out of fashion. For example, the use of diathermy as a deep-heating agent was very popular over 30 years ago, but because the machines are large and awkward to move around and set up, and because this agent can easily burn patients if not used appropriately and can interfere with the functioning of nearby computer-controlled equipment, diathermy was not commonly used in the United States until more recently. With the development of less cumbersome and safer devices, diathermy is regaining popularity and is presented in this book as a means of deep heating to facilitate an active treatment program and as a nonthermal agent to promote tissue healing.

This book focuses on the physical agents most commonly used in the United States at the present time. Physical agents that are not commonly used in the United States but that were popular in the recent past, as well as agents that are popular abroad or are expected to come back into favor as new delivery systems and applications are developed, are covered briefly. The popularity of particular physical agents is based on their history of clinical use and, in most cases, on evidence to support their efficacy; however, in some cases, their clinical application has continued despite a lack of or limited supporting evidence. More research is needed to clarify which interventions and patient characteristics provide optimal results. Further study is also needed to determine precisely what outcomes should be expected from the application of physical agents in rehabilitation.

Approaches to Rehabilitation

Rehabilitation is a goal-oriented intervention designed to maximize independence in individuals with compromised function. Function is usually compromised because of an underlying pathology and secondary **impairments** and is affected by environmental and personal factors. Compromised function may lead to **disability.** Rehabilitation generally addresses the sequelae of pathology to maximize a patient's function and ability to participate in usual activities, rather than being directed at resolving the pathology itself, and should take into consideration the environmental and personal factors affecting each patient's individual activity and participation limitations and goals.

A number of classification schemes exist to categorize the sequelae of pathology. In 1980, the World Health Organization (WHO) published the first scheme to classify the consequences of diseases, known as the International Classification of Impairments, Disabilities, and Handicaps (ICIDH).[10] This scheme, derived primarily from the work of Wood, is based on a linear model in which the sequelae of pathology or disease are impairments that lead to disabilities and handicaps.[11,12] In this scheme, *impairment* is characterized as an abnormality of structure or function of the body or an organ, including mental function. *Disability* is characterized as a restriction of activities resulting from impairment, and *handicap* is the social level of the consequences of diseases, characterized as the individual's disadvantage resulting from impairment or disability. Shortly after the **ICIDH model** was published, Nagi developed a similar model that classified the sequelae of pathology as impairments, **functional limitations,** and disabilities.[13] He defined *impairments* as alterations in anatomical, physiological, or psychological structures or functions that result from an underlying pathology. In the **Nagi model,** *functional limitations* were defined as restrictions in the ability to perform an activity in an efficient, typically expected, or competent manner, and *disabilities* were defined as the inability to perform activities required for self-care, home, work, and community roles.

The WHO updated the ICIDH model in 2001 to reflect and create changes in perceptions of people with disabilities and to meet the needs of different groups of individuals. The updated version of the ICIDH model is known as the *ICIDH-2* or the *International Classification of Functioning, Disability and Health (ICF)* (Fig. 2.1).[14] The ICF is a classification of health and health-related domains and is the WHO framework for measuring health and disability at both individual and population levels. In contrast to the earlier linear model, the **ICF model** views functioning and disability as a complex,

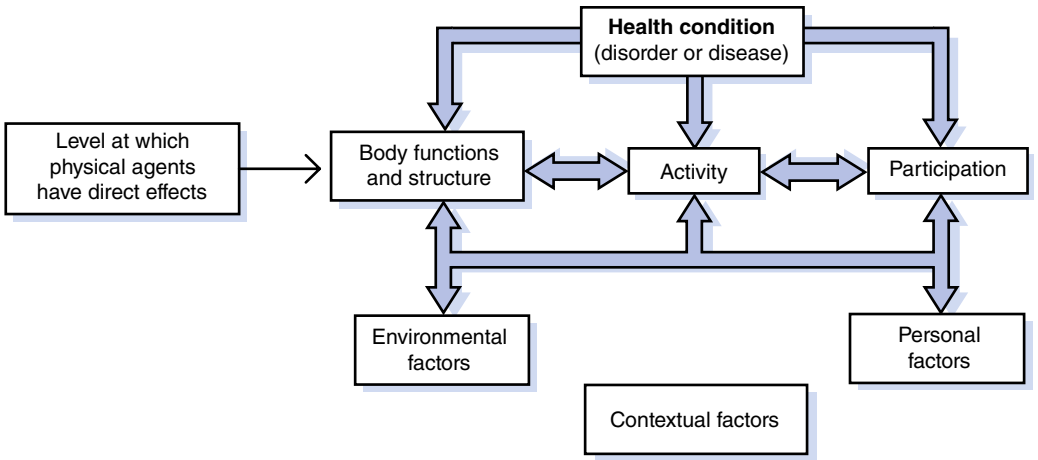

FIGURE 2.1 Model for the International Classification of Functioning, Disability and Health (ICF). (From World Health Organization [WHO]: *ICIDH-2: International Classification of Functioning, Disability and Health,* Geneva, 2001, WHO.)

dynamic interaction between the health condition of the individual and contextual factors of the environment, as well as personal factors. It is applicable to all people, whatever their health condition. The language of the ICF model is neutral to cause, placing the emphasis on function rather than on the condition or disease. It is designed to be relevant across cultures, as well as age groups and genders, making it appropriate for heterogeneous populations. The ICF is operationalized through the WHO Disability Assessment Schedule (WHODAS 2.0).[15]

Clinical Pearl

The International Classification of Functioning, Disability and Health (ICF) model views functioning and disability as a complex, dynamic interaction between the health condition of the individual and contextual factors of the environment, as well as personal factors. The ICF model emphasizes function and considers the body, the whole person, and the person in society.

The original ICIDH and Nagi models, developed primarily for use by rehabilitation professionals, were intended to differentiate disease and pathology from the limitations they produced. The new ICF model has a more positive perspective on the changes associated with pathology and disease and is intended for use by a wide range of people, including members of the community, as well as national and global institutions that create policy and allocate resources for persons with disabilities. The ICF model has tried to change the perspective of disability from the negative focus of "consequences of disease" used in the ICIDH model to a more positive focus on "components of health." The ICIDH model used categories of impairments, disabilities, and handicaps to describe sequelae of and limitations associated with pathology, whereas the ICF model uses categories of health conditions, body functions, activities, and participation to focus on abilities rather than limitations.

Consistent with the most recent edition of the APTA's *Guide to Physical Therapist Practice 3.0 (Guide 3.0),*[16] this book uses the terminology and framework of the ICF model to evaluate clinical findings and determine a plan of care for the individuals described in the case studies. The ICF model reflects the interactions between health conditions and contextual factors as they affect disability and functioning. Health conditions include diseases, disorders, and injuries. Contextual factors include environmental factors, such as social attitudes, legal structures, and one's community, and personal factors, such as gender, age, education, experience, and character. The ICF model is intended to be used in conjunction with the International Classification of Diseases (ICD), a classification system used throughout the U.S. health care system to document and code medical diagnoses.

The ICF model is structured around three levels of functioning: (1) the body or a part of the body, (2) the whole person, and (3) the whole person in a social context. Dysfunction at any of these levels is termed a *disability* and results in impairments (at the body level), activity limitations (at the whole-person level), and participation restrictions (at the social level). For example, a person who experienced a stroke may be weak on one side of the body (impairment). This impairment may cause difficulty with activities of daily living (activity limitation). The person may be unable to attend social gatherings that they previously enjoyed (participation restriction).

The ICF model was developed by combining medical and social models of disability. In the medical model, disability is the result of an underlying pathology, and to treat the disability, one must treat the pathology. In the social model, disability is the result of the social environment, and to treat the disability, one must change the social environment to make it more accommodating.

Medical treatment is generally directed at the underlying pathology or disease, whereas rehabilitation focuses primarily on reversing or minimizing impairments, activity limitations, and participation restrictions. Rehabilitation professionals must assess and set goals not only at the levels of impairment, such as pain, decreased range of motion, and **hypertonicity** (increased muscle tone) but also at the levels of activity and participation. These goals should include the patient's goals, such as being able to get out of bed, ride a bicycle, work, or run a marathon.

The Role of Physical Agents in Rehabilitation

Physical agents are tools to be used when appropriate as components of rehabilitation. The position statement of the APTA regarding the *exclusive* use of physical agents, first published in 1995 and reiterated in 2005, stated, "Without documentation which justifies the necessity of the exclusive use of physical agents/modalities, the use of physical agents/modalities, in the absence of other skilled therapeutic or educational interventions, should not be considered physical therapy."[17] In 2015, related to physical agents, as part of its Choosing Wisely initiative, the APTA specifically stated with regard to heat, "don't use (superficial or deep) heat to obtain clinically important long term outcomes in musculoskeletal conditions … the addition of heat should be supported by evidence and used to facilitate an active treatment program."[7] Most recently, in 2018, the APTA updated its position statement on the exclusive use of biophysical agents, stating, "The use of biophysical agents as a standalone intervention, or the use of multiple biophysical agents with a similar physiologic effect, is not considered physical therapy nor is it considered medically necessary without documentation that justifies the use of the biophysical agents for those purposes."[18] In other words, the APTA believes that the use of single or multiple physical agents alone does not constitute physical therapy.

The use of physical agents as a component of rehabilitation involves integration with other appropriate interventions. This integration may include applying a physical agent or educating the patient in its application as part of a complete program to help patients achieve their activity and participation goals. However, because the aim of this book is to give clinicians a better understanding of the theory and appropriate application of physical agents, the emphasis is on the use of physical agents, and other components of the rehabilitation program are described in less detail.

Practitioners Using Physical Agents

Physical therapists, physical therapist assistants, occupational therapists, occupational therapy assistants, athletic trainers, physiatrists, chiropractors, acupuncturists, and patients all apply physical agents. These individuals may have slightly different goals when applying these interventions and slightly different training and educational requirements for their use.

Physical therapists commonly use physical agents and supervise physical therapist assistants in the application of physical agents. The APTA includes physical agents within the interventions that define the practice of physical therapy and notes that when physical agents are used, this should be as a part of a complete rehabilitation program.[19] Training in the use of physical agents is a required part of entry-level education and licensure for physical therapists and physical therapist assistants. The Commission on Accreditation in Physical Therapy Education (CAPTE), the granting agency for the accreditation of physical therapist and physical therapist assistant education programs, requires evidence of "content, learning experiences, and student testing and evaluation" to ensure competent use of biophysical agents.[20] The APTA states that the minimum required skills of a physical therapist graduate at the entry level include competency in the use of physical agents such as cryotherapy, hydrotherapy, ultrasound, and thermotherapy; mechanical modalities such as compression therapies and traction devices; and electrotherapeutic modalities such as biofeedback, electrotherapeutic delivery of medications (e.g., iontophoresis), and electrical stimulation.[21] When caring for patients, physical therapists are expected to select and use the most appropriate interventions according to the best scientific evidence while considering the patient's perspective and exercising professional judgment.

Occupational therapists and occupational therapy assistants, especially those involved in hand therapy, also commonly use physical agents. In its most recent position paper,[22] published in 2018, the American Occupational Therapy Association (AOTA) referenced a 2014 document supporting that physical agents and mechanical modalities "may be used by occupational therapy practitioners as part of a comprehensive plan of intervention designed to enhance engagement in occupation.[23]" The AOTA discourages exclusive or standalone use of physical agents and mechanical modalities and promotes their use as adjunctive to "purposeful and occupation-based intervention activities."[24] Occupational therapists and occupational therapy assistants, under the supervision of occupational therapists, integrate physical agents and mechanical modalities into the intervention plan to prepare clients to complete purposeful and meaningful activities in the areas of activities of daily living, instrumental activities of daily living, rest and sleep, education, work, play, leisure, and social participation, with the overall goal of maximizing functional independence in activities.

The Accreditation Council for Occupational Therapy Education (ACOTE), the body that accredits occupational therapy educational programs in the United States, first introduced physical and mechanical agents into educational standards in 2006 to go into effect in 2008.[25] As of 2018, the ACOTE mandates that entry-level occupational therapy programs include in their curricula coursework that prepares practitioners who can "demonstrate knowledge and use of the safe and effective application of superficial thermal agents, deep thermal agents, electrotherapeutic agents, and mechanical devices as a preparatory measure to improve occupational performance."[26] Similarly, occupational therapy assistant programs must include in their curricula coursework that prepares occupational therapy assistants to understand "the safe and effective application of superficial thermal agents, deep thermal agents, electrotherapeutic agents, and mechanical devices as a preparatory measure to improve occupational performance."[26] Both occupational therapists and occupational therapy assistants must know the indications, contraindications, and precautions for the use of physical agents and mechanical modalities.

As the AOTA notes, it is important for professionals to understand that an association's policies and position do not take precedence over state laws and regulations.[23] Laws and regulations regarding the use of physical agents by occupational therapists vary among states, with many requiring additional training and experience beyond that offered during entry-level education. As of June 2019, only 15 states did not have statutes or regulations regarding the use of physical agents and mechanical modalities by occupational therapy practitioners, whereas the remaining states have, pending or in effect, such statutes or regulations.[26] Occupational therapists and occupational therapy assistants who wish to use physical agents and mechanical modalities in their clinical

practice should check the laws and regulations in the state in which they practice and are licensed.

ACOTE requires all accredited occupational therapy programs to address the safe and effective application of superficial thermal and mechanical modalities for pain management and improvement of occupational performance. ACOTE first introduced modalities into educational standards in 2006 to go into effect in 2008. This education must include "foundational knowledge, underlying principles, indications, contraindications, and precautions." Students must also be able to explain the use of deep thermal and electrotherapeutic modalities to improve occupational performance and must know the indications, contraindications, and precautions for the clinical application of these physical agents. ACOTE also requires accredited occupational therapy assistant programs to recognize the use of superficial thermal and mechanical modalities as a preparatory method for other occupational therapy interventions.[25]

The National Athletic Trainers' Association (NATA) states that training in therapeutic modalities is a required part of the curriculum to become a certified athletic trainer for accredited programs.[28,29] Continuing education in modality devices is also a component of required athletic trainer continuing education.[30]

In addition to having physical agents applied by professionals, patients can learn about and apply modalities independently. For example, agents such as heat, cold, compression, and TENS can be safely applied at home after the patient is instructed in and demonstrates proper use of the agent. Patient education has several advantages, including the option for more prolonged and frequent application, decreased cost, and increased convenience for the patient. Most important, education allows patients to be active participants in achieving their own therapeutic goals.

Evidence-Based Practice

If several agents could promote progress toward the goals of treatment, they are not contraindicated, and they can be applied with appropriate precautions, selecting which to use should be based on evidence for or against the intervention. **Evidence-based practice (EBP)** is "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients."[31,32] EBP is based on the application of the scientific method to clinical practice. EBP requires that clinical practice decisions be guided by the best available relevant clinical research data in conjunction with the clinician's experience and individual patient's pathology and preferences.

Clinical Pearl

Evidence-based practice (EBP) requires that clinical practice decisions be guided by the best available relevant clinical research data *in conjunction with* the clinician's experience and individual patient's pathology and preferences.

The goal of EBP is to provide the best possible patient care by assessing available research and applying it to each individual patient. When searching for evidence, one may encounter thousands of studies to sift through or very few studies. It is important to understand which studies constitute the highest level of evidence. To use EBP, the clinician should understand the differences between types of research studies and the advantages and disadvantages of each. Evidence used in EBP can be classified by factors such as study design, types of subjects, the nature of controls, outcome measures, and types of statistical analysis.[33]

Study design: Research studies range in quality from the low-level case report (an individual description of a particular patient that does not necessarily reflect the population as a whole) to the high-level meta-analysis of RCTs (the gold standard of EBP, a quantitative synthesis and summary of the results from previously published high-quality RCTs on the same topic). When directly relevant **meta-analyses** do not exist on a particular therapy or treatment, **systematic reviews** or individual RCTs are preferred to case reports and nonrandomized studies. RCTs minimize bias through blinded, randomized assignment to an intervention or a control group and assessment of outcomes.[34] A general overview of study types is presented in Table 2.1.[35] This table provides the general hierarchy as accepted by

TABLE 2.1 Levels of Evidence From Highest Quality to Lowest[35]

Meta-analyses (highest quality)	The use of statistical methodology to quantify the conclusions of many previously published trials evaluating a particular treatment or intervention. Studies are included in the meta-analysis if they meet predetermined criteria, and the statistical methods used should be well documented.
Systematic reviews	An applied, methodical search of existing literature on a specific treatment and/or pathology. Studies meeting predetermined parameters are included, and a narrative conclusion summarizes the findings. Systematic reviews should include the search strategy used when surveying studies so that the search can be reproduced at a later date.
Randomized controlled trials	A preplanned study that uses random assignment to one of two groups, and blinding of both the investigators to group assignment, in order to minimize bias. One group receives the treatment being evaluated, and the other group does not. In general, the group not receiving the active treatment receives a placebo. The same outcome measures are performed in each group.
Cohort studies	An observational study comparing participants who receive a treatment, or have certain features, to participants who do not receive that treatment, or do not have those features.
Case-control study	An observational study comparing a group of participants with the same diagnosis or pathology with a healthy group without the diagnosis.
Case report	A report of the signs, symptoms, interventions, and outcomes for a single patient.

the clinical community, but there are exceptions. For example, a well-powered observational study run over several decades could provide stronger evidence for a particular treatment than a single RCT with a small sample size. Additionally, not all publications that call themselves "systematic reviews" are equally rigorous. A high-quality systematic review should be exhaustive and reproducible.[36] It should utilize multiple databases so that all relevant literature is found. It should also include the names of the databases searched, the search terms and search strategy used in each database, and the dates the searches were run, and it should provide a **Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)** flow diagram giving the number of studies initially found in the search and the final studies selected for inclusion.[37]

Subject type: Studies with demographic variety that include male and female participants of varying ages and from different backgrounds are preferred if the ailment or condition under study affects both sexes across a wide age spectrum. For example, because low back pain commonly affects both men and women of a wide range of ages, with no particular predilection for a specific racial group, studies on the treatment of low back pain should include men and women of various ages and various races to make the results generalizable to the target population. In addition, studies with many participants having homogeneous ailments are preferred over small, heterogeneous groups of participants with varying degrees of ailment, so a study of many people with acute low back pain is better than a study of few people with back pain of varying duration. When an intervention is applied to a group with varying degrees of ailment, the effectiveness of the treatment may be difficult to assess. When the sample size is large and all participants experience the same degree of ailment, the outcomes are more likely to be valid. Subjects with confounding pathologies that may affect the results of treatment should generally be excluded from the study.

Outcome measures: Outcome measures are the assessment strategies used to determine if a treatment is successful. Measures should be reliable—reproducing the same or similar result when repeated, regardless of the test administrator. Measures should also be valid, appropriately assessing the property, unit, or characteristic they intend to measure. Outcome measures can be patient reported,[38] such as self-report on a quality-of-life questionnaire, or clinician measured,[39] such as the speed at which a patient completes a timed walk. Outcome measures can assess functional limitations or the degree of impairment and be sufficiently generic to use across pathologies or specific to pathologies with a specific diagnosis.[40] When considering the quality of outcome measurements, it is important that one consider the reliability and validity of the measure and whether the measurement will provide meaningful data.[41]

Statistical analysis: Once the outcome data have been collected, a study should report the results of preplanned statistical analyses. Results are often considered statistically significant when there is less than a 5% chance that the findings occurred by chance. This is denoted by "$p < 0.05$." Using EBP to guide the selection and application of physical agents as part of rehabilitation is often challenging. It can be difficult to find published high-quality studies because high-quality studies are difficult to perform. Blinding patients and clinicians to rehabilitation treatments may not be possible, outcomes may be difficult to assess, and it is costly and time consuming to include large numbers of subjects. A good initial approach to evaluating the quality of an individual study is to examine the quality of the question being asked. All well-built questions should have four readily identifiable components: (1) the patients, (2) the intervention, (3) the comparison intervention, and (4) the outcome. These components can be readily remembered by the mnemonic *PICO* (Table 2.2).

TABLE 2.2 PICO Table Used by Clinicians When Structuring Questions

P	Patient or Population	The question should apply to a specific person or group (e.g., adults with low back pain; children with lower-extremity spasticity)
I	Intervention	The question should focus on a specific intervention (e.g., specified exercise applied at a specified frequency and duration)
C	Comparison or Control	The question should compare the selected intervention with the gold-standard treatment or no intervention at all
O	Outcome	The question should state clearly the desired outcome from the intervention (e.g., increased walking speed, decrease in self-reported pain)

When exploring the literature to find applicable evidence, one should use the PICO table to structure well-defined searches. Most databases of the clinical literature rely on the use of **Medical Subject Headings (MeSH)** and other specialized vocabulary when indexing or inputting the literature. Translating PICO terms to the specialized language of the database facilitates a strategic and efficient search. At the end of each subsequent chapter in this book, case studies present various pathologies with structured PICO searches for treatment approaches mapped to MeSH terms that you can apply for yourself in PubMed (Table 2.3). This search will provide citations with abstracts, and often full-text articles, that are continuously updated by the National Library of Medicine.

As noted previously, meta-analyses and systematic reviews typically provide the highest-quality evidence. There are several specialized databases of systematic reviews and meta-analyses of medical and rehabilitation-related research, including the well-respected Cochrane Database of Systematic Reviews and PubMed Health (Box 2.1). For clinical questions not included in these databases, individual studies may be found in other online databases of medical and rehabilitation-oriented publications, such as MEDLINE, which is accessed via PubMed; CINAHL (Cumulative Index of Nursing and Allied Health Literature); and PEDro (Physiotherapy Evidence Database) (Box 2.2). When searching the literature to find and evaluate the latest and most relevant evidence, it is important to understand the strengths and limitations of each database you plan to use. A librarian can suggest the best

TABLE 2.3 Sample Find the Evidence Table With PICO Elements Mapped to MeSH Terms

PICO Terms	Natural-Language Example	Sample PubMed Search
P (Population)	Patients with symptoms due to soft tissue shortening	("Contracture*"[MeSH] OR "Contracture"[Text Word] OR "Therapy, Soft Tissue"[MeSH] OR "Tissue Shortening"[Text Word])
I (Intervention)	Ultrasound therapy	AND "Ultrasonic Therapy*"[MeSH] AND English[lang] AND "Humans"[MeSH Terms]
C (Comparison)	No ultrasound therapy	
O (Outcome)	Increased range of motion	

Box 2.1 Databases of Systematic Reviews and Meta-Analyses

The Cochrane Database of Systematic Reviews	A collection of systematic reviews and corresponding editorials that have been carried out by highly trained Cochrane Review Groups
PubMed Health	A resource for systematic reviews provided by the National Library of Medicine including Cochrane's DARE database
Joanna Briggs Institute	A refereed, online library that publishes systematic review protocols and systematic reviews of health care research, as performed by Joanna Briggs Library and international collaboration centers
PROSPERO	An international prospective register of systematic reviews
Epistemonikos	A multilingual database of published research reviews in the clinical, rehabilitation, and public health fields

databases for your study question and demonstrate the various features of the platform so that you can efficiently find relevant literature.

Most databases have advanced search features. For example, when searching MEDLINE through the PubMed interface, you can limit your searches to review articles or randomized trials only. You can also search by keyword at the title level to retrieve only citations that include your selected term or terms in the title. Additionally, in PubMed, articles related to the last selected citation are suggested to you, and references within selected articles are hyperlinked to ease the search and discovery process.

Box 2.2 Sources of Studies Answering Specific Clinical Questions

TRIP Database	A clinical search engine that allows users to structure searches by PICO terms to quickly locate high-quality research evidence
PEDro	An Australian database with citations, abstracts, and full-text articles of more than 23,000 randomized controlled trials, 5200 systematic reviews, and 513 evidence-based clinical practice guides in physiotherapy
MEDLINE (searchable via PubMed)	An online database of over 25 million citations and abstracts from health and medical journals and other news sources
CINAHL	A database of studies and evidence-based care sheets from over 1300 nursing journals
GuidelineCentral	GuidelineCentral is the publisher of American Medical Association guidelines. GuidelineCentral provides a free app and covers a range of rehabilitation topics.

Clinical practice guidelines can also be good sources of evidence. Clinical practice guidelines are systematically developed statements that attempt to interpret current research to provide evidence-based guidelines to guide practitioner and patient decisions about appropriate health care for specific clinical circumstances.[42] Clinical practice guidelines give recommendations for diagnostic and prognostic measures and for preventive and therapeutic interventions. For any of these, the specific types of patients or problems, the nature of the intervention or test, alternatives to the intervention being evaluated, and outcomes of the intervention for which these guidelines apply will be stated. For example, some guidelines for the treatment of acute low back pain and for the treatment of pressure ulcers include evidence-based recommendations for tests and measures, interventions, prevention, and prognosis. Often, such recommendations are classified according to the strength of the evidence supporting them. General clinical practice guidelines used to be available on the Agency for Healthcare Research and Quality (AHRQ) National Guideline Clearinghouse (NGC) website, but funding for this clearinghouse ended, and the clearinghouse closed on July 16, 2018, and has yet to be replaced. Other repositories and libraries with guidelines include the International Guideline Library[44]; the National Institute for Health and Care Excellence (NICE) United Kingdom–based searchable website of evidence-based guidance; and the CPG Infobase, which is the Canadian repository for guidelines.[44] In addition, GuidelineCentral,[45] which provides free access to thousands of current clinical practice guidelines and guideline summaries online and via an app, is currently working with a handful of other organizations to establish a new nonprofit initiative that will aim to fill the gap left by the sudden closure of AHRQ's NGC. This new initiative will include a

Box 2.3 Sources of Clinical Practice Guidelines

International Guideline Library	The International Guideline Library contains around 3000 guidelines, which have mainly been developed or endorsed by organizational members of the Guideline International Network (GIN). The library is free to access.
National Institute for Health and Care Excellence (NICE)	NICE guidelines provide evidence-based recommendations developed by independent committees, including professionals and lay members, and consulted on by stakeholders.
CPG Infobase	This database contains approximately 1200 evidence-based Canadian clinical practice guidelines (CPGs) developed or endorsed by authoritative medical or health organizations in Canada.
Centre for Evidence-Based Medicine (CEBM)	The CEBM website includes information for health care professionals on learning, practicing, and teaching EBM, as well as definitions of terminology and calculators.

database of quick-reference guideline summaries, along with a focus on developing a repository of various guideline-implementation tools (including machine-computable guidelines for electronic health records [EHRs]). This new database will be made available for free to all health care providers in both web and mobile app formats (Box 2.3).

EBP is accepted practice and should be incorporated into every patient's plan of care. However, it is important to remember that every study cannot be applied to every patient, and research-supported interventions should not be applied without considering each patient's situation. EBP requires the careful combination of patient preference, clinical circumstances, clinician expertise, and research findings.

Using Physical Agents Within Different Health Care Delivery Systems

Clinicians may be called on to treat patients within different health care delivery systems in the United States and abroad. These systems may vary in terms of the quantity and nature of available health care resources. Some systems provide high levels of resources in the form of skilled clinicians and costly equipment, and others do not. Over the last several years, the health care delivery system in the United States has tried to contain the growing costs of medical care and focused on the cost-effective use of resources. The emphasis on cost-effectiveness is even greater in socialized medical systems, where there are fewer counterpressures from the for-profit provision of health care.

To help control costs, services that can be self-administered are often not paid for by insurance. For example, since 1997, Medicare has bundled the payment for hot-pack and cold-pack treatments into the payment for all other services, rather than reimbursing separately for these treatments, because hot and cold packs can be administered by patients independently.[46] Nonetheless, this intervention may be indicated, and patients may benefit from education on how and when to apply these agents themselves at home.

Within the context of attending to cost-effectiveness, the goals of health care continue to be, as they always have been, to obtain the best outcome for the patient within the constraints of the health care delivery system. The clinician should find and use the most efficient ways to provide interventions to help patients progress toward the goals of treatment. To use physical agents in this manner, the clinician must be able to assess the presenting problem and know when a physical agent is or is not likely to be an effective component of treatment. The clinician must know when and how to use physical agents most effectively, which ones can be used by patients to treat themselves, and which are not likely to be effective (Box 2.4). To achieve the most cost-effective treatment, the clinician should use evidence-based interventions and optimize the use of practitioners of varying skill levels and of home programs when appropriate. In many cases, the licensed therapist may not need to apply the physical agent but instead may assess and analyze the presenting clinical findings; determine the intervention plan; provide the aspects of care that require the skills of the licensed therapist; and train the patient to apply, or supervise other personnel in applying, interventions that require a lower level of skill. The therapist can then reassess the patient regularly to determine the effectiveness of the interventions provided and the patient's progress toward their goals and can adjust the plan of care accordingly.

Cost-efficiency may also be increased by providing an intervention to groups of patients, such as group water exercise programs for patients recovering from total joint arthroplasty or for patients with osteoarthritis. Such programs may be designed to facilitate the transition to a community-based exercise program when the patient reaches the appropriate level of function and recovery. When used in this manner, physical agents can provide cost-effective care and can involve the patient in promoting recovery and achieving the goals of treatment.

Box 2.4 Requirements for Cost-Effective Use of Physical Agents

- Assess and analyze the presenting problem.
- Know when physical agents can be an effective component of treatment.
- Know when and how to use physical agents most effectively.
- Know the skill level required to apply the different physical agents.
- Optimize the use of different practitioners' skill levels.
- Use home programs when appropriate.
- Treat in groups when appropriate.
- Reassess patients regularly to determine the efficacy of treatments provided.
- Adjust the plan of care according to the findings of reassessments.

Chapter Review

1. The ICF model assesses the impact of a disease or condition on a patient's function. This model considers the effects of a patient's health condition, environment, and personal circumstances on their impairments, activity limitations, and participation restrictions. The ICF model looks at the patient on three levels: body, whole person, and social. Physical agents primarily affect the patient at the body, or impairment, level. A complete rehabilitation program should affect the patient at all levels of functioning, disability, and health.
2. EBP is the incorporation of research-based evidence into a patient's rehabilitation plan. EBP integrates the clinician's experience and judgment with the patient's preferences, the clinical situation, and available evidence. This book attempts to include the current, best-quality evidence available while teaching readers how to conduct independent searches to get the most relevant and up-to-date information when they need it.
3. Physical agents are used in the clinic, at home, and in various health care delivery systems. Depending on the system, the selection and application of physical agents may vary. Reimbursement for applying physical agents is constantly in flux, and the potential for conflict between minimizing cost and maximizing benefit can make intervention selection difficult.

Glossary

Clinical practice guidelines: Systematically developed statements that attempt to interpret current research to provide evidence-based guidelines to guide practitioner and patient decisions about appropriate health care for specific clinical circumstances.

Disability: The inability to perform activities required for self-care, home, work, and community roles.

Evidence-based practice (EBP): The conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients.

Functional limitations: Restrictions in the ability to perform an activity in an efficient, typically expected, or competent manner.

Gate control theory of pain modulation: Theory of pain control and modulation that states that pain is modulated at the spinal cord level by inhibitory effects of nonnoxious afferent input.

Hypertonicity: High muscle tone or increased resistance to stretch compared with normal muscles.

ICF model: International Classification of Functioning, Disability and Health (ICF) model of disability and health created by the World Health Organization (WHO) that views functioning and disability as a complex interaction between the health condition of the individual and contextual factors, including environmental and personal factors. ICF uses categories of health conditions, body functions, activities, and participation to focus on abilities rather than limitations.

ICIDH model: International Classification of Impairments, Disabilities, and Handicaps (ICIDH) model of disability created by the World Health Organization (WHO) that was a precursor to the International Classification of Functioning, Disability, and Health (ICF) model and focused on disability rather than ability.

Impairments: Alterations in anatomical, physiological, or psychological structures or functions as the result of an underlying pathology.

Medical Subject Headings (MeSH): The National Library of Medicine's controlled vocabulary thesaurus.

Meta-analyses: Systematic reviews that use statistical analysis to integrate data from a number of independent studies.

Nagi model: A linear model of disability in which pathology causes impairments, leading to functional limitations that result in disabilities; this was a precursor to the International Classification of Functioning, Disability and Health (ICF) model.

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA): An evidence-based minimum set of items for reporting in systematic reviews and meta-analyses. The aim of the PRISMA Statement is to help authors improve the reporting of systematic reviews and meta-analyses.

Systematic reviews: Reviews of studies that answer clearly formulated questions by systematically searching for, assessing, and evaluating literature from multiple sources.

Transcutaneous electrical nerve stimulation (TENS): The application of electrical current through the skin to modulate pain.

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3

Inflammation and Tissue Repair

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CHAPTER OUTLINE

CHAPTER OBJECTIVES

After reading this chapter, the reader will be able to do the following:

- Define *inflammation*.
- Describe the phases of inflammation.
- Explain the tissue healing process.
- List the factors that affect the tissue healing process.
- Discuss the healing process of specific musculoskeletal tissues.

Injury to vascularized tissue results in a coordinated, complex, and dynamic series of events collectively referred to as **inflammation** and repair. Although there are variations among the responses of different tissue types, overall, the processes are remarkably similar. The sequelae depend on the source and site of injury, the state of local homeostasis, and whether the injury is acute or chronic. The goal of inflammation and repair is to restore function by eliminating the pathological or physical insult, replacing the damaged or destroyed tissue, and promoting regeneration of normal tissue structure.

Rehabilitation professionals treat a variety of inflammatory conditions resulting from trauma, surgical procedures, or problematic healing. The clinician called on to manage such injuries needs to understand the physiology of inflammation and healing and how it can be modified. The clinician can enhance healing by applying the appropriate physical agents, therapeutic exercises, or manual techniques. A successful rehabilitation program requires an understanding of biomechanics; the phases of tissue healing; and the effects of immobilization, therapeutic interventions, and nutritional status on the healing process.

Phases of Inflammation and Healing

This chapter provides readers with information on the processes involved in inflammation and tissue repair so that they can understand how physical agents may be used to modify these processes and improve patient outcomes. The process of inflammation and repair consists of three phases: inflammation, proliferation, and maturation. The **inflammation phase** prepares the wound for healing, the **proliferation phase** rebuilds damaged structures and strengthens the wound, and the **maturation phase** modifies scar tissue into its mature form (Fig. 3.1). The duration of each phase varies to some degree, and the phases generally overlap. Thus, the timetables for the various phases of healing provided in this chapter are only general guidelines, not precise definitions (Fig. 3.2).

Clinical Pearl

The process of regeneration and repair after injury consists of three phases: inflammation, proliferation, and maturation.

INFLAMMATION PHASE (DAYS 1 TO 6)

Inflammation, from the Latin *inflamer,* meaning "to set on fire," begins when the normal physiology of tissue is altered by disease or trauma.[1] This immediate protective response attempts to destroy, dilute, or isolate the cells or agents that may be at fault. It is a normal and necessary prerequisite to healing. If no inflammation occurs, healing cannot take place. Inflammation can also be harmful, particularly when it is directed at the wrong tissue or is overly exuberant. For example, inappropriately directed inflammatory reactions that underlie autoimmune diseases such as rheumatoid arthritis can damage and destroy joints. Although the inflammatory process follows the same sequence of events regardless of the cause of injury, some causes result in exaggeration or prolongation of certain events.

Nearly 2000 years ago, Cornelius Celsus characterized the inflammatory phase by the four cardinal signs of calor, rubor, tumor, and dolor (Latin terms for "heat," "redness," "swelling," and "pain"). A fifth cardinal sign, functio laesa ("loss of function"), was added to this list by Virchow (Table 3.1).

Clinical Pearl

Inflammation is characterized by heat, redness, swelling, pain, and loss of function.

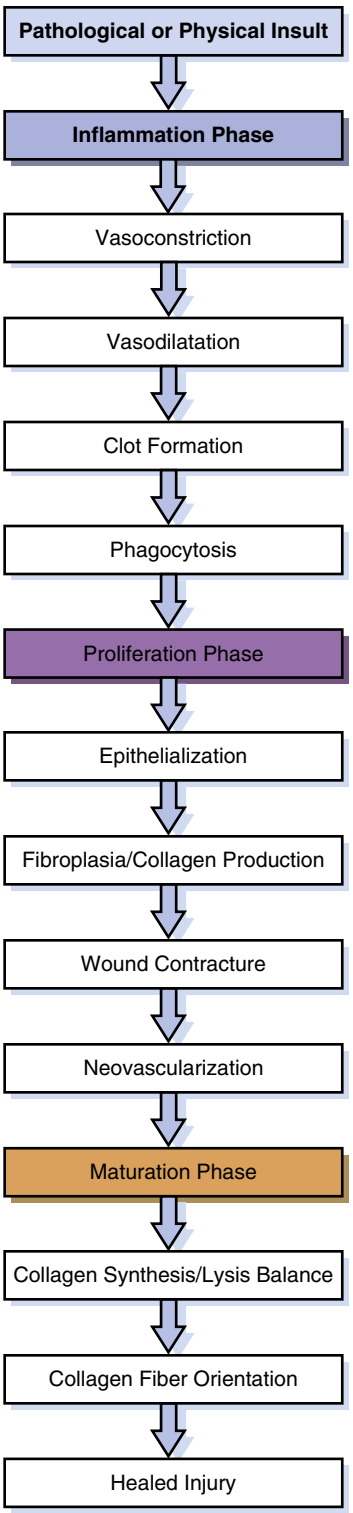


FIGURE 3.1 Flow diagram of the normal phases of inflammation and repair.

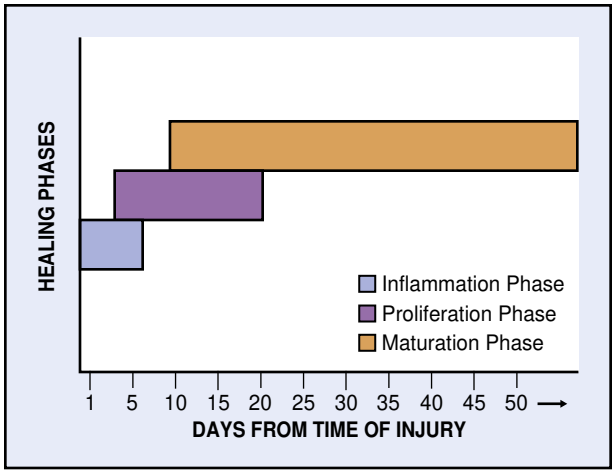


FIGURE 3.2 Timeline of the phases of inflammation and repair.

TABLE 3.1 Cardinal Signs of Inflammation

Sign (English)	Sign (Latin)	Cause
Heat	Calor	Increased vascularity
Redness	Rubor	Increased vascularity
Swelling	Tumor	Blockage of lymphatic drainage
Pain	Dolor	Physical pressure or chemical irritation of pain-sensitive structures
Loss of function	Functio laesa	Pain and swelling

An increase in blood in a given area, known as **hyperemia,** accounts primarily for the increased temperature and redness in the area of **acute inflammation.** The onset of hyperemia at the beginning of the inflammatory response is controlled by neurogenic and chemical mediators.[2] Local swelling results from increased permeability and vasodilation of local blood vessels and infiltration of fluid into interstitial spaces of the injured area. Pain results from the pressure of swelling and from irritation of pain-sensitive structures by chemicals released from damaged cells.[2] Both pain and swelling may result in loss of function.

There is some disagreement in the literature about the duration of the inflammation phase. Some investigators state that it is relatively short, lasting for fewer than 4 days[3,4]; others believe it may last for up to 6 days.[5,6] This discrepancy may be the result of individual and injury-specific variation, or it may reflect the overlapping nature of phases of inflammation and tissue healing.

The inflammatory phase involves a complex sequence of interactive and overlapping events, including vascular, cellular, hemostatic, and immune processes. **Humoral mediators** and **neural mediators** act to control the inflammatory phase. Evidence indicates that immediately after injury, **platelets** and **neutrophils** predominate and release a number of factors that amplify the platelet aggregation response, initiate a coagulation cascade, or act as chemo-attractants for cells involved in the inflammatory phase.[7] Neutrophil infiltration ceases after a few days, and neutrophils are replaced by **macrophages** starting 2 days after injury.[8] This shift in cell type at the site of injury correlates with a shift from the inflammation phase to the proliferation phase of healing.

Vascular Response

Alterations in the anatomy and function of the microvasculature, including capillaries, postcapillary venules, and lymphatic vessels, are among the earliest responses noted in the inflam-

matory phase.[9] Trauma such as a laceration, sprain, or contusion physically disrupts these structures and may produce bleeding, fluid loss, cell injury, and exposure of tissues to foreign material, including bacteria. Damaged vessels respond rapidly with transient constriction to minimize blood loss. This response, which is mediated by norepinephrine, generally lasts for 5 to 10 minutes but can be prolonged in small vessels by serotonin released from mast cells and platelets.

After the transient vasoconstriction of injured vessels, uninjured vessels near the injured area dilate. Capillary permeability is also increased by injury to the capillary walls and in response to chemicals released from injured tissues (Fig. 3.3). The vasodilation and increase in capillary permeability are initiated by histamine, Hageman factor, bradykinin, prostaglandins, and complement fractions. Vasodilation and increased capillary permeability last for up to 1 hour after tissue damage.

Histamine is released primarily by mast cells, as well as by platelets and basophils at the injury site.[10] Histamine causes vasodilation and increased vascular permeability in venules, which contribute to local **edema** (swelling). Histamine also attracts **leukocytes** (white blood cells) to the damaged tissue area.[11] The ability of a chemical to attract cells is known as **chemotaxis.** Histamine is one of the first inflammatory mediators released after tissue injury and is active for approximately 1 hour after injury (Fig. 3.4).[12]

Hageman factor (also known as *clotting factor XII*), an enzyme found in the blood, is activated by contact with negatively charged surfaces of the endothelial lining of vessels that are exposed when vessels are damaged. The role of Hageman factor is twofold. First, it activates the coagulation system to stop local bleeding. Second, it causes vasoconstriction and increased vascular permeability by activating other **plasma** proteins. It converts plasminogen to plasmin and prekallikrein to kallikrein, and it activates the alternative complement pathway (Fig. 3.5).[13]

Plasmin augments vascular permeability in both skin and lungs by inducing the breakdown of fibrin and by cleaving components of the **complement system.** Plasmin also activates Hageman factor, which initiates the cascade that generates bradykinin.

Plasma kallikrein attracts neutrophils and cleaves kininogen to generate several kinins, such as bradykinin. Kinins are biologically active peptides that are potent inflammatory substances derived from plasma. Kinins, particularly bradykinin, function similarly to histamine, causing a marked increase in permeability of the microcirculation. They are most prevalent

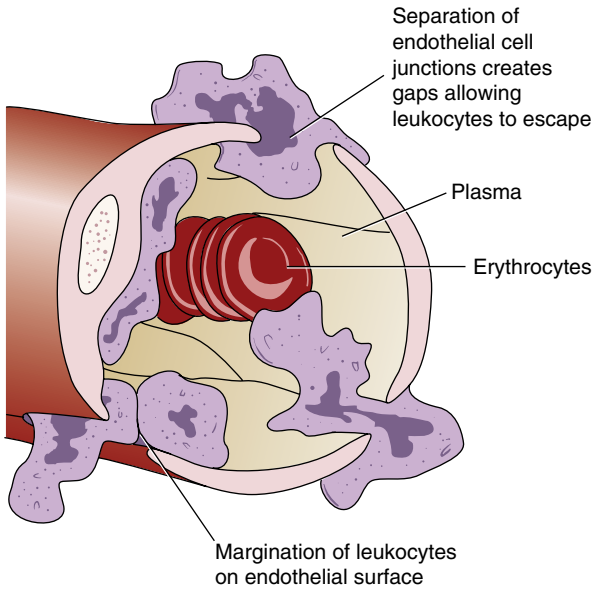


FIGURE 3.3 Vascular response to wound healing.

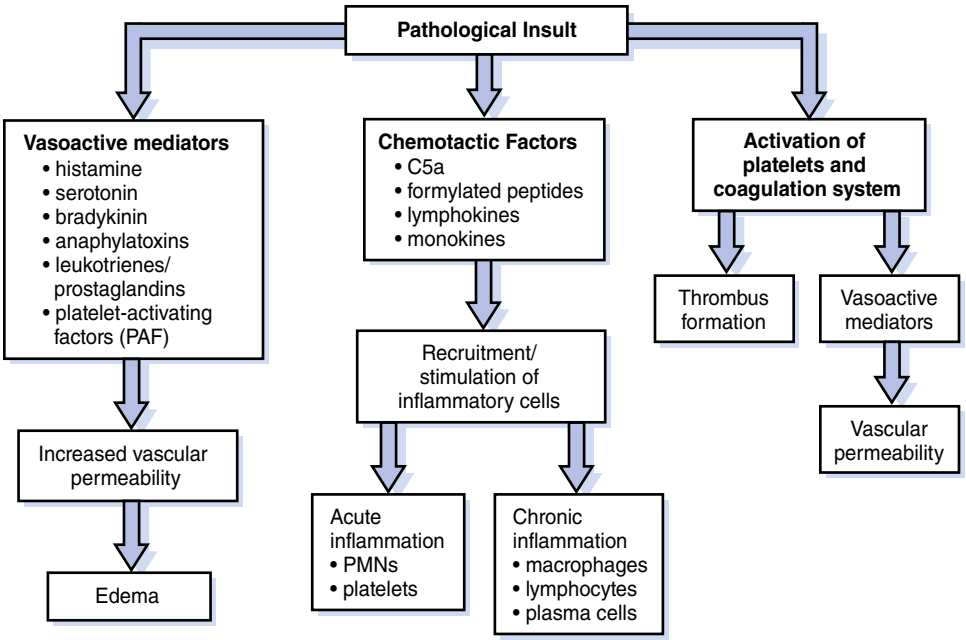


FIGURE 3.4 Mediators of the inflammatory response. *PMNs,* Polymorphonucleocytes.

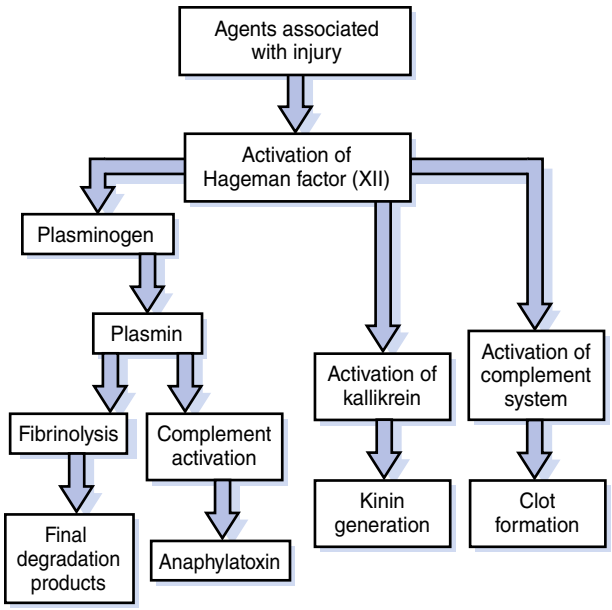


FIGURE 3.5 Hageman factor activation and inflammatory mediator production.

TABLE 3.2 Mediators of the Inflammatory Response

Response	Mediators
Vasodilation	Histamine
	Prostaglandins
	Serotonin
Increased vascular permeability	Bradykinin
	C3a, C5a
	PAF
	Histamine
	Serotonin
	Prostaglandins
Chemotaxis	Histamine
	C5a
	Monokines
	Kallikrein
	Lymphokines
Fever	Prostaglandins
Pain	Prostaglandins
	Hageman factor
	Bradykinin

PAF, Platelet-activating factor.

in the early phases of inflammation, after which they are rapidly destroyed by tissue proteases or kininases.[14]

Prostaglandins are produced by nearly all cells in the body and are released when the cell membrane is damaged. Two prostaglandins affect the inflammatory phase: prostaglandin E_1 (PGE_1) and PGE_2. PGE_1 increases vascular permeability by antagonizing vasoconstriction, and PGE_2 attracts leukocytes and synergizes the effects of other inflammatory mediators, such as bradykinin. Proinflammatory prostaglandins are also thought to be responsible for sensitizing pain receptors and **hyperalgesia**. In the early stages of the healing response, prostaglandins may regulate the repair process; they are also responsible for the later stages of inflammation.[15] Nonsteroidal antiinflammatory drugs (NSAIDs) specifically work by inhibiting prostaglandin synthesis, whereas **corticosteroids** inhibit inflammation through this and other mechanisms. Because prostaglandins are responsible for febrile states, these medications are also effective in reducing fever. More recent studies suggest that proinflammatory growth factors, including fibroblast growth factor and platelet-activating factor, also contribute to hyperalgesia.[16,17]

The anaphylatoxins C3a, C4a, and C5a are important products of the complement system. These complement fractions cause increased vascular permeability and induce mast cell and basophil degranulation, causing further release of histamine and further increasing vascular permeability.

Aside from chemically mediated vascular changes (Table 3.2), changes in physical attraction between blood vessel walls also alter blood flow. During the initial vasoconstriction, the opposing walls of the small vessels become approximated, causing the linings of blood vessels to stick together. Under normal physiological conditions, the cell membranes of inflammatory cells and the basement membranes have mutually repulsive negative charges; however, after injury, this repulsion decreases, and polarity may be reversed. This results in decreased repulsion between circulating inflammatory cells and vessel walls and contributes to the adherence of inflammatory cells to blood vessel linings.

As vasoconstriction of the postcapillary venules and increased permeability of the microvasculature cause blood flow to slow, an increase in cellular concentration occurs in the vessels, resulting in increased viscosity. Blood viscosity also increases as blood velocity slows because blood has shear-thinning properties.[18] In the normal physiological state, cellular components of blood within the microvasculature are confined to a central axial column, and the blood in contact with the vessel wall is relatively cell-free plasma.

Early in the inflammatory response, neutrophils, a type of leukocyte in the circulating blood, begin to migrate to the injured area. Within a few hours of injury, the bulk of neutrophils in the wound transmigrate across the capillary endothelial cell walls. The sequence of events in the journey of these cells from inside the blood vessel to the tissue outside the blood vessel is known as **extravasation.** Neutrophils break away from the central cellular column of blood and start to roll along the blood vessel lining (the endothelium) and adhere. They line the walls of the vessels in a process known as **margination.** Within 1 hour, the endothelial lining of the vessels can be completely covered with neutrophils. As these cells accumulate, they are laid down in layers in a process known as **pavementing.** Certain mediators control the adherence of leukocytes to the endothelium, enhancing or inhibiting this process. For example, fibronectin, a glycoprotein present in plasma and basement membranes, has an important role in the modulation of cellular adherence to vessel walls. After injury to the vessels, increased amounts of fibronectin are deposited at the injury site. Adherence of leukocytes to the endothelium or the vascular basement membrane is critical for their recruitment to the site of injury.

After margination, neutrophils begin to squeeze through the vessel walls in a process known as **diapedesis.** Endothelial

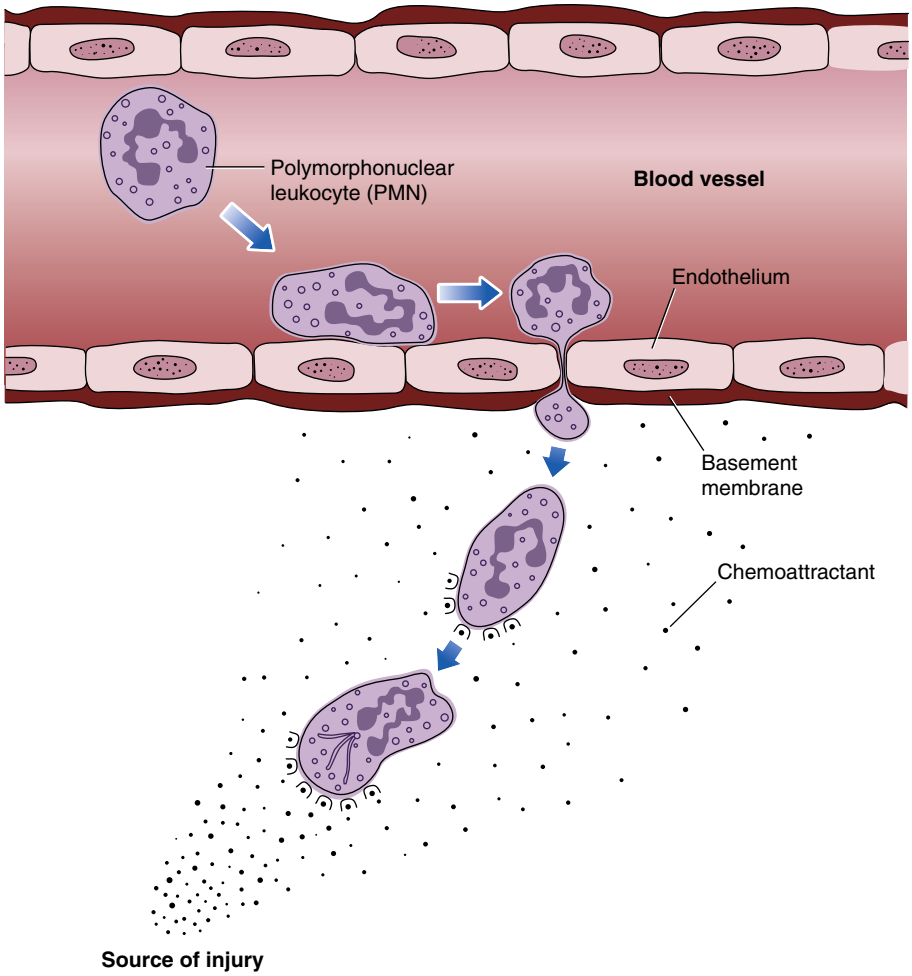


FIGURE 3.6 Illustration of leukocytic events in inflammation: margination, adhesion, diapedesis, and emigration in response to a chemoattractant emanating from the source of the injury.

P-selectin and E-selectin and intercellular adhesion molecule-1 (ICAM-1) and ICAM-2 are adhesion molecules crucial to diapedesis. These adhesion molecules interact with integrins on the surfaces of neutrophils as they insert their pseudopods into junctions between endothelial cells, crawl through widened junctions, and assume a position between the endothelium and the basement membrane. Then, attracted by chemotactic agents, they escape to reach the interstitium. This process of leukocyte migration from blood vessels into perivascular tissues is known as **emigration** (Fig. 3.6). Receptors on white blood cells and endothelial cells that allow rolling, margination, and diapedesis have been identified, and drugs that affect these functions have been developed. In the future, these drugs may play an important role in treating severe inappropriate inflammation.[19,20]

Edema is an accumulation of fluid within the extravascular space and interstitial tissues. Edema is the result of increased capillary hydrostatic pressure, increased interstitial osmotic pressure, increased venule permeability, and an overwhelmed lymphatic system that is unable to accommodate this substantial increase in fluid and plasma proteins. The clinical manifestation of edema is swelling. Edema formation and its control are discussed in detail in Chapter 19.

Clinical Pearl

Edema is swelling caused by fluid accumulation outside the vessels.

Transudate, the fluid that first forms edema during inflammation, has very few cells and very little protein. This fluid is predominantly composed of dissolved electrolytes and water and has a specific gravity of less than 1.0. As the permeability of the vessels increases, more cells and lower-molecular-weight plasma proteins cross the vessel wall, making the extravascular fluid more viscous and cloudy. This cloudy fluid, known as **exudate,** has a specific gravity greater than 1.0. It is also characterized by a high content of lipids and cellular debris. Exudate is often observed early in the acute inflammatory process and forms in response to minor injuries such as blisters and sunburn.

Loss of protein-rich fluid from the plasma reduces osmotic pressure within the vessels and increases the osmotic pressure of interstitial fluids, which increases the outflow of fluid from the vessels, resulting in an accumulation of fluid in the interstitial tissue. When the exudate concentration of leukocytes

increases, it is known as **pus** or suppurative exudate. Pus consists of neutrophils, liquefied digestion products of underlying tissue, fluid exudate, and often bacteria if an infection is present. When localized, suppurative exudate occurs within a solid tissue and results in an abscess, which is a localized collection of pus buried in a tissue, organ, or confined space. Pyogenic bacteria produce abscesses.

Four mechanisms are responsible for the increased vascular permeability seen in inflammation. The first mechanism is endothelial cell contraction, which leads to a widening of intercellular junctions or gaps. This mechanism affects venules while sparing capillaries and arterioles. It is controlled by chemical mediators and is relatively short-lived, lasting for only 15 to 30 minutes.[21] The second mechanism is a result of direct endothelial injury and is an immediate, sustained response that potentially affects all levels of the microcirculation. This effect is often seen in severe burns or lytic bacterial infections and is associated with platelet adhesion and thrombosis or clot formation. The third mechanism is leukocyte-dependent endothelial injury. Leukocytes bind to the area of injury and release various chemicals and enzymes that damage the endothelium, thus increasing permeability. The fourth mechanism is leakage by regenerating capillaries that lack a differentiated endothelium and therefore do not have tight gaps. This may account for the edema characteristic of later-healing inflammation (Fig. 3.7).

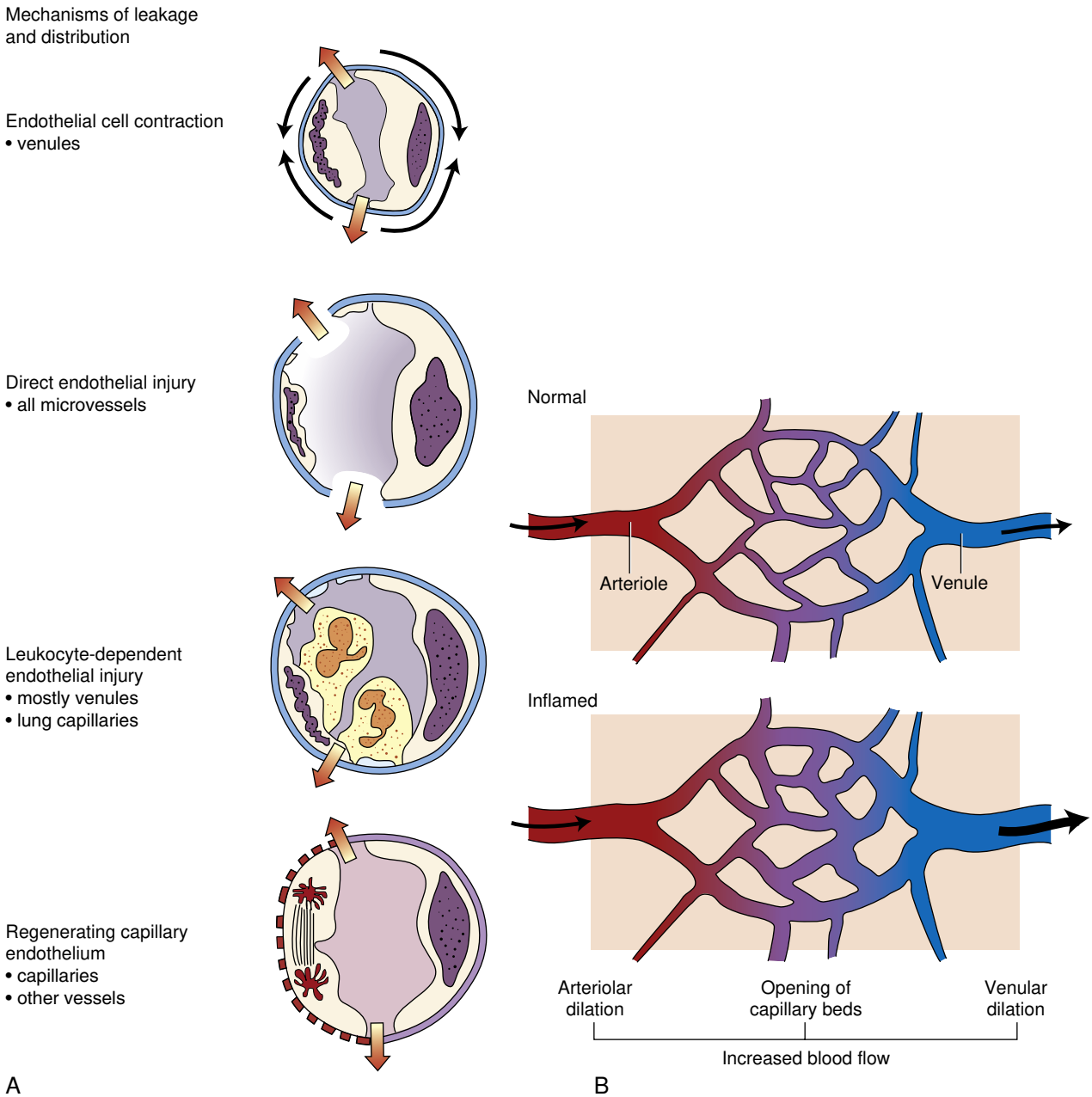


FIGURE 3.7 (A) Illustration of four mechanisms of increased vascular permeability in inflammation. (B) Vascular changes associated with acute inflammation.

Hemostatic Response

The hemostatic response to injury controls blood loss when vessels are damaged or ruptured. Immediately after injury, platelets enter the area and bind to the exposed subendothelial **collagen,** releasing fibrin to stimulate clotting. Platelets also release a regulatory protein known as **platelet-derived growth factor (PDGF),** which is chemotactic and mitogenic to **fibroblasts** and may also be chemotactic to macrophages, **monocytes,** and neutrophils.[22] Thus, platelets not only play a role in hemostasis, but they also contribute to the control of fibrin deposition, fibroblast proliferation, and angiogenesis.

When fibrin and fibronectin enter the injured area, they form cross-links with collagen to create a fibrin lattice. This tenuous structure provides a temporary plug in the blood and lymph vessels, limiting local bleeding and fluid drainage. The lattice seals off damaged vessels and confines the inflammatory reaction to the area immediately surrounding the injury. The damaged, plugged vessels do not reopen until later in the healing process. The fibrin lattice serves as the wound's only source of tensile strength during the inflammatory phase of healing.[23]

Cellular Response

Circulating blood is composed of specialized cells suspended in a fluid known as *plasma.* These cells include **erythrocytes** (red blood cells), leukocytes (white blood cells), and platelets. Erythrocytes play only a minor role in the inflammatory process, although they may migrate into tissue spaces if the inflammatory reaction is intense. Oxygen transport, the primary role of erythrocytes, is carried out within the confines of the vessels. An inflammatory exudate that contains blood usually indicates severe injury to the microvasculature. The accumulation of blood in a tissue or organ is referred to as a **hematoma**; bloody fluid in a joint is called a **hemarthrosis**. Hematomas in muscle can cause pain and can limit motion or function; they can also increase scar tissue formation. Hemoglobin-derived iron from phagocytosed red blood cells also contributes to tissue damage through increased generation of reactive oxygen species.[24]

Clinical Pearl

Muscle hematomas can cause pain, limit motion, and increase scar tissue formation.

A critical function of inflammation is to deliver leukocytes to the area of injury via the circulatory system. Leukocytes are classified according to their structure into **polymorphonucleocytes (PMNs)** and mononuclear cells (Fig. 3.8). PMNs have nuclei with several lobes and contain cytoplasmic granules. They are further categorized as neutrophils, basophils, and eosinophils by their preference for specific histological stains. Monocytes are larger than PMNs and have a single nucleus. In the inflammatory process, leukocytes have the important role of clearing the injured site of debris and microorganisms to set the stage for tissue repair.

Migration of leukocytes into the area of injury occurs within hours of the injury. Each leukocyte is specialized and has a specific purpose. Some leukocytes are more prominent in early inflammation, whereas others become more important during later stages. Initially, the number of leukocytes at the injury site is proportionate to their concentration in the circulating blood.

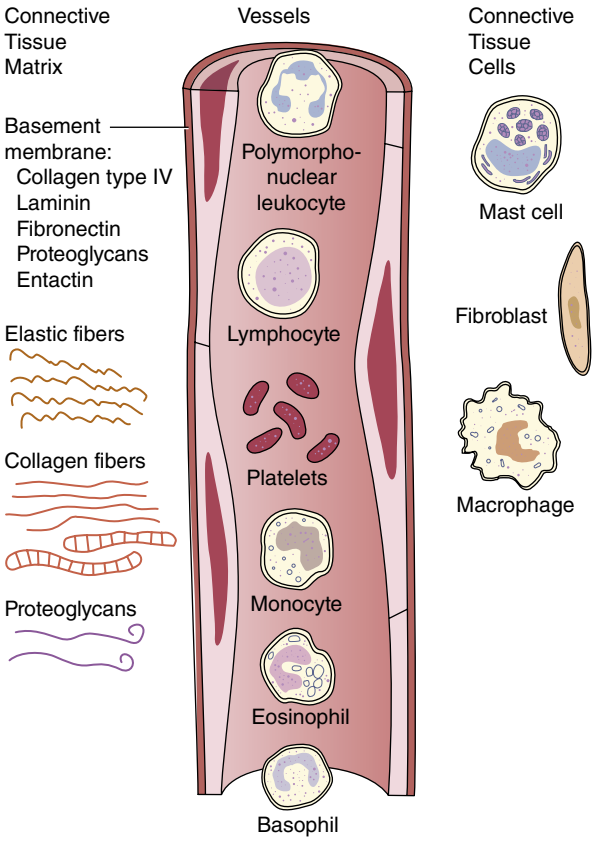


FIGURE 3.8 Connective tissue matrix, intravascular cells, and connective tissue cells involved in the inflammatory response.

Because neutrophils have the highest concentration in the blood, they predominate in the early phases of inflammation. Chemotactic agents released by other cells, such as mast cells and platelets, attract leukocytes at the time of injury. Neutrophils rid the injury site of bacteria and debris by **phagocytosis**. When lysed, lysosomes of the neutrophils release proteolytic enzymes (proteases) and collagenolytic enzymes **(collagenases)**, which begin the debridement process. Neutrophils remain at the site of injury for only 24 hours, after which time they disintegrate. However, they help to perpetuate the inflammatory response by releasing chemotactic agents to attract other leukocytes into the area.

Basophils release histamine after injury and contribute to early increased vascular permeability. Eosinophils may be involved in phagocytosis to some degree, although they are classically involved in allergic inflammation or extra-gastrointestinal parasitic disease.[25]

For 24 to 48 hours after an acute injury, monocytes predominate. Monocytes make up 4% to 8% of the total white blood cell count. The predominance of these cells at this stage of inflammation is thought to result in part from their longer life span. Lymphocytes supply antibodies to mediate the body's immune response. They are prevalent in chronic inflammatory conditions.

Monocytes are converted into macrophages when they migrate from the capillaries into the tissue spaces. The macrophage is considered the most important cell in the

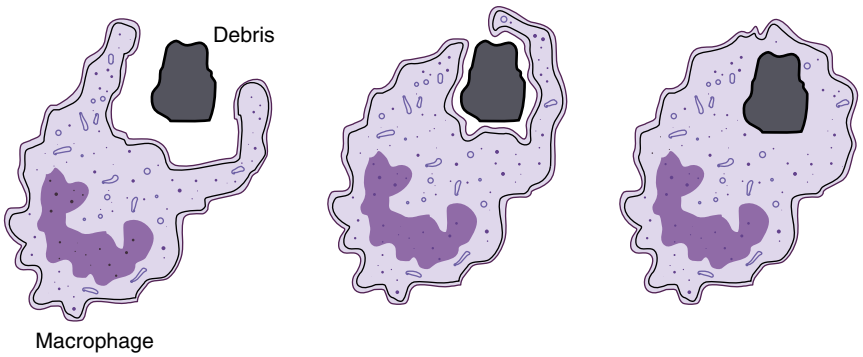


FIGURE 3.9 Diagrammatic representation of the process of phagocytosis.

Box 3.1 Macrophage Products

- Proteases
- Elastase
- Collagenase
- Plasminogen activator
- Chemotactic factors for other leukocytes
- Complement components of alternative and classical pathways
- Coagulation factors
- Growth-promoting factors for fibroblasts and blood vessels
- Cytokines
- Arachidonic acid metabolites

inflammatory phase and is essential for wound healing. Macrophages are important because they produce a wide range of chemicals (Box 3.1). They play a major role in phagocytosis by producing enzymes such as collagenase (Fig. 3.9). These enzymes facilitate the removal of necrotic tissue and bacteria. Macrophages also produce factors that are chemotactic for other leukocytes and growth factors that promote cell proliferation and the synthesis of extracellular matrix molecules by resident skin cells.[26]

Macrophages probably play a role in localizing the inflammatory process and attracting fibroblasts to the injured area by releasing chemotactic factors such as fibronectin. Macrophages activated by type 2 cytokines chemically influence the number of fibroblastic repair cells activated; therefore, in the absence of macrophages, fewer, less mature fibroblasts migrate to the injured site. More recent data suggest that a specific population of activated CD301b+ macrophages regulates a population of fibroblasts that proliferate at the wound site. High numbers of these CD301+ macrophages have been found in keloid scars—a pathological proliferation of scar tissue—which supports a profibrotic function of this macrophage and may be a possible future target for clinical intervention.[27]

In the later stages of **fibroplasia,** macrophages may enhance collagen deposition by causing fibroblasts to adhere to fibrin. Two distinct subsets of macrophages, M1 and M2, have been characterized.[28] Over the course from injury to repair, macrophages switch their phenotype from M1 to M2. In skeletal muscle and renal tissues, M1 macrophages promote inflammation, whereas M2 macrophages promote fibrosis. However, in the liver, M1 macrophages promote inflammation and fibrosis, whereas M2 macrophages promote resolution with matrix degradation and debris clearance, contributing to scar resolution. These functional differences in M1 and M2 macrophages in different tissues highlight the diversity of macrophages in different microenvironments.

As macrophages phagocytose organisms, they release a variety of substances, such as hydrogen peroxide, ascorbic acid, and lactic acid, that enhance the killing of microorganisms.[29] Hydrogen peroxide inhibits anaerobic microbial growth. The other two products signal the extent of damage in the area, and their concentration is interpreted by the body as a need for more macrophages in the area.[30] This interpretation causes increased production of these substances, which results in an increased macrophage population and a more intense and prolonged inflammatory response.

Macrophages are most effective when oxygen is present in injured tissues. However, they can tolerate low-oxygen conditions, as is apparent by their presence in chronic inflammatory states. Adequate oxygen tension in the injured area is also necessary to minimize the risk of infection. Tissue oxygen tension depends on the concentration of atmospheric oxygen available for breathing, the amount of oxygen absorbed by the respiratory and circulatory systems, the volume of blood available for transportation, and the state of the tissues. Local topical application of oxygen to an injured area does not influence tissue oxygen tension as much as the level of oxygen brought to the injured area by the circulating blood.[31–33]

Immune Response

The immune response is mediated by cellular and humoral factors. On a cellular level, macrophages present foreign antigens to T lymphocytes to activate them. Activated T lymphocytes elaborate a host of inflammatory mediators and activate B cells, causing them to evolve into plasma cells, which make antibodies that specifically bind foreign antigens. These antibodies can coat bacteria and viruses, inhibiting their function and opsonizing them so that they are more readily ingested and cleared from the system by phagocytic cells. Antibodies bound to antigens, bacteria, and viruses also activate the complement system, an important source of vasoactive mediators. The complement system is one of the most important plasma protein systems of inflammation because its components participate in virtually every inflammatory response.

The complement system is a series of enzymatic plasma proteins that is activated by two different pathways: classical and alternative.[34] Activation of the first component of either pathway of the cascade results in the sequential enzymatic activation of downstream components of the cascade (Fig. 3.10).

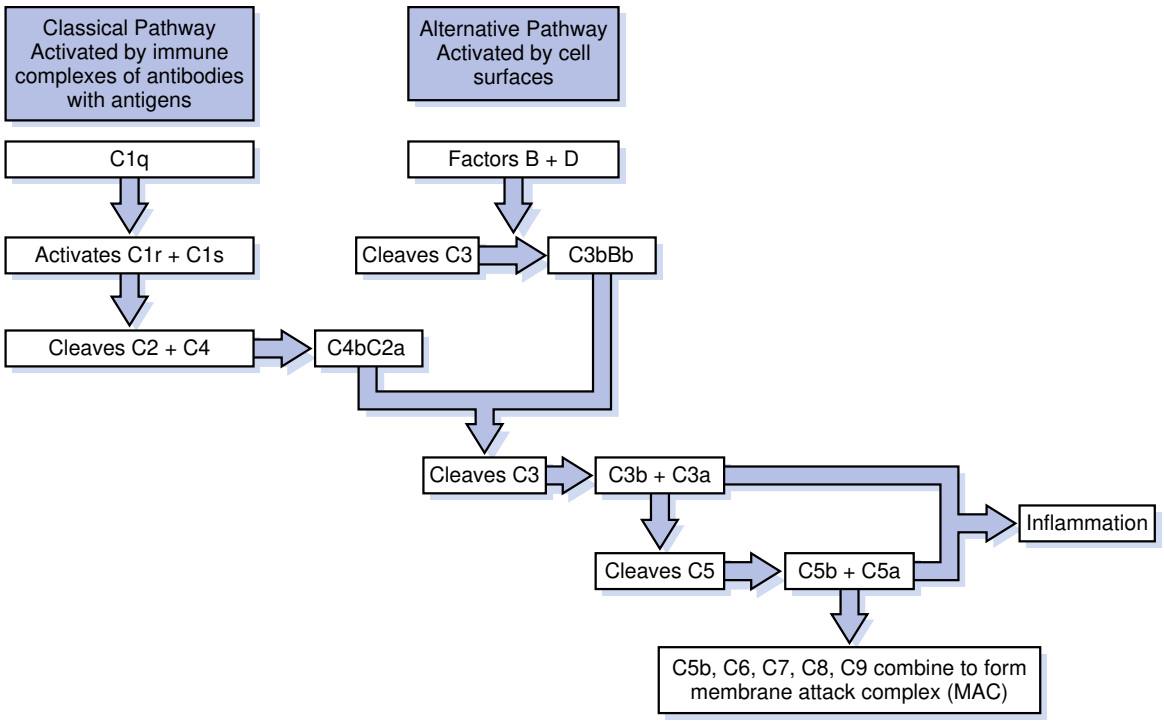


FIGURE 3.10 Overview of the complement system—classical and alternative activation pathways.

The classical pathway is activated by an antibody-antigen association, and the alternative pathway is activated by cellular or microbial substances. The end product of the cascade, by either pathway, is a complex of C5b, C6, C7, C8, and C9, which form the membrane attack complex (MAC). The MAC creates pores in plasma membranes, thereby allowing water and ions into the cell, leading to cell lysis and death.

The subcomponents generated earlier in the cascade also have important functions. Activation of components C1 to C5 produces subunits that enhance inflammation by making bacteria more susceptible to phagocytosis (known as **opsonization**), attracting leukocytes by chemotaxis, and acting as anaphylatoxins. Anaphylatoxins induce mast cell and basophil degranulation, causing the release of histamine, platelet-activating factor, and leukotrienes. These further promote increased vascular permeability.

In summary, the inflammatory phase has three major purposes. First, fibrin, fibronectin, and collagen cross-link to form a fibrin lattice that limits blood loss and provides the wound with some initial strength. Second, neutrophils followed by macrophages begin to remove damaged tissue. Third, endothelial cells and fibroblasts are recruited and stimulated to divide. This sets the stage for the proliferation phase of healing. Table 3.3 summarizes the events of the inflammatory phase of healing.

Clinical Pearl

The inflammatory phase has three major purposes: (1) to form a fibrin lattice that limits blood loss and provides some initial strength to the wound, (2) to remove damaged tissue, (3) to recruit endothelial cells and fibroblasts.

PROLIFERATION PHASE (DAYS 3 TO 20)

The second phase of tissue healing is known as the *proliferation phase.* This phase generally lasts for up to 20 days and involves both **epithelial cells** and **connective tissues.**[23] Its purpose is to cover the wound and impart strength to the injury site.

Clinical Pearl

During the proliferation phase, the wound is covered, and the injury site starts to regain some of its initial strength.

Epithelial cells form the covering of mucous and serous membranes and the epidermis of the skin. Connective tissue consists of fibroblasts, ground substance, and fibrous strands and provides the structure for other tissues. The structure, strength, and elasticity of connective tissue vary, depending on the type of tissue it comprises. Four processes occur simultaneously in the proliferation phase to achieve coalescence and closure of the injured area: **epithelialization,** collagen production, **wound contraction,** and **neovascularization.**

Epithelialization

Epithelialization, the reestablishment of the epidermis, is initiated early in proliferation when a wound is superficial, often within a few hours of injury.[35] When a wound is deep, epithelialization occurs later, after collagen production and neovascularization. Epithelialization provides a protective barrier to prevent fluid and electrolyte loss and to decrease the risk of infection. Healing of the wound surface by epithelialization alone does not provide adequate strength to

TABLE 3.3 Summary of Events of the Inflammatory Phase

Response	Changes in the Injured Area
Vascular	Vasodilation followed by vasoconstriction at the capillaries, postcapillary venules, and lymphatics Vasodilation mediated by chemical mediators—histamine, Hageman factor, bradykinin, prostaglandins, complement fractions Slowing of blood flow Margination, pavementing, and ultimately, emigration of leukocytes Accumulation of fluid in the interstitial tissues resulting in edema
Hemostatic	Retraction and sealing off of blood vessels Platelets form clots and assist in building of fibrin lattice, which serves as the source of tensile strength for the wound in the inflammatory phase
Cellular	Delivery of leukocytes to the area of injury to rid the area of bacteria and debris by phagocytosis Monocytes, the precursors of macrophages, are considered the most important cell in the inflammatory phase Macrophages produce a number of products essential to the healing process
Immune	Mediated by cellular and humoral factors Activation of the complement system via alternative and classical pathways, resulting in components that increase vascular permeability, stimulate phagocytosis, and act as chemotactic stimuli for leukocytes

meet the mechanical demands placed on most tissues. Such strength is provided by collagen produced during fibroplasia.

During epithelialization, uninjured epithelial cells from the margins of the injured area reproduce and migrate over the injured area, covering the surface of the wound and closing the defect. It is hypothesized that the stimulus for this activity is the loss of contact inhibition that occurs when epithelial cells are normally in contact with one another. Migrating epithelial cells stay connected to their parent cells, thereby pulling the intact epidermis over the wound edge. When epithelial cells from one edge meet migrating cells from the other edge, they stop moving because of contact inhibition (Fig. 3.11). Although clean, approximated wounds can be clinically resurfaced within 48 hours, larger open wounds take longer to resurface.[36] It then takes several weeks for this thin layer to become multilayered and to differentiate into the various strata of normal epidermis.

Collagen Production

Fibroblasts make collagen. Fibroblast growth, known as *fibroplasia,* takes place in connective tissue. Fibroblasts develop from undifferentiated mesenchymal cells located around blood vessels and in fat. They migrate to the injured area along fibrin strands, in response to chemotactic influences, and are present throughout the injured area.[37] For fibroplasia to occur, adequate supplies of oxygen; ascorbic acid; and other cofactors, such as zinc, iron, manganese, and copper,

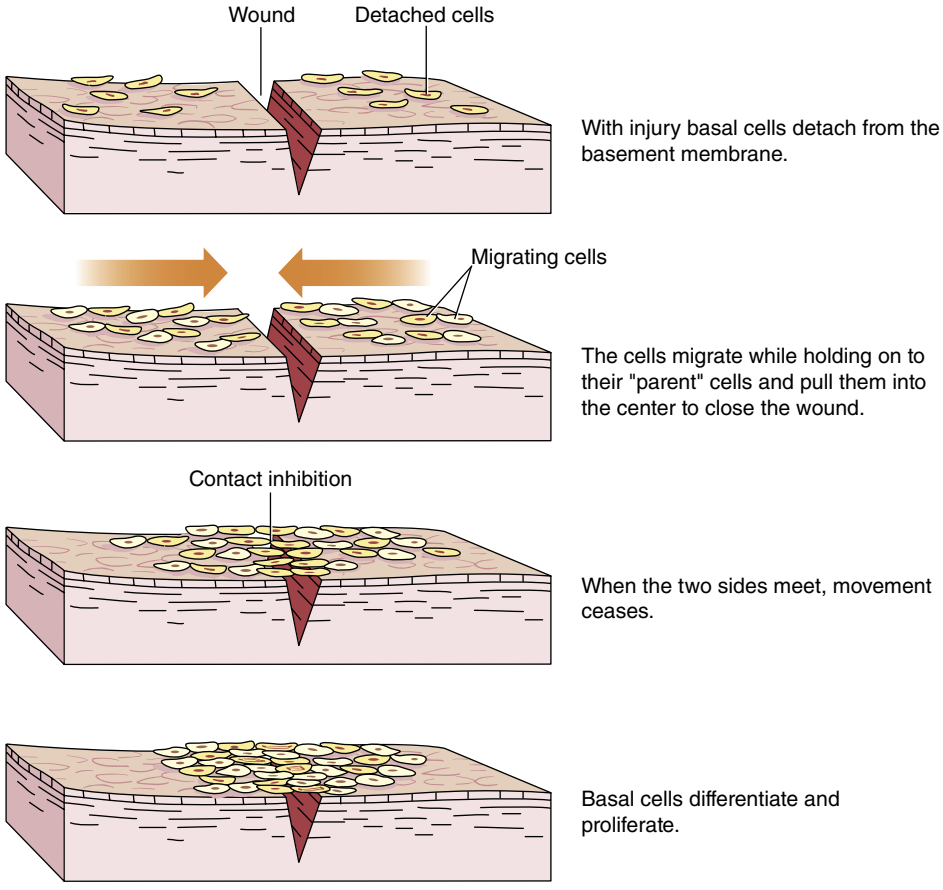


FIGURE 3.11 Schematic diagram of epithelialization.

are necessary.[38] As the number of fibroblasts increases, they begin to align themselves perpendicular to the capillaries.

Fibroblasts synthesize procollagen, which is composed of three polypeptide chains coiled and held together by weak electrostatic bonds into a triple helix. These chains undergo cleavage by collagenase to form tropocollagen. Multiple tropocollagen chains then coil together to form collagen microfibrils, which make up collagen fibrils and ultimately combine to form collagen fibers (Fig. 3.12). Cross-linking between collagen molecules provides further tensile strength to the injured area. Ascorbic acid (vitamin C) is an essential cofactor in collagen synthesis and resultant wound tissue quality.[39] Collagen serves a dual purpose in wound healing, providing increased strength and facilitating the movement of other cells, such as endothelial cells and macrophages, while they participate in wound healing.[40,41]

Tissue containing newly formed capillaries, fibroblasts, and **myofibroblasts** is referred to as **granulation tissue.** As the amount of granulation tissue increases, a concurrent reduction in the size of the fibrin clot allows for the formation of a more permanent support structure. These events are mediated by chemotactic factors that stimulate increased fibroblastic activity and by fibronectin that enhances the migration and adhesion of the fibroblasts. Fibroblasts initially produce a thin, weak-structured collagen with no consistent organization, known as **type III collagen.** This period is the most tenuous time during the healing process because of the limited tensile strength of the tissue. During the proliferation phase, an injured area has the greatest amount of collagen, yet its tensile strength can be as low as 15% of the tensile strength of normal tissue.[42]

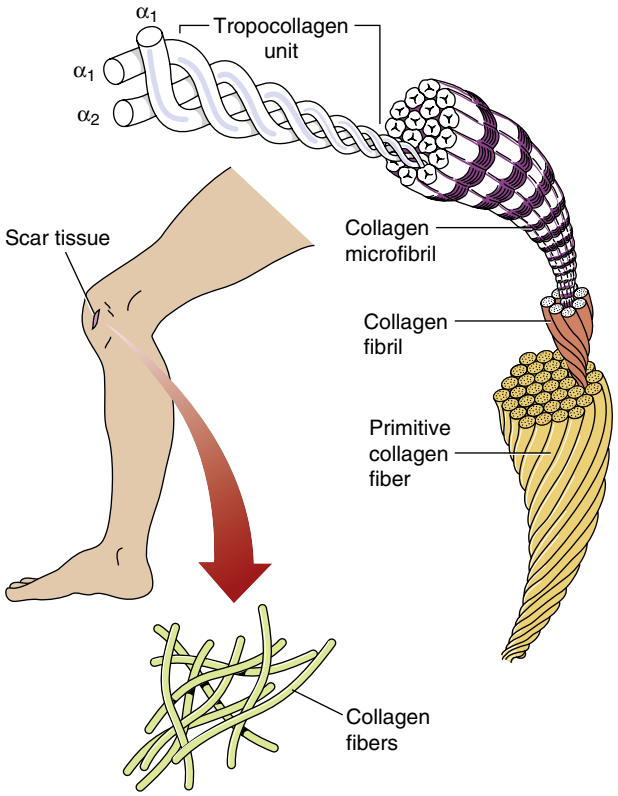


FIGURE 3.12 Diagrammatic representation of one tropocollagen unit joining with others to form collagen filaments and, ultimately, collagen fibers.

Clinical Pearl

During the proliferation phase, an injured area has the greatest amount of collagen, yet its tensile strength can be as low as 15% of the tensile strength of normal tissue.

Fibroblasts also produce hyaluronic acid, a glycosaminoglycan (GAG), which draws water into the area, increases the amount of intracellular matrix, and facilitates cellular migration. It is postulated that the composition of this substance is related to the number and location of the cross-bridges, thereby implying that the relationship between GAG and collagen dictates the scar architecture.[29,43]

The formation of cross-links allows the newly formed tissue to tolerate early, controlled movement without disruption. However, infection, edema, or excessive stress on the healing area may cause further inflammation and additional deposition of collagen. Excessive collagen deposition results in excessive scarring that may limit function.

By the seventh day after injury, a significant increase in the amount of collagen causes the tensile strength of the injured area to increase steadily. By day 12, the initial immature type III collagen starts to be replaced by **type I collagen,** a more mature and stronger form.[23,44,45] The ratio of type I to type III collagen increases steadily from this point forward. The production of collagen is maximal at day 21 of healing, but wound strength at this time is only approximately 20% of that of the normal dermis. By about 6 weeks after injury, when a wound is healing well, it has approximately 80% of its long-term strength.[46]

Wound Contraction

Wound contraction is the final mechanism for repairing an injured area. In contrast to epithelialization, which covers the wound surface, contraction pulls the edges of the injured site together, in effect shrinking the defect. Successful contraction results in a smaller area to be repaired by the formation of a scar. Contraction of the wound begins approximately 5 days after injury and peaks after about 2 weeks.[47] Myofibroblasts are the primary cells responsible for wound contraction. Myofibroblasts, identified by Gabbiani and associates in 1971,[48] are derived from the same mesenchymal cells as fibroblasts. Myofibroblasts are like fibroblasts except that they possess the contractile properties of smooth muscle. Myofibroblasts attach to the margins of intact skin and pull the entire epithelial layer inward. The rate of contraction is proportional to the number of myofibroblasts at and under the cell margins and is inversely proportional to the lattice collagen structure.

According to the "picture frame" theory, the wound margin beneath the epidermis is the location of myofibroblast action.[49] A ring of myofibroblasts moves inward from the wound margin. Although contractile forces are initially equal, the shape of the picture frame predicts the resultant speed of closure (Fig. 3.13). Linear wounds with one narrow dimension contract rapidly; square or rectangular wounds, with no edges close to each other, progress at a moderate pace; and circular wounds contract most slowly.[50]

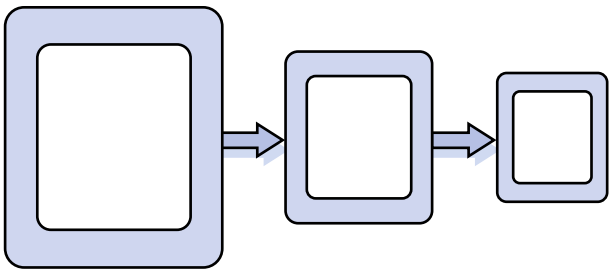


FIGURE 3.13 Illustration of the "picture frame" theory of wound contraction.

If wound contraction is uncontrolled, **contractures** can form. Contractures are conditions of fixed shortening of soft tissues that have high resistance to passive stretch.[51] Contractures may result from adhesions, muscle shortening, or tissue damage. Contractures are discussed further in Chapter 6.

When the initial injury causes minimal tissue loss and minimal bacterial contamination, the wound can be closed with sutures and thus can heal without wound contraction. This is known as **healing by primary intention** (also known as *primary union*) (Fig. 3.14). However, when the initial injury causes significant loss of tissue or bacterial contamination, the wound must first undergo the process of wound contraction to close the wound; this is known as **healing by secondary intention** (also known as *indirect union*) (see Fig. 3.14).[52] Later approximation of wound edges with sutures or the application of skin grafts can reduce wound contraction and is known as **healing by delayed primary intention.**[53,54] To minimize contraction, grafts must be applied early in the inflammatory phase, before the process of contraction begins.[55]

As scar tissue matures, it develops pressure-sensitive and tension-sensitive nerve endings to protect the immature vascular system, which is weak and can bleed easily with any insult. During the proliferation phase, the scar is red and swollen as a result of the increase in vascularity and fluid, the innervation of the healing site, and the relative immaturity of the tissue. The tissue can be damaged easily and is tender to tension or pressure.

Neovascularization

Neovascularization, the development of a new blood supply to the injured area, occurs as a result of **angiogenesis,** the growth of new blood vessels. Healing cannot occur without angiogenesis. These new vessels are needed to supply oxygen and nutrients to injured and healing tissue. It is thought that macrophages signal the initiation of neovascularization through the release of growth factors.[46] Angiogenesis can occur by one of three different mechanisms: (1) generation of a new vascular network, (2) anastomosis to preexisting vessels, or (3) coupling of vessels in the injured area.[56]

Vessels in the wound periphery develop small buds that grow into the wound area. These outgrowths eventually meet and join other arterial or venular buds to form a capillary loop. These vessels fill the injured area, giving it a pinkish to bright-red hue. As the wound heals, many of these capillary loops cease to function and retract, giving the mature scar a more whitish appearance than adjacent tissues. Initially, the walls of these capillaries are thin, making them prone to injury. Therefore, immobilization at this stage may help protect these vessels and permit further regrowth, whereas excessive early motion can cause microhemorrhaging and can increase the likelihood of infection.

MATURATION PHASE (DAY 9 FORWARD)

As the transition from the proliferation to the maturation stage of healing is made, changes in the size, form, and strength of the scar tissue occur. The maturation phase is the longest phase in the healing process. It can persist longer than a year after the initial injury. During this time, the numbers of fibroblasts, macrophages, myofibroblasts, and capillaries decrease, and the water content of the tissue declines. The scar becomes whiter in appearance as collagen matures and vascularity decreases. The goal of this phase is restoration of the prior function of injured tissue.

Clinical Pearl

The goal of the maturation phase is restoration of the prior function of injured tissue. This phase can last longer than a year after the initial injury.

Several factors determine the rate of maturation and the final physical characteristics of the scar, including fiber orientation and the balance of collagen synthesis and lysis. Throughout the maturation phase, synthesis and lysis of collagen occur in a balanced fashion. Hormonal stimulation that results from inflammation causes increased collagen destruction by the enzyme collagenase. Collagenase is derived from polymorphogranular leukocytes, the migrating epithelium, and the granulation bed. Collagenase can break the strong cross-linking bonds of the tropocollagen molecule, causing it to become soluble. It is then excreted as a waste by-product. Although collagenase is most active in the actual area of injury, its effects can be noticed to a greater extent in areas adjacent to the injury site. Thus, remodeling occurs through a process of collagen turnover.

Collagen, a glycoprotein, provides the extracellular framework for all multicellular organisms. Although more than 27 types of collagen have been identified, the following discussion is limited to types I, II, and III (Table 3.4).[57] All collagen molecules are made up of three separate polypeptide chains wrapped tightly together in a triple left-handed helix. Type I collagen is the primary collagen in bone, skin, and **tendon**

TABLE 3.4 Collagen Types

Type	Distribution
I	Most abundant form of collagen: skin, bone, tendons, most organs
II	Major cartilage collagen, vitreous humor
III	Abundant in blood vessels, uterus, skin
IV	All basement membranes
V	Minor component of most interstitial tissues
VI	Abundant in most interstitial tissues
VII	Dermal-epidermal junction
VIII	Endothelium
IX	Cartilage
X	Cartilage

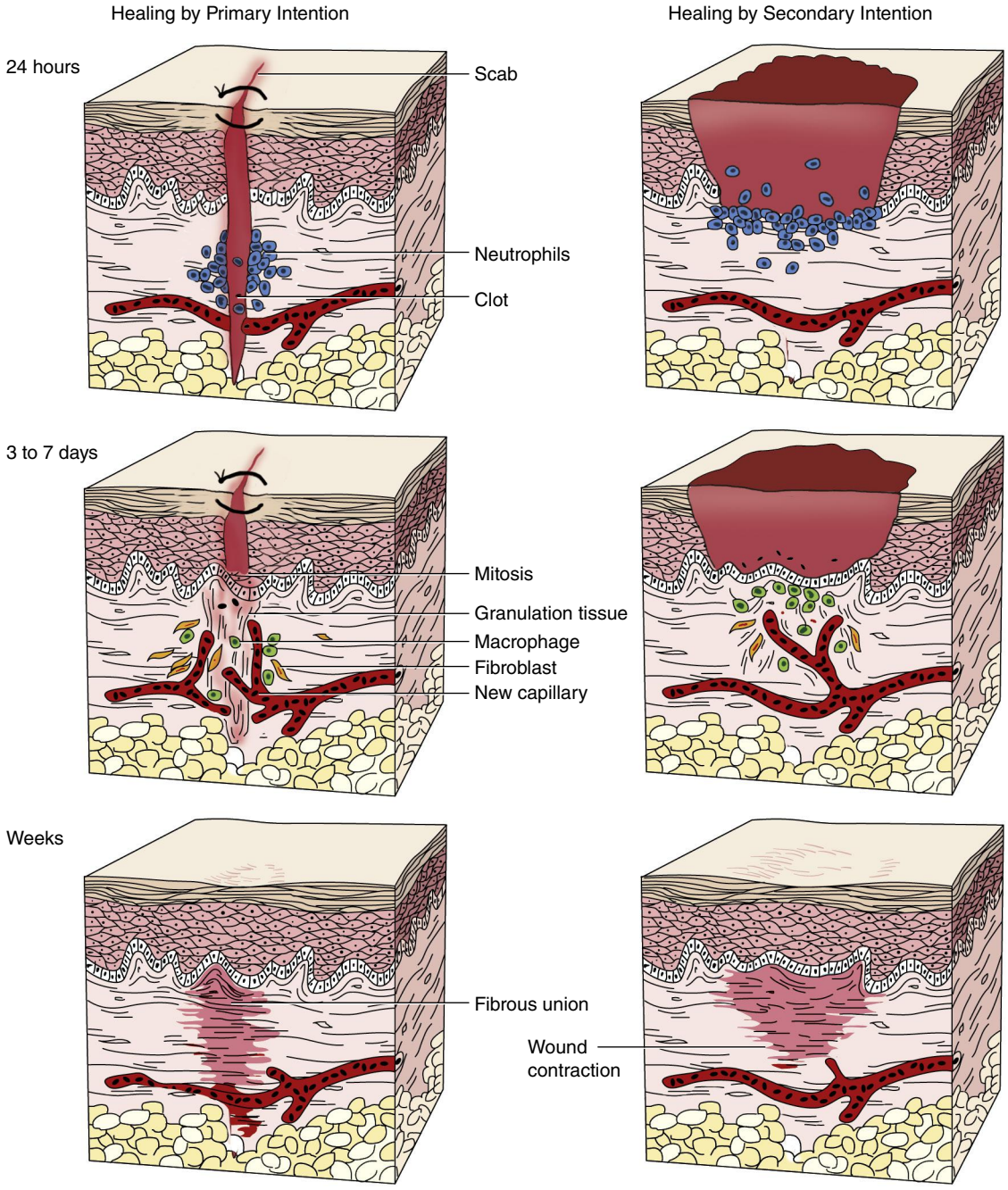


FIGURE 3.14 Diagrammatic comparison of healing by primary intention *(left)* and healing by secondary intention *(right)*.

and is the predominant collagen in mature scars. **Type II collagen** is the predominant collagen in **cartilage.** Type III collagen occurs in the gastrointestinal tract, uterus, and blood vessels of adults. It is also the first type of collagen to be deposited during the healing process.

During the maturation phase, the collagen synthesized and deposited is predominantly type I. Generally, the balance between synthesis and lysis slightly favors synthesis. Because type I collagen is stronger than the type III collagen deposited in the proliferation phase, tensile strength increases faster than mass. If the rate of collagen production is much greater than the rate of lysis, a keloid or hypertrophic scar can result. Keloids and hypertrophic scars are the result of excessive collagen deposition caused by inhibition of lysis. It is believed that this inhibition of lysis is the result of a genetic defect. Keloids extend beyond the original boundaries of an injury and invade surrounding tissue, whereas hypertrophic scars, although raised, remain within the margins of the original wound. Treatment of keloids through surgery, medications, pressure, and irradiation has only limited success.[58–60]

Collagen synthesis is oxygen dependent, whereas collagen lysis is not.[61] Thus, when oxygen levels are low, the process of maturation is weighted toward lysis, resulting in a softer, less bulky scar. Hypertrophic scars can be managed clinically with prolonged pressure, which causes a decrease in oxygen, resulting in decreased overall collagen synthesis

while maintaining the level of collagen lysis.[53] This is one of the bases for the use of pressure garments in the treatment of patients with burn injuries and for the use of elastomer in the management of scars in hand therapy. Eventually, balance is achieved when the scar bulk is flattened to approximate normal tissue.

Collagen synthesis and lysis may last for up to 12 to 24 months after an injury. The high rate of collagen turnover during this period can be viewed as both detrimental and beneficial. If scar tissue appears redder than surrounding tissue, remodeling is still occurring. Although a joint or tissue structure can lose mobility quickly during this stage, such a loss can be reversed through appropriate intervention.

The physical structure of collagen fibers is largely responsible for the final function of the injured area. Collagen in scar tissue is always less organized than collagen in surrounding tissue. Scars are inelastic because elastin, a normal skin component, is not present in scars,[46] so redundant folds are necessary to permit mobility of the structures to which they are attached. To understand this concept better, one may consider a spring, which, although made of an inelastic material, has a spiral form (like the redundant folds of a scar) that allows it to expand and contract. If short, dense adhesions are formed, these will restrict motion because they cannot elongate.

Two theories have been proposed to explain the orientation of collagen fibers in scar tissue: the induction theory and the tension theory. According to the induction theory, the scar attempts to mimic the characteristics of the tissue it is healing.[62] Thus, dense tissue induces a dense, highly cross-linked scar, whereas more pliable tissue results in a loose, less cross-linked scar. Dense tissue types have a preferential status when multiple tissue types are in proximity. Based on this theory, surgeons attempt to design repair fields that separate dense from soft tissues. If this is not possible, as in the case of repaired tendon that is left immobile over bone fractures, adhesions and poorly gliding tendons can result. In such cases, early controlled movement may be beneficial.

According to the tension theory, internal and external stresses placed on the injured area during the maturation phase determine the final tissue structure.[56] Muscle tension, joint movement, soft tissue loading and unloading, fascial gliding, temperature changes, and mobilization are forces that are thought to affect collagen structure. Thus, the length and mobility of the injured area may be modified by the application of stress during appropriate phases of healing. This theory has been supported by the work of Arem and Madden,[63] which has shown that the two most important variables responsible for successful remodeling are (1) the phases of the repair process in which mechanical forces were introduced and (2) the nature of the applied forces. For permanent changes to occur, scars need low-load, long-duration stretch during the appropriate phase.

Studies have shown that applying tension during healing increases tensile strength and that immobilization and stress deprivation reduce tensile strength and the organization of collagen structure. Recovery curves for tissue experimentally immobilized for 2 to 4 weeks reveal that these processes can take months to reverse and that reversal often is incomplete.

Physical loading of soft tissue produces an electrical current that can influence wound healing. This is known as the **piezoelectric** effect and can also be seen in bone. New bone can be formed when an electronegative force is applied and resorbed when an electropositive potential is applied.[64]

Each phase of the healing response is necessary and essential to the subsequent phase. In the optimal scenario, inflammation is a necessary aspect of the healing response and is the first step toward recovery, setting the stage for the other phases of healing. If repeated insult or injury occurs, however, a chronic inflammatory response can adversely affect the outcome of the healing process.

Acute inflammatory processes can have one of four outcomes. The first and most beneficial outcome is complete resolution and replacement of the injured tissue with like tissue. The second and most common outcome is healing by scar formation. The third outcome is the formation of an abscess. The fourth outcome is the possibility of progression to **chronic inflammation.**[12]

Chronic Inflammation

Chronic inflammation is the simultaneous progression of active inflammation, tissue destruction, and healing. Chronic inflammation can arise in one of two ways. The first follows acute inflammation and can be a result of the persistence of the injurious agent (e.g., cumulative trauma) or some other interference with the normal healing process. The second may be the result of an immune response to an altered host tissue or a foreign material (e.g., an implant or a suture), or it may be the result of an autoimmune disease (e.g., rheumatoid arthritis).

The normal acute inflammatory process lasts no longer than 2 weeks. If it continues for longer than 4 weeks, it is known as **subacute inflammation.**[3] Chronic inflammation is inflammation that lasts for months or years.

The primary cells present during chronic inflammation are mononuclear cells, including lymphocytes, macrophages, and monocytes (Fig. 3.15). Occasionally, eosinophils are also present.[13] Progression of the inflammatory response to a chronic state is a result of both immunological and nonimmunological factors. The macrophage is an important source of inflammatory and immunological mediators and is an important component in the regulation of their actions. The role of eosinophils is much less clear, although they are often present in chronic inflammatory conditions caused by an allergic reaction or a parasitic infection.[13]

Chronic inflammation results in increased fibroblast proliferation, which increases collagen production and ultimately increases scar tissue and adhesion formation. This may lead to loss of function as the delicate balance between the optimal tensile strength and mobility of involved tissues is lost.

Factors Affecting the Healing Process

Various local and systemic factors can influence or modify the processes of inflammation and repair (Box 3.2). Local factors such as the type, size, and location of the injury can affect wound healing, as can infection, blood supply, external physical forces, and movement.

Clinical Pearl

Local factors that can affect wound healing include the type, size, and location of the injury; infection; blood supply; external physical forces; and movement. Systemic factors that can affect wound healing include age, disease, medications, and nutrition.

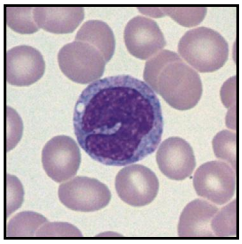
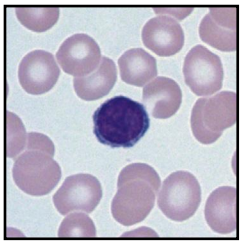
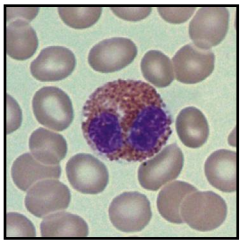
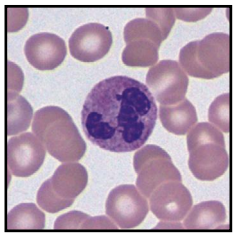
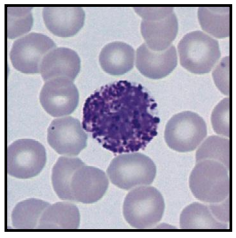
	Leukocyte	Characteristics/Functions
Mononuclear cells	A  **Monocyte/Macrophage**	Associated with • chronic inflammation • phagocytosis Regulates coagulation/fibrolytic pathways Regulates lymphocyte response Monocytes are converted to macrophages when they emigrate from capillaries into the tissue spaces.
	B  **Lymphocyte**	Associated with • chronic inflammation Key cell in humoral and cell-mediated immune response
Polymorphonuclear cells	C  **Eosinophil**	Associated with • allergic reactions • parasitic infections and associated inflammatory reactions Modulates mast cell-mediated reactions
	D  **Neutrophil**	Associated with • acute inflammation • bacterial and foreign body phagocytosis
	E  **Basophil**	Associated with • allergic reactions Contains histamine, which causes increased vascular permeability Contains heparin, which slows blood clotting

FIGURE 3.15 Cellular components of acute and chronic inflammation. (A) Monocyte/macrophage. (B) Lymphocyte. (C) Eosinophil. (D) Neutrophil. (E) Basophil. (Adapted from McPherson R, Pincus M: *Henry's clinical diagnosis and management by laboratory methods,* ed 21, Philadelphia, 2006, Saunders.)

Box 3.2 Factors Influencing Healing

LOCAL	SYSTEMIC
• Type, size, and location of injury	• Age
• Infection	• Infection or disease
• Vascular supply	• Metabolic status
• Movement/excessive pressure	• Nutrition
• Temperature deviation	• Hormones
• Topical medications	• Medication
• Electromagnetic energy	• Fever
• Retained foreign body	• Oxygen

LOCAL FACTORS

Type, Size, and Location of the Injury

Injuries located in well-vascularized tissue, such as the scalp, heal faster than injuries in poorly vascularized areas.[23] Injuries in areas of ischemia, such as injuries that may be caused by arterial obstruction or excessive pressure, heal more slowly.[23]

Smaller wounds heal faster than larger wounds, and surgical incisions heal faster than wounds caused by blunt trauma.[23] Soft tissue injuries over bones tend to adhere to the bony surfaces, preventing contraction and adequate opposition of the edges and delaying healing.[23]

Infection

Infection in an injured area is the most problematic local factor that can affect healing. Among the complications of wound healing, 50% are the result of local infection.[13] Infection can reduce collagen production and increase collagen lysis,[65] prevent or delay healing, and encourage excessive granulation tissue formation.[23]

Vascular Supply

The healing of injuries depends largely on the availability of a sufficient vascular supply. Nutrition, oxygen tension, and the inflammatory response all depend on the microcirculatory system to deliver their components.[66] Decreased oxygen tension resulting from a compromised blood supply can result in inhibition of fibroblast migration and collagen synthesis, leading to decreased tensile strength of the injured area and increased susceptibility to infection.[32]

External Forces

The application of physical agents, including thermal agents, electromagnetic energy, and mechanical forces, can influence inflammation and healing. Cryotherapy (cold therapy), thermotherapy (heat), therapeutic ultrasound, electromagnetic radiation, light, electrical currents, and mechanical pressure have all been used by rehabilitation professionals to modify the healing process. The impact of these physical agents on tissue healing is discussed in the chapters of Part II; each type of physical agent, its effects, and its clinical applications are described.

Clinical Pearl

Physical agents used to modify the healing process include cryotherapy, thermotherapy, ultrasound, electromagnetic radiation, light, electrical currents, and compression.

Movement

Early movement of a newly injured area may delay healing. Therefore, immobilization may be used to aid early healing and repair. However, because immobility can result in adhesions and stiffness by altering collagen cross-linking and elasticity, continuous passive motion (CPM) with strictly controlled parameters is often used to remobilize and restore function safely.[67] CPM used in conjunction with short-term immobilization, compared with immobilization alone, has been shown to achieve a better functional outcome in some studies; however, other studies have found differences only in early range of motion (ROM).[68,69] It has been reported that patients using CPM during the inflammatory phase of soft tissue healing after anterior cruciate ligament reconstruction used significantly fewer pain-relieving narcotics than patients not using CPM.[70] Furthermore, CPM in conjunction with physical therapy after total knee arthroplasty resulted in improved knee ROM and decreased analgesic medication use.[71]

SYSTEMIC FACTORS

Systemic factors such as age, diseases, medications, and nutrition can also affect wound healing.

Age

Age should be considered because of variations in healing between pediatric, adult, and geriatric populations. Wound closure occurs more rapidly in pediatric patients than in adult patients because the physiological changes and cumulative sun exposure that occur with aging can reduce the healing rate.[72] In elderly adults, a decrease in the density and cross-linking of collagen reduces tensile strength, decreases numbers of mast cells and fibroblasts, and slows epithelialization.[72] The poor organization of cutaneous vessels in older patients also adversely affects wound healing.

Disease

A number of diseases can affect wound healing directly or indirectly. For example, poorly controlled diabetes mellitus impairs collagen synthesis, increases the risk of infection as a result of a dampened immune response, and decreases phagocytosis as a result of alterations in leukocyte function.[66,73] Peripheral vascular compromise is also prevalent in this population, leading to a decrease in local blood flow. Neuropathies, which are also common in patients with diabetes mellitus, can increase the potential for trauma and decrease the ability of soft tissue lesions to heal.

Patients who are immunocompromised, such as patients with acquired immunodeficiency syndrome (AIDS) or patients taking immunosuppressive drugs after organ transplantation, are prone to wound infection because they have an inadequate inflammatory response. AIDS also affects many other facets of the healing process through impairment of phagocytosis, fibroblast function, and collagen synthesis.[74]

Problems involving the circulatory system, including atherosclerosis, sickle cell disease, and hypertension, can have an adverse effect on wound healing because inflammation and healing depend on the cardiovascular system for the delivery of components to the local area of injury. Decreased oxygen tension caused by a reduced blood supply can inhibit fibroblast

migration and decrease collagen synthesis, leading to decreased tensile strength and making the injured area susceptible to reinjury. Wounds with a decreased blood supply are also susceptible to infection.[32,75]

Medications

Patients with injuries or wounds often take medications with systemic effects that alter tissue healing. For example, antibiotics can prevent or fight off infection, which can help speed healing, but they may have toxic effects that inhibit healing. Corticosteroids, such as prednisone and dexamethasone, block the inflammatory cascade at a variety of levels, inhibiting many of the pathways involved in inflammation. It is thought that glucocorticoids act mainly by affecting gene transcription inside cells to inhibit the formation of inflammatory molecules, including cytokines, enzymes, receptors, and adhesion molecules.[76] They are thought to stimulate the production of antiinflammatory molecules. Corticosteroids decrease the margination, migration, and accumulation of monocytes at the site of inflammation.[77] They induce antiinflammatory actions by monocytes, such as phagocytosis of other inflammatory molecules, while repressing adhesion, apoptosis, and oxidative burst.[78] They severely inhibit wound contracture, decrease the rate of epithelialization, and decrease the tensile strength of closed, healed wounds.[79–81] Corticosteroids administered at the time of injury have a greater impact because decreasing the inflammatory response at this early stage delays subsequent phases of healing and increases the incidence of infection.

Compared with corticosteroids, NSAIDs, such as ibuprofen, are less likely to impair healing. They interrupt the production of prostaglandins from arachidonic acid but are not thought to adversely affect the function of fibroblasts or tissue macrophages.[82] NSAIDs can cause vasoconstriction and can suppress the inflammatory response[14]; some NSAIDs have been found to inhibit cell proliferation and migration during tendon healing.[83,84]

Nutrition

Nutrition can have a profound effect on healing tissues. Deficiency of a number of important amino acids, vitamins, minerals, or water, as well as insufficient caloric intake, can result in delayed or impaired healing. This occurs because physiological stress from the injury induces a hypermetabolic state. Thus, if insufficient "fuel" is available for the process of inflammation and repair, healing is slowed.

In most cases, healing abnormalities are associated with general protein-calorie malnutrition rather than with the depletion of a single nutrient.[85] Such is the case with patients with extensive burns who are in a prolonged hypermetabolic state. Protein deficiency can result in decreased fibroblastic proliferation, reduced proteoglycan and collagen synthesis, decreased angiogenesis, and disrupted collagen remodeling.[86] Protein deficiency can also adversely affect phagocytosis, which may lead to an increased risk of infection.[75]

Studies have shown that a deficiency of specific nutrients may also affect healing. Vitamin A deficiency can retard epithelialization, the rate of collagen synthesis, and cross-linking.[87] Thiamine (vitamin B_1) deficiency decreases collagen formation, and vitamin B_5 deficiency decreases the tensile strength of healed tissue and reduces the fibroblast number.[88,89] Vitamin C deficiency impairs collagen synthesis by fibroblasts, increases the capillary rupture potential, and increases the susceptibility of wounds to infection.[90]

Many minerals also play an important role in healing. Insufficient zinc can decrease the rate of epithelialization, reduce collagen synthesis, and decrease tensile strength.[91,92] Magnesium deficiency may also cause decreased collagen synthesis, and copper insufficiency may alter cross-linking, leading to a reduction in tensile strength.[90]

ADJUNCTS TO PROMOTE WOUND HEALING

Negative-pressure wound therapy, as discussed in detail in Chapter 19 with hydrotherapy and other physical adjuncts to wound healing, promotes wound healing by decreasing seroma and hematoma formation and promoting the granulation process. Biological dressings containing silver reduce wound infection rates, allowing for a more normalized inflammatory response. Silicone-based wound dressings decrease hypertrophic scar formation by stimulating basic fibroblast growth factor.[93]

Immunonutrition, the use of specific nutrients to influence the immune system, can also improve wound healing. A few of the most common substances used for immunonutrition include l-arginine, glutamine, and omega-3 fatty acids. The impact of antioxidants such as selenium, zinc, vitamin C, vitamin E, and beta-carotene has also been studied and used to facilitate the healing of burn wounds and in the critical care setting. L-arginine, a nonessential amino acid under normal conditions, becomes an essential amino acid under stress. L-arginine can increase lymphocyte and monocyte proliferation through a nitric oxide mechanism.[94] Glutamine may be used as a fuel source in rapidly dividing cells under stress and when converted to glutathione, which is an antioxidant. Omega-3 fatty acids are major structural elements in cell membranes, and omega-3 fatty acid supplementation can reduce clotting and inflammation and increase cell surface activation.[95]

Healing of Specific Musculoskeletal Tissues

The primary determinants of the outcome of any injury are the type and extent of injury, the regenerative capacity of the tissues involved, the vascular supply of the injured site, and the extent of damage to the extracellular framework. The basic principles of inflammation and healing apply to all tissues; however, some tissue specificity applies to the healing response. For example, the liver can regenerate when more than half of it is removed, whereas even a thin fracture line in cartilage is unlikely to heal.

CARTILAGE

Cartilage has a limited ability to heal because it lacks lymphatics, blood vessels, and nerves.[96] However, cartilage reacts differently when injured alone than when injured in conjunction with the subchondral bone to which it is attached. Injuries confined to the cartilage do not form a clot or recruit neutrophils or macrophages, and cells adjacent to the injury show a limited capacity to induce healing. This limited response generally fails to heal the defect, and the lesions seldom resolve.[97]

With injuries that involve both articular cartilage and subchondral bone, vascularization of the subchondral bone allows for the formation of fibrin-fibronectin gel, giving access to the inflammatory cells and permitting the formation of granulation tissue. Differentiation of granulation tissue into chondrocytes can begin within 2 weeks. Normal-appearing cartilage can be seen within 2 months after the injury. However, this cartilage has a low proteoglycan content and therefore is predisposed to degeneration and erosive changes.[98] Recent research has explored the use of stem cells for cartilage repair.

TENDONS AND LIGAMENTS

Tendons and **ligaments** pass through similar stages of healing. Inflammation occurs in the first 72 hours, and collagen synthesis occurs within the first week. Fibroplasia occurs from intrinsic sources, such as adjacent cells, and from extrinsic sources, such as those brought in via the circulatory system.

The repair potential of tendon is controversial. Both intrinsic cells, such as epitendinous and endotendinous cells, and extrinsic peritendinous cells participate in tendon repair. The exact role of these cells and the final outcome depend on several factors, including the type of tendon, the extent of damage to the tendon sheath, the vascular supply, and the duration of immobilization. The first two stages of tendon healing, inflammation and proliferation, are similar to the healing phases of other tissues. The third phase, scar maturation, is unique to tendons in that this tissue can achieve a state of repair close to regeneration.

During the first 4 days after an injury, the inflammatory phase progresses with infiltration of both extrinsic and intrinsic cells. Many of these cells develop phagocytic capabilities, and others become fibroblastic. Collagen synthesis becomes evident by day 7 or day 8, with fibroblasts predominating at approximately day 14. Early in this stage, both cells and collagen are oriented perpendicularly to the long axis of the tendon.[99] This orientation changes at day 10, when new collagen fibers begin to align themselves parallel to the old longitudinal axis of the tendon stumps.[100] For the next 2 months, a gradual transition of alignment occurs, through remodeling and reorientation, parallel to the long axis. Ultimate maturation of the tissue depends on sufficient physiological loading.

If the synovial sheath is absent or uninjured, the relative contributions of intrinsic and extrinsic cells are balanced, and adhesions are minimal. If the synovial sheath is injured, the contributions of the extrinsic cells overwhelm the capacities of the intrinsic cells, and adhesions are common.

Factors affecting the repair of tendons are different from factors associated with the repair of ligaments.[101] Studies have shown that mobilization of tendons by controlled forces accelerates and enhances the strengthening of tendon repair, but mobilization by active contraction of the attached muscle less than 3 weeks after repair generally results in a poor outcome. The poor outcome may be a result of the fact that high tension can lead to ischemia and tendon rupture. Studies have found no significant difference in tendon strength when tendons are exposed to controlled low or high levels of passive force after repair.[102,103] It appears that mechanical stress is needed to promote the appropriate orientation of collagen fibrils and remodeling of collagen into its mature form and to optimize strength, but the amount of tension necessary to promote the optimal clinical response is not known.[104,105]

Many variables influence the healing of ligamentous tissue, the most important of which are the type of ligament, the size of the defect, and the amount of loading applied. For example, injuries to capsular and extracapsular ligaments generally stimulate an adequate repair response, whereas injuries to intracapsular ligaments often do not. Thus, in the knee, the medial collateral ligament often heals without surgical intervention, whereas the anterior cruciate ligament does not. These differences in healing may be a result of the synovial environment, limited neovascularization, or fibroblast migration from surrounding tissues. Treatments that stabilize the injury site and maintain the apposition of the torn ligament can help the ligament heal in its optimal length and can minimize scarring. Early, controlled loading of healing ligaments can also promote healing, although excessive loading may delay or disrupt the healing process.[106,107] Although mature ligamentous repair tissue is approximately 30% to 50% weaker than uninjured ligament,[108] this usually does not significantly impair joint function because the repaired tissue is usually larger than the original uninjured ligament.

SKELETAL MUSCLE

Muscles may be injured by blunt trauma causing a contusion, violent contraction, excessive stretch causing a strain, or muscle-wasting disease. Although skeletal muscle cells cannot proliferate, stem or reserve cells, known as *satellite cells*, can proliferate and differentiate in some circumstances to form new skeletal muscle cells after the death of adult muscle fibers.[98] It is believed that there are functional links between muscle regeneration and inflammation after muscle injury, and recent studies indicate that macrophages are essential to that interplay.[28] After a severe contusion, a calcified hematoma, known as *myositis ossificans*, may develop. Myositis ossificans is rare after surgery if hemostasis is controlled.

BONE

Bone is a specialized tissue that is able to heal itself with like tissue. Bone can heal by primary or secondary healing. Primary healing occurs with rigid internal fixation of the bone, whereas secondary healing occurs in the absence of such fixation. Bone goes through four histologically distinct stages in the healing process: (1) inflammation, (2) soft callus, (3) hard callus, and (4) bone remodeling. Some investigators also include the stages of **impaction** and **induction** before inflammation in this scheme.

Impaction is the dissipation of energy from an insult. The impact of an insult is proportional to the energy applied to the bone and is inversely proportional to the volume of the bone. Thus, a fracture is more likely to occur if the force is great or the bone is small. Energy dissipated by a bone is inversely proportional to its modulus of elasticity. Therefore, the bone of a person with osteoporosis, which has low elasticity, will fracture more easily. Young children have a more elastic bone structure that allows their bones to bend, accounting for the greenstick-type fractures seen in pediatric patients (Box 3.3).

Box 3.3 Stages of Fracture Healing

1. Impaction
2. Induction
3. Inflammation
4. Soft callus
5. Hard callus
6. Remodeling

Induction is the stage when cells that possess osteogenic capabilities are activated and is the least understood stage of bone healing. It is thought that cells may be activated by oxygen gradients, forces, bone morphogenetic proteins, or noncollagenous proteins. Although the timing of this process is not known exactly, it is thought to be initiated after the moment of impact. The duration of this stage is unknown, although the influence of induction forces seems to lessen with time. Therefore, optimizing early conditions for healing to minimize the potential for delayed union or nonunion is imperative.

Inflammation begins shortly after impact and lasts until some fibrous union occurs at the fracture site. At the time of fracture, the blood supply is disrupted, a fracture hematoma is formed, and oxygen tension and pH are decreased. This environment favors the growth of early fibrous or cartilaginous callus. This callus forms more easily than bone and helps stabilize the fracture site, decrease pain, and lessen the likelihood of a fat embolism. It also rapidly and efficiently provides a scaffold for further circulation and for cartilage and endosteal bone production. The amount of movement at the fracture site influences the amount and quality of the callus. Small amounts of movement stimulate the formation of a callus, whereas excessive movement can disrupt the formation of a callus and can inhibit bony union.

The soft callus stage begins when pain and swelling subside and lasts until bony fragments are united by fibrous or cartilaginous tissue. This period is marked by a great increase in vascularity, growth of capillaries into the fracture callus, and increased cell proliferation. Tissue oxygen tension remains low, but pH returns to normal. The hematoma becomes organized with fibrous tissue cartilage and bone formation; however, no callus is visible radiographically. The callus is electronegative relative to the rest of the bone during this period. Osteoclasts remove the dead bone fragments.

The hard callus stage begins when a sticky, hard callus covers the ends of the fracture and ends when new bone unites with the fragments. This period corresponds to the period of clinical and radiological fracture healing. The duration of this period depends on the fracture location and the patient's age and can range from 3 weeks to 4 months.

The remodeling stage begins when the fracture is clinically and radiologically healed. It ends when the bone has returned to its normal state and the patency of the medullary canal is restored. Fibrous bone is converted to lamellar bone, and the medullary canal is revised. This process can take several months to several years to complete.[109]

CLINICAL CASE STUDIES

The following case studies summarize the concepts of inflammation and repair discussed in this chapter. Based on the scenario presented, an evaluation of clinical findings and goals of treatment is proposed.

CASE STUDY 3.1

Inflammation and Repair

Examination

History

JP is a 16-year-old high school student. She injured her right ankle 1 week ago playing soccer and was treated conservatively with crutches; rest, ice, compression, and elevation (RICE); and NSAIDs. She reports some improvement, although she is unable to play soccer because of continued right lateral ankle pain. Her x-ray showed no fracture, and her family physician diagnosed the injury as a grade II lateral ankle sprain. She comes to your clinic with an order to "evaluate and treat."

JP sustained this injury during a cutting motion while dribbling a soccer ball. She noted an audible pop, immediate pain and swelling, and an inability to bear weight. She reports that her pain has decreased in intensity from 8/10 to 6/10, but the pain increases with weight bearing and with certain demonstrated movements.

Tests and Measures

The objective examination reveals moderate warmth of the skin of the anterolateral aspect of the right ankle. Moderate ecchymosis and swelling are also noted, with a girth measurement of 34 cm on the right ankle compared with 30 cm on the left. JP's ROM is restricted to 0 degrees dorsiflexion, 30 degrees plantar flexion, 10 degrees inversion, and 5 degrees eversion, with pain noted especially with plantar flexion and inversion. She exhibits a decreased stance phase on the right lower extremity. Pain and weakness occur on strength tests of the peroneals and gastrocnemius and soleus muscles. She also exhibits a marked decrease in proprioception, as evidenced by the single-leg balance test. Her anterior drawer test is positive, and her talar tilt is negative.

This patient is in what stage of healing? What kind of injury does she have? What physical agents could be useful for this patient?

Continued

CLINICAL CASE STUDIES—*cont'd*

Evaluation and Goals

ICF Level	Current Status	Goals
Body structure and function	Right ankle pain Loss of subtalar and talocrural motion Increased girth Decreased strength of evertors and plantar flexors Decreased proprioception	Reduce inflammation to reduce pain and edema and increase ROM
Activity	Difficulty ambulating	Increase ability to walk
Participation	Unable to play soccer	Return to playing soccer in next 2 to 3 months

ICF, International Classification of Functioning, Disability and Health; *ROM,* range of motion.

Prognosis

This patient has had a recent injury and is in the inflammatory phase of tissue healing, as evidenced by her signs of pain, edema, bruising, and warmth at the injured site. She is likely at the beginning of the proliferation phase of healing. Given her positive anterior drawer test, it is likely that the patient has injured her anterior talofibular ligament. The expected time of healing with a grade II ankle sprain and partial tear of the talofibular ligament is 2 to 3 months. At this stage of healing, the plan is to minimize the effects of inflammation and accelerate the healing process so that she can move on to the proliferation and maturation phases and regain normal function.

Intervention

Physical agents that may be used to help accelerate the acute inflammatory phase of healing include cryotherapy and compression. She should avoid applying heat. The patient should continue the RICE regimen accompanied by NSAIDs as needed for pain. Physical agents should be used as part of a rehabilitation program in which the patient slowly resumes passive motion followed by active motion and motion with weight bearing. Hydrotherapy may be used to facilitate non–weight-bearing movement.

CASE STUDY 3.2

Inflammation and Repair

Examination

History

HP is a 45-year-old man who sustained an on-the-job injury in which he had a severe abdominal wall strain while trying to stabilize a falling 200-lb metal object. He noted severe acute pain at his umbilicus. One week later, he noted a 3-cm defect and bulge that was painful. He could not reduce the bulge and sought medical attention. He underwent surgical repair of the abdominal wall defect and had what was thought to be a good repair. Six weeks later, the incision was well healed and the integrity of the repaired abdominal wall defect was good. He had increased his activity and was subsequently released to work, where he felt increasing discomfort and pain despite icing and ibuprofen, with no associated swelling at the repair site. There is no evidence of recurrent hernia with ultrasound. He is referred to your clinic for scar release, muscle strengthening, and mobility improvement.

Tests and Measures

There is a well-healed surgical scar with a palpable healing ridge under the scar but no areas of softness or infection. HP shows decreased ability to bend at the waist and pain with reaching overhead and squatting.

Evaluation and Goals

ICF Level	Current Status	Goals
Body structure and function	Anterior abdominal pain after umbilical hernia repair	Scar release, increased mobility, and rectus strengthening
Activity	Work activity including lifting, bending, and twisting	Improve ability to perform work activities
Participation	Cannot work at full duty	Return to full duty

ICF, International Classification for Functioning, Disability and Health.

Prognosis

This patient has an acute injury on top of an overuse injury. The wound is in the maturation phase of remodeling; therefore, techniques for improving function, muscle strengthening, and decreasing inflammation would be most effective.

Intervention

Suitable physical agents to release the patient's scar and improve functioning include heat and mechanical stress through stretching and ROM exercises. An exercise program to improve muscle strength and flexibility without reinjuring the area will help with his recovery and return to work. NSAIDs can be used to control muscular pain and swelling.

Chapter Review

1. The processes of inflammation and tissue repair involve a complex and dynamic series of events, the ultimate goal of which is restoration of normal function. In these events, the involved tissue progresses through three sequential but overlapping stages: (1) inflammation, (2) proliferation, and (3) maturation. This series of events follows a timely and predictable course.
2. The inflammation phase involves the interaction of hemostatic, vascular, cellular, and immune responses mediated by a number of neural and chemical factors. Characteristics of the inflammation phase include heat, redness, swelling, pain, and loss of function in the injured area.
3. The proliferation phase is characterized by epithelialization, fibroplasia, wound contraction, and neovascularization. During this phase, the wound appears red, and swelling decreases, but the wound is still weak and therefore is easily susceptible to damage from excessive pressure and tension.
4. The maturation phase involves balanced collagen synthesis and lysis to ultimately remodel the injured area. The optimal outcome of the maturation phase is new tissue that resembles the previously uninjured tissue. More frequently, scar tissue forms that is slightly weaker than the original tissue. Over time, the scar lightens in color.
5. If the normal healing process is disturbed, healing may be delayed, or chronic inflammation may result. Drugs such as corticosteroids, NSAIDs, and antibiotics are used to limit inflammation, but they can also hinder healing.
6. Physical agents may influence the progression of inflammation and tissue repair. Physical agents used at various stages of the healing process include thermotherapy, cryotherapy, electromagnetic radiation, light, electrical stimulation, ultrasound, and compression. The rehabilitation specialist must assess the stage of inflammation and repair to determine the appropriate agent to incorporate into the treatment plan for an optimal outcome.
7. The reader is referred to the Evolve website for additional resources and references.

Glossary

Acute inflammation: Inflammation that occurs immediately after tissue damage.

Angiogenesis: The growth of new blood vessels.

Cartilage: A fibrous connective tissue that lines the ends of the bones, forming the weight-bearing surface of joints, and the flexible parts of the nose and ears.

Chemotaxis: Movement of cells toward or away from chemicals.

Chronic inflammation: The simultaneous progression of active inflammation, tissue destruction, and healing. Chronic inflammation may last for months or years.

Collagen: The protein in the fibers of skin, tendon, bone, cartilage, and all other connective tissue. Collagen is made up of individual polypeptide molecules combined in triplets forming helical tropocollagen molecules that then associate to form collagen fibrils.

Collagenases: Enzymes that destroy collagen.

Complement system: A system of enzymatic plasma proteins activated by antigen-antibody complexes, bacteria, and foreign material that participates in the inflammatory response through cell lysis, opsonization, and the attraction of leukocytes by chemotaxis.

Connective tissues: Tissues consisting of fibroblasts, ground substance, and fibrous strands that provide the structure for other tissues.

Contractures: Conditions of fixed shortening of soft tissues that have high resistance to passive stretch, often producing deformity or distortion.

Corticosteroids: Drugs that decrease the inflammatory response through many mechanisms involving many cell types.

Diapedesis: The process by which leukocytes squeeze through intact blood vessel walls; a part of the process of extravasation.

Edema: Swelling that results from accumulation of fluid in the interstitial space.

Emigration: The process by which leukocytes migrate from blood vessels into perivascular tissues; a part of the process of extravasation.

Epithelial cells: Cells that form the epidermis of the skin and the covering of mucous and serous membranes.

Epithelialization: Healing by growth of epithelium over a denuded surface, thus reestablishing the epidermis.

Erythrocytes: Red blood cells.

Extravasation: The movement of leukocytes from inside a blood vessel to tissue outside the blood vessel.

Exudate: Wound fluid composed of serum with a high content of protein and white blood cells or solid materials from cells.

Fibroblasts: Cells in many tissues, particularly in wounds, that are the primary producers of collagen.

Fibroplasia: Fibroblast growth.

Granulation tissue: Tissue composed of new blood vessels, connective tissue, fibroblasts, and inflammatory cells that fills an open wound when it starts to heal; typically appears deep pink or red with an irregular, berry-like surface.

Healing by delayed primary intention: Healing in which wound contraction is reduced by delayed approximation of wound edges with sutures or application of skin grafts.

Healing by primary intention: Healing without wound contraction that occurs when wounds are rapidly closed with sutures with minimal loss of tissue and minimal bacterial contamination.

Healing by secondary intention: Healing with wound contraction that occurs when significant loss of tissue or bacterial contamination is present and wound edges are not approximated.

Hemarthrosis: Bloody fluid present in a joint.

Hematoma: The accumulation of blood in a tissue or organ.

Humoral mediators: Antibodies, hormones, cytokines, and a variety of other soluble proteins and chemicals that contribute to the inflammatory process.

Hyperalgesia: Increased sensitivity to painful stimuli.