Schwartz's PRINCIPLES OF SURGERY

TENTH EDITION

F. Charles Brunicardi

Dana K. Andersen • Timothy R. Billiar
David L. Dunn • John G. Hunter
Jeffrey B. Matthews • Raphael E. Pollock

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Notice

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Stephen Lowry, MD, MBA (1947-2011)

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The tenth edition of *Schwartz's Principles of Surgery* is dedicated to the late Dr. Stephen Lowry, consummate surgeon-scientist, educator, colleague, mentor, and long-time contributor to *Schwartz's Principles of Surgery*. At the time of his death, Dr. Lowry served as Richard Harvey Professor and Chair of the Department of Surgery and Senior Associate Dean for Education at the Rutgers-Robert Wood Johnson Medical School (RWJMS) in New Brunswick, New Jersey. He was the inaugural holder of the Richard Harvey Professorship at RWJMS, which honors excellence in innovative teaching and exemplified his absolute dedication to medical education. Dr. Lowry's dedicated and distinguished surgical career produced valuable contributions to both scientific knowledge and patient care, including his seminal investigations utilizing the human endotoxemia model that defined important aspects of the host inflammatory response following injury. His investigations had been supported by continuous National Institute of Health (NIH) funding for more than 25 years and were recognized by the coveted Method to Extend Research in Time (MERIT) award from the NIH. He authored more than 400 scientific publications and was the recipient of numerous honors that recognized his academic achievements. Although Dr. Lowry received many accolades and awards throughout his career, he was first and foremost an enthusiastic teacher and sincere supporter of people, their goals, and their lives. Dr. Lowry genuinely enjoyed listening, learning, and sharing his knowledge and did so with a depth of feeling that inspired and encouraged those around him. As his wife Susette wrote, "Steve knew he would be remembered for his professional accomplishments, but never imagined he would be honored and missed for his personality and style that set him apart from the rest. The world really was a better place with Steve in it!" The loss of his warmth, professionalism, intellect, and enthusiasm for medical education will be greatly missed.

Siobhan Corbett, MD, and the editors of *Schwartz's Principles of Surgery,* Tenth edition

Robert S. Dorian, MD, MBA (1954-2014)

Photo provided by Saint Barnabas Medical Center. Used with permission.

The Editors of *Schwartz's Principles of Surgery* wish to dedicate this tenth edition to the memory of Dr. Robert S. Dorian, the sole author of the "Anesthesia" chapter in the last three editions. Dr. Dorian was born in Philadelphia and grew up in Livingston, New Jersey where his father was a prominent gynecologist. He received his undergraduate degree in Physics and Music from Tufts University in Boston while at the same time studying piano at the New England Conservatory of Music. Bob received his medical education at Rutgers Medical School in Piscataway, New Jersey. After completing an internship in surgery at Downstate Medical Center in Brooklyn, he trained in anesthesiology at Weill Cornell Medical College and New York Hospital in New York City. He completed a fellowship in pediatric anesthesiology at Boston Children's Hospital and Harvard Medical School. After his training, Bob established practice at the St. Barnabas Medical Center and rose to become the Chairman of the Department of Anesthesiology, a position he held for 14 years until his death. He was highly respected on both a national and international basis as an outstanding chairman.

Bob was a consummate anesthesiologist, educator, mentor, and wonderful friend. He was the greatest of clinical anesthesiologists and was dedicated to providing the highest level of care to his patients. He was an extraordinary teacher and as the Program Director of the St. Barnabas anesthesia residency program for ten years, he trained scores of residents. His residents adored him because of the tremendous amount of attention he gave to each resident to assure they were highly trained in their craft and that they were placed in the top fellowships around the nation. Bob was also an incredibly gifted musician, scholar, and thinker. His intellect, humanity, and humor were inspiring to everyone who knew him. Bob was respected on an international basis for his humanitarian work with frequent medical missions to underserved populations around the world. In this endeavor, he was often accompanied by his wife, Linda, and their daughters, Rose and Zoe.

Dr. Dorian had a most special gift and that was to bring out the best in every person that he met and make them feel very special. He lit up every room and made each encounter an occasion to remember. Having a conversation with Bob was one of life's great pleasures. Colleagues, nurses, and patients would look forward to his arrival because he would make them laugh and brighten their day. He was loved by all and will be sorely missed. Bob's memory and legacy will live on in the thousands of patients that he cared for, in the academic programs that he fostered, in the generations of anesthesiologists that he trained, and in his remarkable family. His words and intellect will be preserved in this textbook of surgery.

James R. Macho, MD, FACS, and the editors of *Schwartz's Principles of Surgery,* Tenth edition

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Foreword

The adjective "tenth" connotes a milestone, and, in the case of a "tenth edition" of a textbook, it is evidence of readership acceptability. This continued reader response would evoke parental pride from those who generated the original publication more than 45 years ago. I can still vividly recall the meeting in New York City at which John DeCarville, an editor at McGraw-Hill, brought together David M. Hume, Richard C. Lillehei, G. Thomas Shires, Edward H. Storer, Frank C. Spencer, and me to create a new surgical textbook. The new surgical publication was to serve as a companion to Harrison's recently introduced medical textbook. The favorable reception of the first edition was most encouraging. The consistency of style and the deliberate inclusion of 52 chapters to allow for review of one chapter a week throughout the year were particularly appealing. Subsequent to the initial publication and following the tragic and premature deaths of Dr. Lillehei, Dr. Hume, and Dr. Storer, Dr. Shires, Dr. Spencer, and I were privileged to shepherd six additional editions over the ensuing 35 years. Under the direction of Dr. F. Charles Brunicardi and his associate editors, a new vitality was infused over the three most recent editions.

The ten editions, as they are considered in sequence, serve as a chronicle of the dramatic evolution that has occurred in surgery over the past half century. Those, who have been charged with providing current information to the readership, have had to filter and incorporate extraordinary and unanticipated scientific breakthroughs and technical innovations. At the time of the genesis of the first edition, success had not been achieved in cardiac, hepatic, or intestinal transplantation. Adjuvant therapy for a broad variety of malignancies was in its infancy. Minimally invasive surgery would not become a reality for two decades. On the other side of the spectrum, operative procedures that occupied the focus of symposia have slipped into obscurity. Vagotomy for peptic ulcer has become a rarity, as a consequence of an appreciation of the role of *Helicobacter pylori* and the efficacy of proton pump inhibitors. Surgical procedures to decompress portal hypertension in the treatment of bleeding esophagogastric varices have essentially disappeared from the operating room schedule. They have been replaced by transjugular intrahepatic portosystemic shunt (TIPS) and the liberal application of hepatic transplantation.

As Bob Dylan pointed out, "The Times They Are A-changin." And they most assuredly will continue to change, and at an unanticipated rate. The scientific basis for the practice of surgery is increasing at an ever accelerating pace, and the technologic improvements and breakthroughs are equally extraordinary. The dissemination of the expansion of knowledge has resulted in a shrinking of the globe, necessitating an extension or adaptation of the more modern approaches to underdeveloped nations and underprivileged populations. Global medicine has become a modern concern. The importance of internationalism is manifest in the clinical trials and data acquisition provided by our surgical colleagues on the other sides of the oceans that surround us. It is therefore appropriate that a more international flavor has been developed for *Principles of Surgery* related both to citations and contributors. A distinct consideration of global medicine and, also, the qualities of leadership in surgery that must be nurtured are evidence of the editorial credo of "maintaining modernization" and "anticipating the future."

As the editors and contributors continue to provide the most up-to-date information with a clarity that facilitates learning, it is the hope that the seed, which was planted almost a half century ago, will continue to flourish and maintain the approval of its audience.

Seymour I. Schwartz, MD, FACS
Distinguished Alumni Professor of Surgery
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Preface

Each new edition of this book is approached by the editorial team with a dual vision keeping a dedicated eye affixed to the foundations of surgery while bringing into sharper focus on new and emerging elements. We are entering into a spectacular era of surgery in which the highest quality of care is merging with minimally invasive surgery, robotic surgery, the use of supercomputers, and personalized genomic surgery, all designed to improve the outcomes and quality of life for our patients. With these advances in mind, several new chapters have been added and all previous chapters have been updated with an emphasis on evidence-based, state-of-the-art surgical care. While this tried-and-true method remains the basis for upholding and maintaining the superb efforts and achievements of Dr. Seymour Schwartz and previous co-editors and contributors, this edition expands its vision to see beyond the operating theater and takes a look at the making of a surgeon as a whole, with the addition of the chapter, Fundamental Principles of Leadership Training in Surgery. Surely excellence in craft must be mastered and equal importance must also be given to the nontechnical training of what it means to be a leader of a surgical team.

To this effort, the editors were keen to include as the first chapter in this edition a comprehensive review of leadership methods and ideologies as well as underscoring the importance of instituting a formal leadership-training program for residents that emphasizes mentoring. Our own paths as surgeons have been defined by the mentoring relationship and we have undoubtedly benefitted greatly from the efforts of our mentors; we sincerely hope that those with whom we have entered into this time-honored tradition have reaped the benefit as well. Simply stated, leadership skills can and should be taught to surgical trainees and in doing so this will help them improve quality of care.

The editors are thankful that this text is a relied-on source for training and crafting surgeons on a global basis. This is due in large part to the extraordinary efforts of our contributors, the leaders in their fields, who not only do so to train up-and-coming surgeons, but to impart their knowledge and expertise to the benefit of patients worldwide. The recent inclusion of many international authors to the chapters within is ultimately a testament to mentorship, albeit on a broader scale, and we thank them all, both near and far.

To our fellow editorial board members who have tirelessly devoted their time and knowledge to the integrity and excellence of their craft and this textbook, we extend our gratitude and thanks. We are to thankful to Brian Belval, Christie Naglieri, and all at McGraw-Hill for the continued belief in and support of this textbook. We wish to thank Katie Elsbury for her dedication to the organization and editing of this textbook. Last, we would like to thank our families who are the most important contributors of all.

F. Charles Brunicardi, MD, FACS

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Preface to the First Edition

The raison d'être for a new textbook in a discipline which has been served by standard works for many years was the Editorial Board's initial conviction that a distinct need for a modern approach in the dissemination of surgical knowledge existed. As incoming chapters were reviewed, both the need and satisfaction became increasingly apparent and, at the completion, we felt a sense of excitement at having the opportunity to contribute to the education of modern and future students concerned with the care of surgical patients.

The recent explosion of factual knowledge has emphasized the need for a presentation which would provide the student an opportunity to assimilate pertinent facts in a logical fashion. This would then permit correlation, synthesis of concepts, and eventual extrapolation to specific situations. The physiologic bases for diseases are therefore emphasized and the manifestations and diagnostic studies are considered as a reflection of pathophysiology. Therapy then becomes logical in this schema and the necessity to regurgitate facts is minimized. In appreciation of the impact which *Harrison's Principles of Internal Medicine* has had, the clinical manifestations of the disease processes are considered in detail for each area. Since the operative procedure represents the one element in the therapeutic armamentarium unique to the surgeon, the indications, important technical considerations, and complications receive appropriate emphasis. While we appreciate that a textbook cannot hope to incorporate an atlas of surgical procedures, we have provided the student a single book which will satisfy the sequential demands in the care and considerations of surgical patients.

The ultimate goal of the Editorial Board has been to collate a book which is deserving of the adjective "modern." We have therefore selected as authors dynamic and active contributors to their particular fields. The au courant concept is hopefully apparent throughout the entire work and is exemplified by appropriate emphasis on diseases of modern surgical interest, such as trauma, transplantation, and the recently appreciated importance of rehabilitation. Cardiovascular surgery is presented in keeping with the exponential strides recently achieved.

There are two major subdivisions to the text. In the first twelve chapters, subjects that transcend several organ systems are presented. The second portion of the book represents a consideration of specific organ systems and surgical specialties.

Throughout the text, the authors have addressed themselves to a sophisticated audience, regarding the medical student as a graduate student, incorporating material generally sought after by the surgeon in training and presenting information appropriate for the continuing education of the practicing surgeon. The need for a text such as we have envisioned is great and the goal admittedly high. It is our hope that this effort fulfills the expressed demands.

Seymour I. Schwartz, MD, FACS

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Part

Basic Considerations

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chapter 1

Fundamental Principles of Leadership Training in Surgery

Amy L. Hill, James Wu, Mark D. Girgis, Danielle Hsu, Areti Tillou, James Macho, Vishad Nabili, and F. Charles Brunicardi

INTRODUCTION

The field of surgery has evolved greatly from its roots, and surgical practice now requires the mastery of modern leadership principles and skills as much as the acquisition of medical knowledge and surgical technique. Historically, surgeons took sole responsibility for their patients and directed proceedings in the operating room with absolute authority, using a command-and-control style of leadership. Modern surgical practice has now evolved from single provider–based care toward a team-based approach, which requires collaborative leadership skills. Surgical care benefits from the collaboration of surgeons, anesthesiologists, internists, radiologists, pathologists, radiation oncologists, nurses, pharmacists, social workers, therapists, hospital staff, and administrators. Occupying a central role on the healthcare team, surgeons[1] have the potential to improve patient outcomes, reduce medical errors, and improve patient satisfaction through their leadership of the multidisciplinary team. 1▶ Thus, in the landscape of modern healthcare systems, it is imperative that surgical training programs include formal instruction on leadership principles and skills to cultivate their trainees' leadership capabilities.

Many medical and surgical communities, including residency training programs, acknowledge the need for improved physician leadership.[2] Surgical trainees identify leadership skills as important, but report themselves as "not competent" or "minimally competent" in this regard.[2,3] While a small number of surgical training programs have implemented formal curriculum focused on teaching leadership principles, it is now imperative that all surgical training programs teach these important skills to their trainees.[4,5] Interviews of academic chairpersons identified several critical leadership success factors,[6] including mastery of visioning, communication, change management, emotional intelligence, team building, business skills, personnel management, and systems thinking. These chairpersons stated that the ability of emotional intelligence was "fundamental to their success and its absence the cause of their failures," regardless of medical knowledge.[6] Thus, training programs need to include leadership training to prepare trainees for success in modern healthcare delivery.

In the United States, the Accreditation Council for Graduate Medical Education (ACGME) has established six core competencies—patient care, medical knowledge, practice-based learning and improvement, interpersonal and communication skills, professionalism, and systems-based practice (Table 1-1)[4]—that each contain principles of leadership. The ACGME has mandated the teaching of these core competencies but has not established a formal guide on how to teach the leadership skills described within the core competencies. Therefore, this chapter offers a review of fundamental principles of leadership and an introduction of the concept of a leadership training program for surgical trainees.

DEFINITIONS OF LEADERSHIP

Many different definitions of leadership have been described. Former First Lady Rosalynn Carter once observed that, "A leader takes people where they want to go. A *great* leader takes people where they don't necessarily want to go, but where they ought to be." Leadership does not always have to come from a position of authority. Former American president John Quincy Adams stated, "If your actions inspire others to dream more, learn more, do more, and become more, you are a leader." Another definition is that leadership is the process of using social influence to enlist the aid and support of others in a common task.[7]

FUNDAMENTAL PRINCIPLES OF LEADERSHIP

Clearly, leadership is a complex concept. Surgeons should strive to adopt leadership qualities that provide the best outcomes for their patients, based on the following fundamental principles.

Vision

The first and most fundamental principle of leadership is to establish a vision that people can live up to, thus providing direction and purpose to the constituency. Creating a vision is a declaration 2▶ of the near future that inspires and conjures motivation.[8] A classic example of a powerful vision that held effective impact is President Kennedy's declaration in 1961 that ". . . this nation should commit itself to achieving the goal, before this decade is out, of landing a man on the moon and returning him safely to the earth." Following his declaration of this vision with a timeline to achieve it, the United Sates mounted a remarkable unified effort, and by the end of the decade, Neil Armstrong

Key Points

1. Effective surgical leadership improves patient care.
2. A fundamental principle of leadership is to provide a vision that people can live up to, thereby providing direction and purpose to the constituency.
3. Surgical leaders have the willingness to lead through an active and passionate commitment to the vision.
4. Surgical leaders have the willingness to commit to lifelong learning.
5. Surgical leaders have the willingness to communicate effectively and resolve conflict.
6. Surgical leaders must practice effective time management.
7. Different leadership styles are tools to use based on the team dynamic.
8. Surgical trainees can be taught leadership principles in formal leadership training programs to enhance their ability to lead.
9. Mentorship provides wisdom, guidance, and insight essential for the successful development of a surgical leader.

took his famous walk and the vision had been accomplished (Fig. 1-1).

On a daily basis, surgeons are driven by a powerful vision: the vision that our surgical care will improve patients' lives. The great surgical pioneers, such as Hunter, Lister (Fig. 1-2), Halsted, von Langenbeck, Billroth, Kocher (Fig. 1-3), Carrel, Gibbon, Blalock, Wangensteen, Moore, Rhoads, Huggins, Murray, Kountz, Longmire, Starzl, and DeBakey (Fig. 1-4), each possessed visions that revolutionized the field of surgery. In the nineteenth century, Joseph Lister changed the practice of surgery with his application of Pasteur's germ theory. He set a young boy's open compound leg fracture, a condition with a 90% mortality rate at that time, using carbolic acid dressings and aseptic surgical technique. The boy recovered, and Lister gathered nine more patients. His famous publication on the use of aseptic technique introduced the modern era of sterile technique. Emil Theodor Kocher was the first to master the thyroidectomy, thought to be an impossible operation at the time, and went on to perform thousands of thyroidectomies with a mortality of less than 1%. He was awarded the Nobel Prize in Physiology or Medicine in 1909 for describing the thyroid's physiologic role in metabolism. Michael E. DeBakey's powerful vision led to the development of numerous groundbreaking procedures that helped pioneer the field of cardiovascular surgery. For example, envisioning an artificial artery for arterial bypass operations, Dr. DeBakey invented the Dacron graft, which has helped millions of patients suffering from vascular disease and enabled the development of endovascular surgery. Dr. Frederick Banting, the youngest recipient of the Nobel Prize in Physiology or Medicine, had a vision to discover the biochemical link between diabetes and glucose homeostasis. His vision and perseverance led to the discovery of insulin.[9] In retrospect, the power and clarity of their visions were remarkable, and their willingness and dedication were inspiring. By studying their careers and accomplishments, surgical trainees can appreciate the potential impact of a well-developed vision.

Leaders must learn to develop visions to provide direction for their team. The vision can be as straightforward as providing quality of care or as lofty as defining a new field of surgery. One can start developing their vision by brainstorming the answers to two simple questions: "Which disease needs to be cured?" and "How can it be cured?"[10] The answers represent a vision and should be recorded succinctly in a laboratory notebook or journal. Committing pen to paper enables the surgical trainee to define their vision in a manner that can be shared with others.

Willingness

The Willingness Principle represents the active commitment of the leader toward their vision. A surgical leader must be willing

Table 1-1

Accreditation Council for Graduate Medical Education core competencies

CORE COMPETENCY	DESCRIPTION
Patient care	To be able to provide compassionate and effective healthcare in the modern-day healthcare environment
Medical knowledge	To effectively apply current medical knowledge in patient care and to be able to use medical tools (i.e., PubMed) to stay current in medical education
Practice-based learning and improvement	To critically assimilate and evaluate information in a systematic manner to improve patient care practices
Interpersonal and communication skills	To demonstrate sufficient communication skills that allow for efficient information exchange in physician-patient interactions and as a member of a healthcare team
Professionalism	To demonstrate the principles of ethical behavior (i.e., informed consent, patient confidentiality) and integrity that promote the highest level of medical care
Systems-based practice	To acknowledge and understand that each individual practice is part of a larger healthcare delivery system and to be able to use the system to support patient care

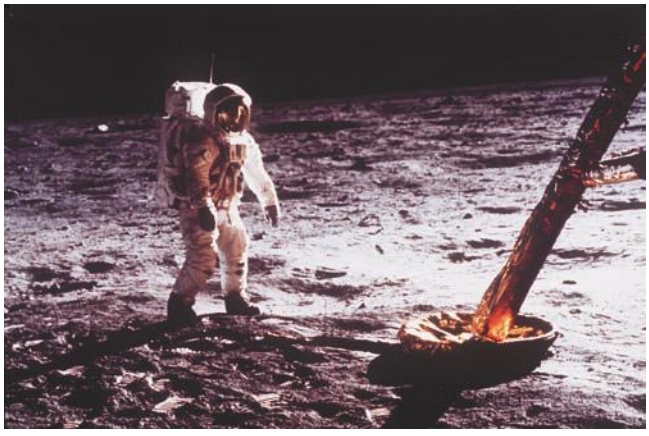

Figure 1-1. Apollo 11 Lunar Module moon walk. Astronaut Edwin "Buzz" Aldrin walks by the footpad of the Apollo 11 Lunar Module, July 1969. *(Reproduced with permission from AP Photo/NASA. © 2014 The Associated Press.)*

to lead, commit to lifelong learning, communicate effectively, and resolve conflict.

To Lead. A key characteristic of all great leaders is the willingness to serve as the leader. Dr. Martin Luther King, Jr., who championed the civil rights movement with a powerful vision of equality for all based on a commitment to nonviolent methods,[11] did so at a time when his vocalization of this vision ensured harassment, imprisonment, and threats of violence against himself, his colleagues, and his family and friends (Fig. 1-5). King, a young, highly educated pastor, had the security of employment and family, yet was willing to accept enormous responsibility and personal risk and did so in order to lead a nation toward his vision of civil rights, for which he was awarded the Nobel Peace Prize in 1964. Steve Jobs, co-founder of Apple Inc., chose to remain in his position as chief executive officer (CEO) to pursue his vision of perfecting the personal computer at great personal expense. He described this experience as ". . . rough, really rough, the worst time in my life . . . . I would go to work at 7 a.m. and I'd get back at 9 at night, and the kids would be in bed. And I couldn't speak, I literally couldn't, I was so exhausted . . . . It got close

Figure 1-2. Joseph Lister directing use of carbolic acid spray in one of his earliest antiseptic surgical operations, circa 1865. *(Copyright Bettmann/Corbis/AP Images.)*

Figure 1-3. Emil Theodor Kocher. *(Courtesy of the National Library of Medicine.)*

to killing me."[12] Both individuals demonstrated a remarkable tenacity and devotion to their vision.

Willingness to lead is a necessity in any individual who desires to become a surgeon. By entering into the surgical theater, a surgeon accepts the responsibility to care for and operate on patients despite the risks and burdens involved. They do so, believing fully in the improved quality of life that can be achieved. Surgeons must embrace the responsibility of leading surgical teams that care for their patients, as well as leading surgical trainees to become future surgeons. A tremendous sacrifice is required for the opportunity to learn patient care. Surgical trainees accept the hardships of residency with its

Figure 1-4. Michael E. DeBakey. *(Reproduced with permission from AP Photo/David J. Phillip. © 2014 The Associated Press.)*

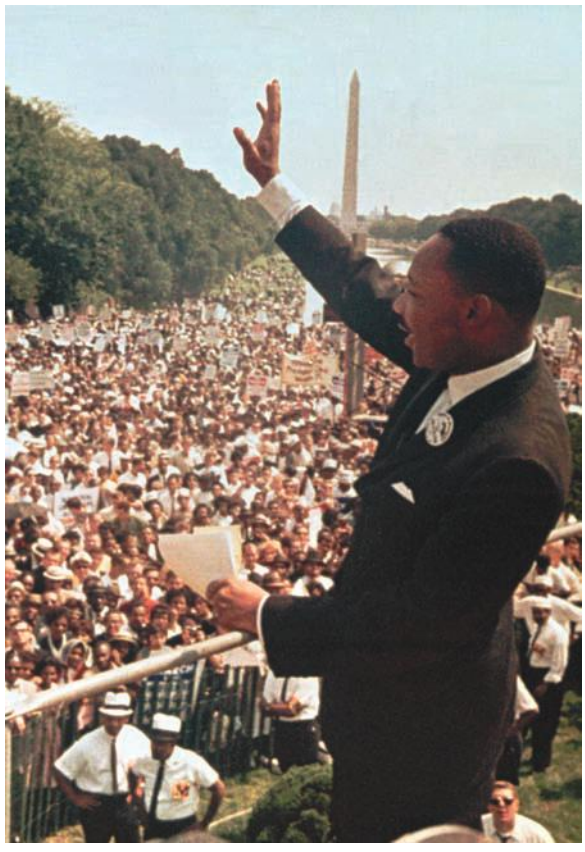

Figure 1-5. Dr. Martin Luther King, Jr. acknowledges the crowd at the Lincoln Memorial for his "I Have a Dream" speech during the March on Washington, D.C., August 28, 1963. *(Reproduced with permission from AP Photo. © 2014 The Associated Press.)*

accompanying steep learning curve, anxiety, long work hours, and time spent away from family and friends. The active, passionate commitment to excellent patient care reflects a natural willingness to lead based on altruism and a sense of duty toward those receiving care. Thus, to ensure delivery of the utmost level of care, surgical trainees should commit to developing and refining leadership skills. These skills include a commitment to lifelong learning, effective communication, and conflict resolution.

3▶

To Learn. Surgeons and surgical trainees, as leaders, must possess willingness to commit to continuous learning. Modern surgery is an ever-changing field with dynamic and evolving healthcare systems and constant scientific discovery and innovation. Basic and translational science relating to surgical care is growing at an exponential rate. The sequencing of the human genome and the enormous advances in molecular biology and signaling pathways are leading to the transformation of personalized medicine and surgery in the twenty-first century (see Chap. 15).[13] Performing prophylactic mastectomies with immediate reconstruction for *BRCA1* mutations and thyroidectomies with thyroid hormone replacement for *RET* proto-oncogene mutations are two of many examples of genomic information guiding surgical care. Technologic advances in minimally invasive surgery and robotic surgery as well as electronic records and other information technologies are revolutionizing the craft of surgery. The expansion of minimally invasive and endovascular surgery over the past three decades required surgeons to retrain in new techniques using new skills and equipment. In this short time span, laparoscopy and endovascular operations are now recognized as the standard of care for many surgical diseases, resulting in shorter hospital stay, quicker recovery, and a kinder and gentler manner of practicing surgery. Remarkably, during the last century, the field of surgery has progressed at an exponential pace and will continue to do so with the advent of using genomic analyses to guide personalized surgery, which will transform the field of surgery this century. Therefore, surgical leadership training should emphasize and facilitate the continual pursuit of knowledge.

Fortunately, surgical organizations and societies provide surgeons and surgical trainees a means to acquire new knowledge on a continuous basis. There are numerous local, regional, national, and international meetings of surgical organizations that provide ongoing continuing medical education credits, also required for the renewal of most medical licenses. The American Board of Surgery requires all surgeons to complete meaningful continuing medical education to maintain certification.[14] These societies and regulatory bodies enable surgeons and surgical trainees to commit to continual learning, and ensure their competence in a dynamic and rapidly growing field.

4▶

Surgeons and trainees now benefit from the rapid expansion of web-based education as well as mobile handheld technology. These are powerful tools to minimize nonproductive time in the hospital and make learning and reinforcement of medical knowledge accessible. Currently web-based resources provide quick access to a vast collection of surgical texts, literature, and surgical videos. Surgeons and trainees dedicated to continual learning should be well versed in the utilization of these information technologies to maximize their education. The next evolution of electronic surgical educational materials will likely include simulation training similar to laparoscopic and Da Vinci device training modules. The ACGME, acknowledging the importance of lifelong learning skills and modernization of information delivery and access methods, has included them as program requirements for residency accreditation.

To Communicate Effectively. The complexity of modern healthcare delivery systems requires a higher level and collaborative style of communication. Effective communication directly impacts patient care. In 2000, the U.S. Institute of Medicine published a work titled, *To Err Is Human: Building a Safer Health System*, which raised awareness concerning the magnitude of medical errors. This work showcased medical errors as the eighth leading cause of death in the United States with an estimated 100,000 deaths annually.[15] Subsequent studies examining medical errors have identified communication errors as one of the most common causes of medical error.[16,17] In fact, the Joint Commission identifies miscommunication as the leading cause of sentinel events. Information transfer and communication errors cause delays in patient care, waste surgeon and staff time, and cause serious adverse patient events.[18] Effective communication between surgeons, nurses, ancillary staff, and patients is not only a crucial element to improved patient outcomes, but it also leads to less medical litigation.[19-21] A strong correlation exists between communication and patient outcomes.

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Establishing a collaborative atmosphere is important since communication errors leading to medical mishaps are not simply failures to transmit information. Communication errors "are far more complex and relate to hierarchical differences, concerns

with upward influence, conflicting roles and role ambiguity, and interpersonal power and conflict."[17,22] Errors frequently originate from perceived limited channels of communication and hostile, critical environments. To overcome these barriers, surgeons and surgical trainees should learn to communicate in an open, universally understood manner and remain receptive to any team member's concerns. A survey of physicians, nurses, and ancillary staff identified effective communication as a key element of a successful leader.[23] As leaders, surgeons and surgical trainees who facilitate an open, effective, collaborative style of communication reduce errors and enhance patient care. A prime example is that successful communication of daily goals of patient care from the team leader improves patient outcomes. In one recent study, the modest act of explicitly stating daily goals in a standardized fashion significantly reduced patient length of intensive care unit stay and increased resident and nurse understanding of goals of care.[24] Implementing standardized daily team briefings in the wards and preoperative units led to improvements in staff turnover rates, employee satisfaction, and prevention of wrong site surgery.[22] In cardiac surgery, improving communication in the operating room and transition to the postanesthesia care unit was an area identified to decrease risk for adverse outcomes.[25] Behaviors associated with ineffective communication, including absence from the operating room when needed, playing loud music, making inappropriate comments, and talking to others in a raised voice or a condescending tone, were identified as patient hazards; conversely, behaviors associated with effective collaborative communication, such as time outs, repeat backs, callouts, and confirmations, resulted in improved patient outcomes.

One model to ensure open communication is through standardization of established protocols. A commonly accepted protocol is the "Time Out" that is now required in the modern operating room. During the Time Out protocol, all team members introduce themselves and state a body of critical information needed to safely complete the intended operation. This same standardization can be taught outside the operating room. Within the Kaiser system, certain phrases have been given a universal meaning: "I need you now" by members of the team is an understood level of urgency and generates a prompt physician response 100% of the time.[22] As mentioned earlier, standardized forms can be useful tools in ensuring universally understood communication during sign-out. The beneficial effect of standardized communication further demonstrates how effective communication can improve patient care and is considered a vital leadership skill.

To Resolve Conflict. Great leaders are able to achieve their vision through their ability to resolve conflict. During the pursuit of any vision, numerous conflicts arise on a daily basis; numerous conflicts arise on a daily basis when surgeons and surgical trainees provide high-quality care. Therefore, the techniques for conflict resolution are essential for surgical leaders.

To properly use conflict resolution techniques, it is important for the surgeon and surgical trainee to always remain objective and seek personal flexibility and self-awareness. The gulf between self-perception and the perception of others can be profound; in a study of cooperation and collaboration among operating room staff, the quality of their own collaboration was rated at 80% by surgeons, yet was rated at only 48% by operating room nurses.[26] Systematic inclusion of modern conflict resolution methods that incorporate the views of all members of a multidisciplinary team help maintain objectivity. Reflection is often overlooked in surgical residency training but is a critical component of learning conflict resolution skills. Introspection allows the surgeon to understand the impact of his or her actions and biases. Objectivity is the basis of effective conflict resolution, which can improve satisfaction among team members and help deliver optimal patient care.

Modern conflict resolution techniques are based on objectivity, willingness to listen, and pursuit of principle-based solutions.[27] For example, an effective style of conflict resolution is the utilization of the "abundance mentality" model, which attempts to achieve a solution that benefits all involved and is based on core values of the organization, as opposed to the utilization of the traditional fault-finding model, which identifies sides as right or wrong.[28] Application of the abundance mentality in surgery elevates the conflict above the affected parties and focuses on the higher unifying goal of improved patient care. Morbidity and mortality (M&M) conferences are managed in this style and have the purpose of practice improvement and improving overall quality of care within the system, as opposed to placing guilt or blame on the surgeon or surgical trainees for the complication being reviewed. The traditional style of command-and-control technique based on fear and intimidation is no longer welcome in any healthcare system and can lead to sanctions, lawsuits, and removal of hospital privileges or position of leadership.

Another intuitive method that can help surgical trainees learn to resolve conflict is the "history and physical" model of conflict resolution. This model is based on the seven steps of caring for a surgical patient that are well known to the surgical trainee.[29] (1) The "history" is the equivalent of gathering subjective information from involved parties with appropriate empathy and listening. (2) The "laboratory/studies" are the equivalent of collecting objective data to validate the subjective information. (3) A "differential diagnosis" is formed of possible root causes of the conflict. (4) The "assessment/plan" is developed in the best interest of all involved parties. The plan, including risks and benefits, is openly discussed in a compassionate style of communication. (5) "Preoperative preparation" includes the acquisition of appropriate consultations for clearances, consideration of equipment and supplies needed for implementation, and the "informed consent" from the involved parties. (6) The "operation" is the actual implementation of the agreed-upon plan, including a time-out. (7) "Postoperative care" involves communicating the operative outcome, regular postoperative follow-up, and the correction of any complications that arise. This seven-step method is an example of an objective, respectful method of conflict resolution. Practicing different styles of conflict resolution and effective communication in front of the entire group of surgical trainees attending the leadership training program is an effective means of teaching conflict resolution techniques.

Time Management

It is important for leaders to practice effective time management. Time is the most precious resource, as it cannot be bought, saved, or stored. Thus, management of time is essential for a productive and balanced life for those in the organization. The effective use of one's time is best done through a formal time management program to improve one's ability to lead by setting priorities and making choices to achieve goals. The efficient use of one's time helps to improve both productivity and quality of life.

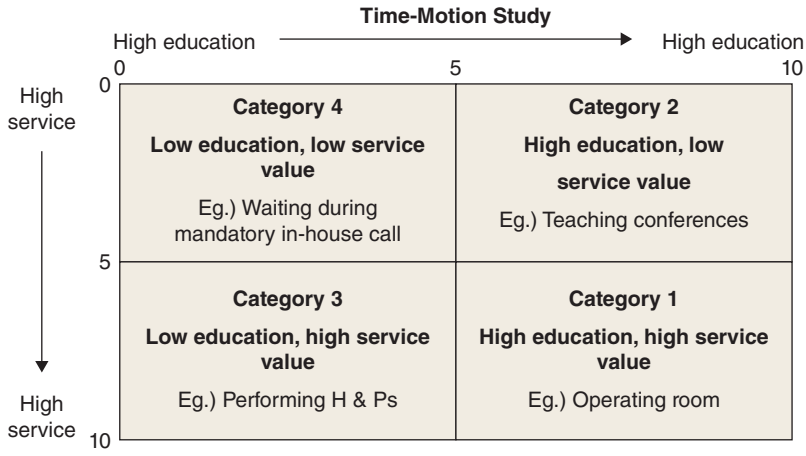

Figure 1-6. Surgery resident time-motion study. H & P = history and physical examination.

It is important for surgeons and surgical trainees to learn and use a formal time management program. There are ever-increasing demands placed on surgeons and surgical trainees to deliver the highest quality care in highly regulated environments. Furthermore, strict regulations on limitation of work hours demand surgical trainees learn patient care in a limited amount of time.[30] All told, these demands are enormously stressful and can lead to burnout, drug and alcohol abuse, and poor performance.[30] A time-motion study of general surgery trainees analyzed residents' self-reported time logs to determine resident time expenditure on educational/service-related activities (Fig. 1-6).[31] Surprisingly, senior residents were noted to spend 13.5% of their time on low-service, low-educational value activities. This time, properly managed, could be used to either reduce work hours or improve educational efficiency in the context of new work hour restrictions. It is therefore critical that time be used wisely on effectively achieving one's goals.

Parkinson's law, proposed in 1955 by the U.K. political analyst and historian Cyril Northcote Parkinson, states that work expands to fill the time available for its completion, thus leading individuals to spend the majority of their time on insignificant tasks.[32] Pareto's 80/20 principle states that 80% of goals are achieved by 20% of effort and that achieving the final 20% requires 80% of their effort. Therefore, proper planning of undertaking any goal needs to include an analysis of how much effort will be needed to complete the task.[32] Formal time management programs help surgeons and surgical trainees better understand how their time is spent, enabling them to increase productivity and achieve a better balanced lifestyle.

Various time allocation techniques have been described.[32] A frequently used basic technique is the "prioritized list," also known as the ABC technique. Individuals list and assign relative values to their tasks. The use of the lists and categories serves solely as a reminder, thus falling short of aiding the user in allocating time wisely. Another technique is the "time management matrix technique."[28] This technique plots activities on two axes: importance and urgency, yielding four quadrants (Fig. 1-7). Congruous with the Pareto's 80/20 principle and Parkinson's law, the time management matrix technique channels efforts into quadrant II (important but nonurgent) activities. The activities in this quadrant are high yield and include planning, creative activity, building relationships, and maintaining productivity. Too often, surgeons spend a majority of their time attending to quadrant I (important and urgent) tasks. Quadrant I tasks include emergencies and unplanned or disorganized situations that require intensive and often inefficient effort. While most surgeons and surgical trainees have to deal with emergencies, they often develop the habit of inappropriately assigning activities into quadrant I; excess time spent on quadrant I tasks leads to stress or burnout for the surgeon and distracts from long-term goals. Efficient time management allows surgeons and surgical trainees to be proactive about shifting energy from quadrant I tasks to quadrant II, emphasizing preplanning and creativity over always attending to the most salient issue at hand, depending on the importance and not the urgency.

Finally, "the six areas of interest" is an alternative effective time management model that can help surgeons and surgical trainees achieve their goals, live a better balanced lifestyle, and improve the quality of their lives.[32] The process begins by performing a time-motion study in which the activities of 6-hour increments of time over a routine week are chronicled. At the end of the week, the list of activities is analyzed to determine how the 168 hours in 1 week have been spent. The surgical trainee then selects six broad categories of areas of interest (i.e., family, clinical care, education, health, community service, hobbies, etc.), and sets a single activity goal in each category every day and monitors whether those goals are achieved. This technique is straightforward and improves one's quality of life by setting and achieving a balanced set of goals of personal interest, while eliminating time-wasting activities.

A formal time management program is essential for modern leadership. The practice and use of time management strategies can help surgeons and surgical trainees achieve and maintain their goals of excellent clinical care for their patients, while maintaining a more balanced lifestyle.

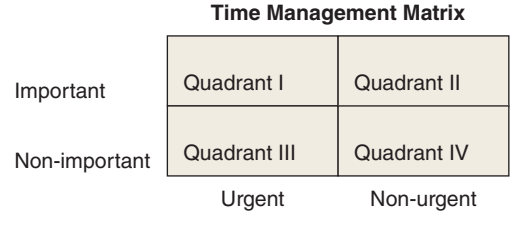

Figure 1-7. Time management. *(From Covey S.* The Seven Habits of Highly Effective People. *New York: Simon & Schuster; 1989.)*

LEADERSHIP STYLES

The principles of leadership can be practiced in a variety of styles. Just as there are many definitions of leadership, many classifications of styles exist as well. A landmark study by Daniel Goleman in *Harvard Business Review* identified six distinct leadership styles, based on different components of emotional intelligence.[33] Emotional intelligence is the ability to recognize, understand, and control the emotions in others and ourselves. By learning different styles, surgeons and trainees can recognize their own leadership style and the effect on the team dynamic. Furthermore, it teaches when the situation may demand change in style for the best outcome. The six leadership styles identified are *Coercive, Authoritative, Affiliative, Democratic, Pacesetting, and Coaching*.

The Coercive leader demands immediate compliance. This style reflects the command and control style that has historically dominated surgery. Excessive coercive leadership erodes team members' sense of responsibility, motivation, sense of participation in a shared vision, and ultimately, performance. However, it is effective in times of crisis to deliver clear, concise instruction. This style should be used sparingly and is best suited for emergencies.

The Authoritative leader embodies the phrase "Come with me," focusing on mobilizing the team toward a common, grand vision. This type of leader allows the team freedom to innovate, experiment, and devise its own means. Goleman's research indicates this style is often the most effective. These leaders display self-confidence, empathy, and proficiency in initiating new ideas and leading people in a new direction. This is best used when a shift in paradigm is needed.

The Affiliative leader creates harmony and builds emotional bonds. This requires employment of empathy, building relationships, and emphasis on communication. An affiliative leader frequently gives positive feedback. This style can allow poor performance to go uncorrected if too little constructive/critical advice is given. Affiliative leadership is most useful when motivating people during stressful circumstances or healing rifts in a team.

The Coaching style of leadership focuses on developing people for the future. Coaching is leadership through mentorship. The coach gives team members challenging tasks, counsels, encourages, and delegates. Unlike the affiliative leader who focuses on positive feedback, the coach helps people identify their weaknesses and improve their performance, and ties their work into their long-term career aspirations. This leadership style builds team capabilities by helping motivated learners improve. However, this style does not work well when team members are defiant and unwilling to change or learn, or if the leader lacks proficiency.

The Democratic leader forges consensus through participation. This leadership style listens to and values each member's input. It is not the best choice in an emergency situation, when time is limited, or when teammates cannot contribute informed guidance to the leader. It can also be exasperating if a clear vision does not arise from the collaborative process. This style is most appropriate when it is important to obtain team consensus, quell conflict, or create harmony.

The Pacesetter leader sets high standards for performance and exemplifies them. These leaders identify poor performers and demand more from them. However, unlike the coach, the pacesetter does not build the skills of those who are not keeping up. Rather, a pacesetter will either take over the task himself or delegate the task to another team member. This leadership style works well when it is important to obtain high-quality results and there is a motivated, capable team. However, pacesetters can easily become micromanagers who have difficulty delegating tasks to team members, which leads to burn out on the part of the leader. Additionally, team members can feel overwhelmed and demoralized by the demands for excellence without an empathic counter balance.

Each of the above styles of leadership has strengths and weakness. Importantly, leaders who are the most successful do not rely only on one leadership style alone. They use several of them seamlessly depending on the situation and the team members at hand. Therefore, the more styles a leader has mastered, the better, with particular emphasis on the Authoritative, Affiliative, Democratic, and Coaching styles. Each leadership style is a tool that is ultimately employed to guide a team to realizing a vision or goal. Thus, leadership training programs should teach the proper use of all leadership styles while adhering to the principles of leadership.

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FORMAL LEADERSHIP TRAINING PROGRAMS IN SURGERY

Since it has been shown that effective leadership can improve patient outcomes, leadership principles and skills should be taught to surgical trainees using formal leadership training programs. The importance of teaching leadership skills is reflected by the ACGME mandated core competencies (see Table 1-1). However, surgical trainees, most notably chief residents, find themselves in various leadership roles without ever having experienced formalized leadership training, which has been shown to result in a self-perceived lack of leadership ability.[23] When surveyed on 18 core leadership skills (Table 1-2), 92% of residents rated all 18 skills as important, but over half rated themselves as "minimally" or "not competent" in 10 out of 18 skills.[2] It has been documented that trainees are requesting leadership training and wish to close the gap between perceived need for training and the implementation of formal leadership training programs.[34–37]

A number of leadership workshops have been created. Extracurricular leadership programs have been designed mostly for physicians with an MBA or management background but have not been incorporated into the core residency training program.[38] Also, there are many institutions that have published experiences with leadership retreats or seminars for residents or young physicians.[39–42] The ACGME hosts multiple leadership skills workshops for chief residents, mostly targeted toward pediatricians, family practitioners, and psychiatrists.[43] Similarly, the American College of Surgeons leads an annual 3-day leadership conference focusing on leadership attributes, consensus development, team building, conflict resolution, and translation of leadership principles into clinical practice.[44] These programs were all received well by participants and represent a call for a formal leadership program for all surgical trainees.

An innovative leadership curriculum first implemented in 1999 taught general surgery trainees collaborative leadership skills, at a time when the traditional command-and-control leadership style predominated.[45] Surgical residents participated in 18-hour-long modules based on the leadership principles and skills listed in Table 1-2, taught by the surgical faculty.

Table 1-2

18 leadership training modules

SKILLS	IMPORTANCE MEAN SCORE	COMPETENCE MEAN SCORE
Academic program development	3.2	2.4*
Leadership training	3.8	2.3*
Leadership theory	3.2	2.1*
Effective communication	3.7	2.7*
Conflict resolution	3.8	3*
Management principles	3.7	2.7*
Negotiation	3.7	2.8*
Time management	4	2.8*
Private or academic practice, managed care	3.6	2*
Investment principles	3.5	2.2*
Ethics	3.6	3.2
Billing, coding, and compliance	3.5	1.7*
Program improvement	3	2*
Writing proposals	3.3	2.2*
Writing reports	3.4	2.4*
Public speaking	3.7	2.7*
Effective presentations	3.7	2.7*
Risk management	3.5	2.1*
Total	3.6	2.5*

Source: Reprinted with permission from Itani KMF, Liscum K, Brunicardi FC. Physician leadership is a new mandate in surgical training. *Am J Surg*. 2004;187:328-331. © Copyright Elsevier.
* P<0.001 by Student t test between mean importance and mean competence scores.

A number of leadership techniques, including time management techniques and applied conflict resolution techniques described earlier, were designed and implemented as part of this leadership training program. Within 6 months of implementation, residents' self-perceived total commitment to the highest personal and professional standards, communication skills, visualization of clear missions of patient care, and leadership of others toward that mission increased significantly.[45] Remarkably, the positive impact of this leadership curriculum was significant when measured using tools, such as the Multifactor Leadership Questionnaire (MLQ), social skills inventory, personality inventory, and internal strength scorecard.[2,37,45-47] The MLQ is a well-validated instrument that objectively quantifies leadership beliefs and self-perceived outcomes across medical and nonmedical disciplines. Based on the MLQ, surgical residents more often use a passive-avoidant style of leadership that emphasizes taking corrective action only after a problem is "significant and obvious."[37] This tool can also be used to track progress toward more effective, collaborative styles of leadership. These studies demonstrated the ability to measure leadership behavior of surgical trainees in a standardized, quantifiable format.[2,37,45-47] Taken together, these studies support the concept that leadership skills can and should be taught to surgical trainees, and there are many validated tools 8▶ to measure outcomes.

Mentoring

A formal leadership training program for surgical trainees should include mentoring. Mentoring is the active process by which an experienced, empathetic person guides another individual in the development and self-recognition of their own vision, learning, core competencies, and professional development. Halstead established the concept of a surgical mentor who directly provided the trainees with professional and technical guidance. Halstead's concept went beyond a simple preceptorship by emphasizing clinical decision making based on scientific evidence. His goal was to develop surgeons who would go on to become outstanding leaders and innovators in the field. Although surgery has changed dramatically since Halstead's era, mentorship remains crucial in surgical training. In addition to teaching technical skills, clinical judgment, and scientific inquiry, modern-day mentors must also model effective communication, empathy, humanism, and the prioritization of competing professional and personal activities.

The mentor must also be an experienced and trusted advisor committed to the success of the mentee. A greater level of trust and commitment distinguishes the mentor from the teacher. More than a teacher, a mentor is a coach. The goal of a teacher is to pass on a defined level of knowledge for each stage of a student's education. The underlying premise is a limited level of advancement for the student. The coach, on the other hand, has the sole purpose to make his or her student the best at their game with an unlimited level of advancement. Modern mentorship implies a partnership between the mentor and the mentee. Surgical residency program chairs and program directors must recruit and develop faculty "coaches" to mentor residents to optimize their potential. Emeritus Chair of University of California, Los Angeles Head and Neck Surgery, Dr. Paul Ward, said it best: "We strive to produce graduates of our residency program who are among those who change the way we think and practice . . . ." Having more than 25 former residents become chairs of academic head and neck surgical programs, Dr. Ward embodied the role as a surgeon's coach. The responsibilities of an effective mentor are summarized by Barondess: "Mentoring, to be effective, requires of the mentor empathy, maturity, self-confidence, resourcefulness, and willingness to commit time and energy to another. The mentor must be able to offer guidance for a new and evolving professional life, to stimulate and challenge, to encourage self-realization, to foster growth, and to make more comprehensible the landscape in which the protégé stands."[48]

One of the major goals of a mentor is to assess the aptitudes and abilities of the mentee with regard to the appropriateness of their vision for their surgical career. Proper selection of the appropriate mentor can bring to the mentee much needed wisdom, guidance, and resources and can expand the scope of their 9▶ vision. In addition, the mentor can refine the leadership skills taught to their mentees in formal training programs. Highly successful surgeons most often have had excellent surgical mentors. It is impressive to note that more than 50% of United States Nobel laureates have served under other Nobel laureates in the capacity of student, postdoctoral fellow, or junior collaborator.[49] In academic medicine, evidence-based studies have shown benefits to the mentees that include enhanced

research productivity, higher likelihood of obtaining research grants, and greater success in obtaining desired positions in practice or at academic institutions.[50] Mentoring provides benefits to the mentors themselves, including refinement of their own personal leadership skills and a strong sense of satisfaction and accomplishment.

Mentorship is essential to accomplish the successful development of surgical trainees and to help cultivate their vision. Therefore, formal leadership training programs that have a goal of training the future leaders in surgery should include mentoring.

CONCLUSION

Although there are several definitions of leadership and a variety of leadership styles, all end with the common goal of improving patient care in the modern era. All forms of leadership require a vision and willingness—the willingness to assume the responsibility to lead, continue learning, practice effective communication styles, and resolve conflict. Effective leadership can change surgical departments and improve patient care through innovation. A growing body of evidence suggests the mastery of leadership requires practice through intentional curriculum and reinforcement through mentorship.

Surgical leadership is bred through its training programs. Thus, innovation in surgical training programs is needed to enhance the development of leadership skills of surgical trainees, to prepare them for practice in modern healthcare systems, and to optimize patient care, as well as compliance with requirements set forth by regulatory institutions governing surgery and surgical education. A growing body of literature supports the value of effective leadership in improving patient care, productivity, and the work environment while it validates the ability to measure the impact of leadership training. Therefore, it is of paramount importance to teach modern leadership principles and skills to surgical trainees in order to create a new generation of surgeon leaders who will shape the modern era of surgery in the context of rapidly evolving science, technology, and systems of healthcare delivery.

REFERENCES

Entries highlighted in blue are key references.

1. Levinson W, Chaumeton N. Communication between surgeons and patients in routine office visits. *Surgery*. 1999;125:127-134.
2. **Itani KM, Liscum K, Brunicardi FC. Physician leadership is a new mandate in surgical training. *Am J Surg*. 2004; 187:328-331.**
3. Jensen AR, Wright A, Lance A, et al. The emotional intelligence of surgical residents: a descriptive study. *Am J Surg*. 2008;195:5-10.
4. Lee L, Brunicardi FC, Scott BG, et al. Impact of a novel education curriculum on surgical training within an academic training program. *J Surg Res*. 2008;145:308-312.
5. Larkin AC, Cahan MA, Whalen G, et al. Human Emotion and Response in Surgery (HEARS): a simulation-based curriculum for communication skills, systems-based practice, and professionalism in surgical residency training. *J Am Coll Surg*. 2010;211:285-292.
6. Lobas JG. Leadership in academic medicine: capabilities and conditions for organizational success. *Am J Med*. 2006;119: 617-621.
7. Chemers MM. *An Integrative Theory of Leadership.* Mahwah, NJ: Lawrence Erlbaum Associates; 1997:200.
8. Slap S. *Bury My Heart at Conference Room B: The Unbeatable Impact of Truly Committed Managers.* New York, NY: Portfolio Penguin; 2010:234.
9. NobelPrize.org. Frederick G. Banting: Biography. Available at: http://www.nobelprize.org/nobel_prizes/medicine/laureates/1923/banting-bio.html. Accessed June 23, 2013.
10. Brunicardi FC. Presidential Address. Academic program development. *J Surg Res*. 1999;83(1):1-6.
11. **Brunicardi FC, Cotton R, Cole G, et al. The leadership principles of Dr. Martin Luther King, Jr. and their relevance to surgery. *J Natl Med Assoc*. 2007;99:7-14.**
12. Isaacson W. *Steve Jobs*. New York, NY: Simon & Schuster; 2011.
13. Brunicardi FC, Gibbs R, Wheeler D, et al. Overview of the development of personalized genomic medicine and surgery. *World J Surg*. 2011;35:1693-1699.
14. American Board of Surgery CME Requirements for Recertification. Available at: http://www.absurgery.org/default.jsp?newscontinuingmedicaledrequirements. Accessed October 2, 2013.
15. Kohn LT, Corrigan J, Donaldson MS. *To Err Is Human: Building a Safer Health System*. Washington, DC: National Academy Press; 2000.
16. Gawande AA, Zinner MJ, Studdert DM, et al. Analysis of errors reported by surgeons at three teaching hospitals. *Surgery*. 2003;133:614-621.
17. Sutcliffe KM, Lewton E, Rosenthal MM. Communication failures: an insidious contributor to medical mishaps. *Acad Med*. 2004;79:186-194.
18. Williams RG, Silverman R, Schwind C, et al. Surgeon information transfer and communication: factors affecting quality and efficiency of inpatient care. *Ann Surg*. 2007;245:159-169.
19. Ambady N, Laplante D, Nguyen T, et al. Surgeons' tone of voice: a clue to malpractice history. *Surgery*. 2002;132:5-9.
20. Nolin CE. Malpractice claims, patient communication, and critical paths: a lawyer's perspective. *Qual Manag Health Care*. 1995;3:65-70.
21. Stewart MA. Effective physician-patient communication and health outcomes: a review. *CMAJ*. 1995;152:1423-1433.
22. Leonard M. The human factor: the critical importance of effective teamwork and communication in providing safe care. *Qual Safe Health Care*. 2004;13(Suppl 1):i85-i90.
23. **Dine CJ, Kahn JM, Abella BS, et al. Key elements of clinical physician leadership at an academic medical center. *J Grad Med Educ*. 2011;3:31-36.**
24. Pronovost P, Berenholtz S, Dorman T, et al. Improving communication in the ICU using daily goals. *J Crit Care*. 2003;18:71-75.
25. Gurses AP, Kim G, Martinez E, et al. Identifying and categorising patient safety hazards in cardiovascular operating rooms using an interdisciplinary approach: a multisite study. *BMJ Qual Saf*. 2012;21:810-818.
26. Makary MA, Sexton JB, Freischlag JA, et al. Operating room teamwork among physicians and nurses: teamwork in the eye of the beholder. *J Am Coll Surg*. 2006;202:746-752.
27. Weeks D. *The Eight Essential Steps to Conflict Resolution: Preserving Relationships at Work, at Home, and in the Community.* New York, NY: J.P. Tarcher/Perigee; 1994:290.
28. Covey SR. *The Seven Habits of Highly Effective People: Restoring the Character Ethic*. New York, NY: Free Press; 2004.
29. **Lee L, Berger DH, Awad SS, et al. Conflict resolution: practical principles for surgeons. *World J Surg*. 2008;32:2331-2335.**
30. Antiel RM, Reed DA, Van Arendonk KJ, et al. Effects of duty hour restrictions on core competencies, education, quality of life, and burnout among general surgery interns. *JAMA Surg*. 2013;148:448-455.
31. Lyssa Ochoa M. Evaluation of resident training activities using a novel time-motion study prior to the implementation of the 80 hour work week. Chicago, IL: American College of Surgeons Annual Conference, 2006.

32. Brunicardi FC, Hobson FL. Time management: a review for physicians. *J Natl Med Assoc*. 1996;88:581-587.
33. Goleman D. Leadership that gets results. *Harvard Business Review*. 2000;78:78-93.
34. Xirasagar S, Samuels ME, Stoskopf CH. Physician leadership styles and effectiveness: an empirical study. *Med Care Res Rev*. 2005;62:720-740.
35. Baird DS, Soldanska M, Anderson B, et al. Current leadership training in dermatology residency programs: a survey. *J Am Acad Dermatol.* 2012;66:622-625.
36. Kiesau CD, Heim KA, Parekh SG. Leadership and business education in orthopaedic residency training programs. *J Surg Orthop Adv*. 2011;20:117-121.
37. Horwitz IB, Horwitz S, Daram P, et al. Transformational, transactional, and passive-avoidant leadership characteristics of a surgical resident cohort: analysis using the multifactor leadership questionnaire and implications for improving surgical education curriculums. *J Surg Res*. 2008;148:49-59.
38. Ackerly DC, Sangvai DG, Udayakumar K, et al. Training the next generation of physician-executives: an innovative residency pathway in management and leadership. *Acad Med*. 2011;86:575-579.
39. Stoller JK, Rose M, Lee R, et al. Teambuilding and leadership training in an internal medicine residency training program. *J Gen Intern Med*. 2004;19:692-697.
40. Hanna WC, Mulder D, Fried G, et al. Training future surgeons for management roles: the resident-surgeon-manager conference. *Arch Surg*. 2012;147:940-944.
41. Boulanger B, Buencamino A, Dovichi S. Training young pediatricians as leaders. *Pediatrics*. 2005;116:518.
42. Leslie LK, Miotto MB, Liu GC, et al. Training young pediatricians as leaders for the 21st century. *Pediatrics*. 2005;115:765-773.
43. Accreditation Council for Graduate Medical Education. Leadership Skills for Chief Residents. Available at: http://www.acgme.org/acgmeweb/. Accessed January 1, 2014.
44. American College of Surgeons. Surgeons as leaders: from operating room to boardroom. Available at: http://www.facs.org/education/surgeonsasleaders.html. Accessed January 1, 2014.
45. Awad SS, Hayley B, Fagan SP, et al. The impact of a novel resident leadership training curriculum. *Am J Surg*. 2004;188:481-484.
46. Horwitz IB, Horwitz S, Brandt M, et al. Assessment of communication skills of surgical residents using the Social Skills Inventory. *Am J Surg*. 2007;194:401-405.
47. Horwitz IB, Horwitz S, Brunicardi F, et al. Improving comprehensive surgical resident training through use of the NEO Five-Factor Personality Inventory: results from a cohort-based trial. *Am J Surg*. 2011;201:828-834.
48. Barondess JA. On mentoring. *J R Soc Med*. 1997;90:347-349.
49. Zuckerman H. *Scientific Elite: Nobel Laureates in the United States*. New York, NY: Free Press; 1977:335.
50. Sambunjak D, Straus SE, Marusic A. Mentoring in academic medicine: a systematic review. *JAMA*. 2006;296:1103-1115.

chapter 2

Systemic Response to Injury and Metabolic Support

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OVERVIEW: INJURY-ASSOCIATED SYSTEMIC INFLAMMATORY RESPONSE

The inflammatory response to injury or infection occurs as a consequence of the local or systemic release of "pathogen-associated" or "damage-associated" molecules, which use similar signaling pathways to mobilize the necessary resources required for the restoration of homeostasis. Minor host insults result in a localized inflammatory response that is transient and in most cases beneficial. Major host insults, however, may lead to amplified reactions, resulting in systemic inflammation, remote organ damage, and multiple organ failure in as many as 30% of those who are severely injured. Recent data support this idea and suggest that severely injured patients who are destined to die from their injuries differ from survivors only in the degree and duration of their dysregulated acute inflammatory response.[1,2]

This topic is highly relevant because systemic inflammation is a central feature[3] of both sepsis and severe trauma. Understanding the complex pathways that regulate local and systemic inflammation is necessary to develop therapies to intervene during overwhelming sepsis or after severe injury. Sepsis, defined by a systemic inflammatory response to infection, is a disease process with an incidence of over 900,000 cases per year. Further, trauma is the leading cause of mortality and morbidity for individuals under age 45.

*This chapter is dedicated to its previous author, Dr. Stephen Lowry, my mentor and friend.

Key Points

1. Endogenous **damage-associated molecular patterns (DAMPs)** are produced following tissue and cellular injury. These molecules interact with immune and nonimmune cell receptors to initiate a "sterile" systemic inflammatory response following severe traumatic injury.
2. In many cases, DAMP molecules are sensed by **pattern recognition receptors (PRRs),** which are the same receptors that cells use to sense invading pathogens. This explains, in part, the similar clinical picture of systemic inflammation observed in injured and/or septic patients.
3. The central nervous system receives information with regard to injury-induced inflammation via soluble mediators as well as **direct neural projections** that transmit information to regulatory areas in the brain. The resulting neuroendocrine reflex plays an important modulatory role in the immune response.
4. Inflammatory signals activate key **cellular stress responses** (the oxidative stress response, the heat shock protein response, the unfolded protein response, autophagy, and programmed cell death), which serve to mobilize cellular defenses and resources in an attempt to restore homeostasis.
5. The cells, mediators, signaling mechanisms, and pathways that compose and regulate the systemic inflammatory response are **closely networked** and **tightly regulated** by transcriptional events as well as by epigenetic mechanisms, posttranslational modification, and microRNA synthesis.
6. Nutritional assessments, whether clinical or laboratory guided, and intervention should be considered at an early juncture in all surgical and critically ill patients.
7. Management of critically ill and injured patients is optimized with the use of evidence-based and algorithm-driven therapy.

In this chapter, we will review what is known about the soluble and cellular effectors of the injury-induced inflammatory response; how the signals are sensed, transduced, and modulated; and how their dysregulation is associated with immune suppression. We will also discuss how these events are monitored and regulated by the central nervous system. Finally, we will review how injury reprograms cellular metabolism, in an attempt to mobilize energy and structural stores to meet the challenge of restoring homeostasis.

THE DETECTION OF CELLULAR INJURY

The Detection of Injury is Mediated by Members of the Damage-Associated Molecular Pattern Family

Traumatic injury activates the innate immune system to produce a systemic inflammatory response in an attempt to limit damage and to restore homeostasis. It includes two general responses: (a) an acute proinflammatory response resulting from innate immune system recognition of ligands, and (b) an anti-inflammatory response that may serve to modulate the proinflammatory phase and direct a return to homeostasis (Fig. 2-1). This is accompanied by a suppression of adaptive immunity.[4] Rather than occurring sequentially, recent data indicate that all three responses are simultaneously and rapidly induced following severe traumatic injury.[2]

1

The degree of the systemic inflammatory response following trauma is proportional to injury severity and is an independent predictor of subsequent organ dysfunction and resultant mortality. Recent work has provided insight into the mechanisms by which immune activation in this setting is triggered. The clinical features of the injury-mediated systemic inflammatory response, characterized by increased body temperature, heart rate, respirations, and white blood cell count, are similar to those observed with infection (Table 2-1). While significant efforts have been devoted to establishing a microbial etiology for this response, it is now widely accepted that systemic inflammation following trauma is sterile. Although the mechanisms for the sterile response are less well understood, it is likely to result from endogenous molecules that are produced as a consequence of tissue damage or cellular stress, as may occur with hemorrhagic shock and resuscitation.[5] Termed **alarmins or damage-associated molecular patterns (DAMPs),** these effectors, along with the **pathogen-associated molecular patterns (PAMPs)**, interact with specific cell receptors that are located both on the cell surface and intracellularly.[6] The best described of these receptors are members of the toll-like receptor family.

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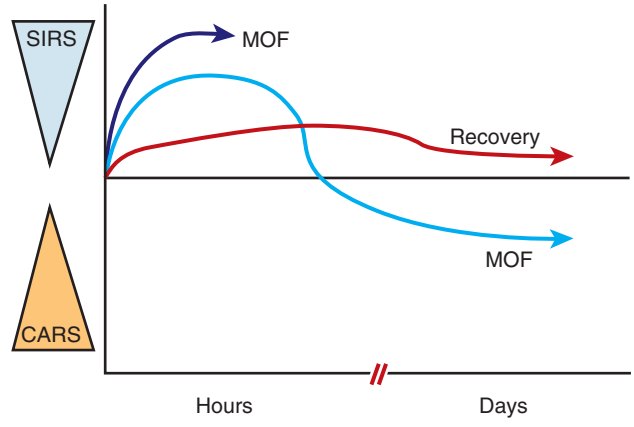

Figure 2-1. Schematic representation of the systemic inflammatory response syndrome (SIRS) after injury, followed by a period of convalescence mediated by the counterregulatory anti-inflammatory response syndrome (CARS). Severe inflammation may lead to acute multiple organ failure (MOF) and early death after injury (*dark blue arrow*). A lesser inflammatory response followed by excessive CARS may induce a prolonged immunosuppressed state that can also be deleterious to the host (*light blue arrow*). Normal recovery after injury requires a period of systemic inflammation followed by a return to homeostasis (*red arrow*). *(Adapted with permission from Guirao X, Lowry SF. Biologic control of injury and inflammation: Much more than too little or too late.* World J Surg. *1996;20:437. With kind permission from Springer Science + Business Media.)*

Table 2-1

Clinical spectrum of infection and systemic inflammatory response syndrome (SIRS)

TERM	DEFINITION
Infection	Identifiable source of microbial insult
SIRS	Two or more of following criteria are met: Temperature ≥38°C (100.4°F) or ≤36°C (96.8°F) Heart rate ≥90 beats per minute Respiratory rate ≥20 breaths per minute or $Paco_2$ ≤32 mmHg or mechanical ventilation White blood cell count ≥12,000/μL or ≤4000/μL or ≥10% band forms
Sepsis	Identifiable source of infection + SIRS
Severe sepsis	Sepsis + organ dysfunction
Septic shock	Sepsis + cardiovascular collapse (requiring vasopressor support)

$Paco_2$ = partial pressure of arterial carbon dioxide.

Trauma DAMPs are structurally diverse endogenous molecules that are immunologically active. Table 2-2 includes a partial list of DAMPs that are released either passively from necrotic/damaged cells or actively from physiologically "stressed" cells by upregulation or overexpression. Once they are outside the cell, DAMPs promote the activation of innate immune cells, as well as the recruitment and activation of antigen-presenting cells, which are engaged in host defense.[7] The best-characterized DAMP with significant preclinical evidence for its release after trauma and with a direct link to the systemic inflammatory response is high-mobility group protein B1 (HMGB1). Additional evidence for the role of DAMP molecules in postinjury inflammation, including mitochondrial proteins and DNA, as well as extracellular matrix molecules, is also presented.

Table 2-2

Damage-associated molecular patterns (DAMPs) and their receptors

DAMP MOLECULE	PUTATIVE RECEPTOR(S)
HMGB1	TLRs (2,4,9), RAGE
Heat shock proteins	TLR2, TLR4, CD40, CD14
S100 protein	RAGE
Mitochondrial DNA	TLR9
Hyaluronan	TLR2, TLR4, CD44
Biglycan	TLR2 and TLR4
Formyl peptides (mitochondrial)	Formyl peptide receptor 1
IL-1α	IL-1 receptor

HMGB1 = high-mobility group protein B1; IL = interleukin; RAGE = receptor for advanced glycosylation end products; TLK = toll-like receptor.

High-Mobility Group Protein B1. The best-characterized DAMP in the context of the injury-associated inflammatory response is HMGB1 protein, which is rapidly released into the circulation within 30 minutes following trauma. HMGB1 is highly evolutionarily conserved across species. It was first described as a constitutively expressed, nonhistone chromosomal protein that participated in a variety of nuclear events, including DNA repair and transcription. HMGB1 was also detected in the cytosol and extracellular fluids at low levels, although its function outside the cell was not clear. Subsequent studies have proven, however, that HMGB1 is actively secreted from immune-competent cells stimulated by PAMPs (e.g., endotoxin) or by inflammatory cytokines (e.g., tumor necrosis factor and interleukin-1). This process occurs outside the classic secretory pathway via a mechanism that is independent of endoplasmic reticulum and the Golgi complex. Moreover, recent data indicate that HMGB1 release can be regulated by the inflammasome.[8] Stressed nonimmune cells such as endothelial cells and platelet also actively secrete HMGB1. Finally, passive release of HMGB1 can occur following cell death, whether it is programmed or uncontrolled (necrosis).

Once outside the cell, HMGB1 interacts with its putative receptors either alone or in concert with pathogenic molecules to activate the immune response, and in this way, functions as a proinflammatory cytokine. HMGB1 has been shown to signal via the toll-like receptors (TLR2, TLR4, TLR9), the receptor for advanced glycosylation end products (RAGE), CD24, and others. The activation of TLRs mainly occurs in myeloid cells, whereas RAGE is thought to be the receptor target in endothelial and somatic cells. The diverse proinflammatory biologic responses that result from HMGB1 signaling include: (a) the release of cytokines and chemokines from macrophages/monocytes and dendritic cells; (b) neutrophil activation and chemotaxis; (c) alterations in epithelial barrier function, including increased permeability; and (d) increased procoagulant activity on platelet surfaces, among others.[9] In particular, HMGB1 binding to TLR4 triggers the proinflammatory cytokine release that mediates "sickness behavior." This effect is dependent on the highly conserved domain structure of HMGB1 that can be recapitulated by a synthetic 20-amino acid peptide containing a critical cysteine residue at position 106.[10]

Recent data have explored the role of this cysteine residue, as well as two others that are highly conserved, in the biologic function of HMGB1. They demonstrate that the redox state of the three residues regulates the receptor binding ability of HMGB1 to influence its activity, including cytokine production. For example, a thiol at C106 is required for HMGB1 to promote macrophage tumor necrosis factor (TNF) release. In addition, a disulfide bond between C23 and C45 is also required for cytokine release because reduction of the disulfide linkage or further oxidation will reduce the ability of HMGB1 to function as a cytokine. Therefore, if all three cysteine residues are in reduced form, HMGB1 lacks the ability to bind and signal through TLR4, but gains the capacity to bind to CXCL12 to activate CXCR4 and serve as a chemotactic mediator. Importantly, shifts between the redox states have been demonstrated and indicate that redox state dynamics are important regulators of HMGB1.[11]

Importantly, HMGB1 levels in human subjects following injury correlate with the Injury Severity Score, complement activation, and an increase in circulating inflammatory mediators such as TNF.[12] Unchecked, excessive HMGB1 has the capacity

to promote a self-injurious innate immune response. In fact, exogenous administration of HMGB1 to normal animals produces fever, weight loss, epithelial barrier dysfunction, and even death.

A Role for Mitochondrial DAMPs in the Injury-Mediated Inflammatory Response. Mitochondrial proteins and/or DNA can act as DAMPs by triggering an inflammatory response to necrosis and cellular stress. Specifically, the release of mitochondrial DNA (mtDNA) and formyl peptides from damaged or dysfunctional mitochondria has been implicated in activation of the macrophage **inflammasome**, a cytosolic signaling complex that responds to cellular stress. In support of this idea, plasma mtDNA has been shown to be thousands of times higher in both trauma patients and patients undergoing femoral fracture repair when compared to normal volunteers. Further, direct injection of mitochondria lysates in an animal model caused remote organ damage, including liver and lung inflammation.[13] These data suggest that with stress or tissue injury, mtDNA and peptides are released from damaged mitochondria where they can contribute to a sterile inflammatory response. From an evolutionary perspective, given that eukaryotic mitochondria derive from bacterial origin, it would make sense that they retain bacterial features capable of eliciting a strong response that is typically associated with a pathogen trigger. For example, mtDNA is circular and contains hypomethylated CpG motifs that resemble bacterial CpG DNA. It is thus capable of producing formylated peptides, which potently induce an inflammatory phenotype in neutrophils, by increasing chemotaxis, oxidative burst, and cytokine secretion. In addition, the mitochondrial transcription factor A (TFAM), a highly abundant mitochondrial protein, is functionally and structurally homologous to HMGB1. It has also been shown be released in high amounts from damaged cells where it acts in conjunction with mtDNA to activate TLR9 signaling.[14]

Extracellular Matrix Molecules Act as DAMPs. Recent work has explored the role of extracellular matrix (ECM) proteins in the TLR-mediated inflammatory response that follows tissue injury. These molecules, which are sequestered under normal conditions, can be released in a soluble form with proteolytic digestion of the ECM. Proteoglycans, glycosaminoglycans, and glycoproteins such as fibronectin have all been implicated as key players in the DAMP/TLR interaction. Proteoglycans, in particular, have also been shown to activate the intracellular inflammasomes that trigger sterile inflammation. These molecules, which consist of a protein core with one or more covalently attached glycosaminoglycan chains, can be membrane-bound, secreted, or proteolytically cleaved and shed from the cell surface.

Biglycan is one of the first proteoglycans to be described as a TLR ligand.[15] It consists of a protein core containing leucine-rich repeat regions, with two glycosaminoglycan (GAG) side chains (chondroitin sulfate or dermatan sulfate). Although biglycan typically exists in a matrix-bound form, with tissue injury, it is released from the ECM in a soluble form where it interacts with TLR2 or TLR4 to generate an immediate inflammatory response.

Various proinflammatory cytokines and chemokines, including TNF-α and interleukin (IL)-1β, are downstream effector molecules of biglycan/TLR2/4 signaling. Among these, the mechanism of biglycan-mediated autonomous synthesis and secretion of mature IL-1β is unique. Usually, release of mature IL-1β from the cell requires two signals, one which is needed to initiate synthesis (TLR2/4-mediated) and the other to process pro-IL-1β to its mature form (inflammasome-mediated). How is it possible for biglycan to provide both signals? Current evidence indicates that when soluble biglycan binds to the TLR, it simultaneously serves as a ligand for a purinergic receptor, which facilitates the inflammasome activation required for IL-1β processing.[16] These data support the idea that DAMP-mediated signals can initiate a robust inflammatory response.

DAMPs Are Ligands for Pattern Recognition Receptors

The inflammatory response that occurs following traumatic injury is similar to that observed with pathogen exposure. 2▶ Not surprising, surface and cytoplasmic receptors that mediate the innate immune response to microbial infection have been implicated in the activation of sterile inflammation. In support of this idea, genes have been identified that are dysregulated acutely both in response to a microbial ligand administered to human volunteers and in response to traumatic injury in a large patient population.[17] The classes of receptors that are important for sensing damaged cells and cell debris are part of the larger group of germline encoded **pattern recognition receptors** (PRRs). The best-described ligands for these receptors are microbial components, the PAMPs. The PRRs of the innate immune system fall into at least four distinct classes: TLRs, calcium-dependent (C-type) lectin receptors (CLRs), retinoic acid–inducible gene (RIG)-I-like receptors (RLRs), and the nucleotide-binding domain, leucine-rich repeat–containing (NBD-LRR) proteins (NLRs; also nucleotide-binding and oligomerization domain [NOD]-like receptors). Following receptor ligation, intracellular signaling modulates transcriptional and posttranslational events necessary for host defense by coordinating the synthesis and release of cytokines and chemokines to either initiate or suppress the inflammatory response. The best described of these, the TLRs, NLRs, and CLRs, are discussed in the following sections.

Toll-Like Receptors. The TLRs are evolutionarily conserved type 1 transmembrane proteins that are the best-characterized PRRs in mammalian cells. They were first identified in *Drosophila,* where a mutation in the *Toll* gene led to its identification as a key component in their immune defense against fungal infection. The first human TLR, TLR4, was identified shortly thereafter. Now, more than 10 human TLR family members have been identified, with distinct ligands that include lipid, carbohydrate, peptide, and nucleic acid components of various pathogens. TLRs are expressed on both immune and nonimmune cells. At first, the expression of TLR was thought to be isolated to professional antigen-presenting cells such as dendritic cells and macrophages. However, mRNA for TLR family members have been detected in most cells of myeloid lineage, as well as natural killer (NK) cells.[18] In addition, activation of T cells increases their TLR expression and induces their survival and clonal expansion. Direct engagement of TLR in T-regulatory (Treg) cells promotes their expansion and reprograms them to differentiate into T helper cells, which in turn provides help to effector cells. In addition, B cells express a distinct subset of the TLR family that determines their ability to respond to DAMPs; however, the significance of restricted TLR expression in these cells is not yet clear.

All TLRs consist of an extracellular domain, characterized by multiple leucine-rich repeats (LRRs), and a carboxy-terminal, intracellular toll/IL-1 receptor (TIR) domain. The LRR domains recognize bacterial and viral PAMPs in the extracellular environment (TLR1, TLR2, TLR4, TLR5, TLR6, and TLR11) or in the endolysosomes (TLR3, TLR7, TLR8, TLR9, and TLR10). Although the role of TLRs in sepsis has been well described, more recent data indicate that a subset of the TLRs, TLR4 in particular, also recognizes DAMPs released from injured cells and tissues.[19] Signal transduction occurs with receptor dimerization and recruitment of cytoplasmic adaptor proteins. These adaptor molecules initiate and amplify downstream signals, resulting in the activation of transcription. The transcription factors, which include nuclear factor-κB (NF-κB), activator protein (AP)-1, and interferon regulatory factor (IRF), bind to regulatory elements in promoters and/or enhancers of target genes leading to the upregulation of a large cohort of genes that include interferon (IFN)-α and IFN-β, nitric oxide synthase 2 (NOS2A), and TNF, which play critical roles in initiating innate immune responses to cellular injury and stress. Given the importance of TLR triggering of the innate immune response to immune homeostasis, it is no surprise that the process is tightly regulated. TLR expression is significantly increased following blunt traumatic injury. Further, TLR signaling is controlled at multiple levels, both posttranscriptionally via ubiquitination, phosphorylation, and microRNA actions that affect mRNA stability, as well as by the localization of the TLRs and their signaling complexes within the cell.

Nucleotide-Binding Oligomerization Domain-Like Receptor Family. The NLRs are a large family of proteins composed of intracellular PRRs that sense both endogenous (DAMPs) and exogenous (PAMPs) molecules to trigger innate immune activation. The best characterized of the NLRs is the NLR family pyrin domain-containing 3 (NLRP3), which is highly expressed in peripheral blood leukocytes. It forms the key "sensing" component of the larger, multiprotein **inflammasome** complex, which is composed of NLRP3; the adapter protein apoptosis-associated speck-like protein containing a CARD (ASC); and the effector protein, caspase 1.[20] In the cytoplasm, the receptor resides in an inactive form due to an internal interaction between two adjacent and highly conserved domains. In conjunction with a priming event, such as mitochondrial stress, phagocytosed DAMPs can be sensed by NLRP3, resulting in the removal of the self-repression. The protein can then oligomerize and recruit other complex members. The net result is the autoactivation of pro-caspase 1 to **caspase 1**. The NLRP3 inflammasome plays a central role in immune regulation by initiating the caspase 1–dependent processing and secretion of the proinflammatory cytokines IL-1β and IL-18. In fact, NLRP3 is the key protein in the mechanism by which IL-1β production is regulated in macrophages. NLRP3 inflammasome activity is tightly regulated by cell-cell interactions, cellular ion flux, and oxidative stress in order to maintain a balanced immune response to danger signals.

While the role of the NLRP3 inflammasome in the sterile inflammatory response following trauma has not been well described, recent evidence suggests that genetic variations in the *NLRP3* gene might affect the magnitude of immune inflammatory responses following trauma. Single nucleotide polymorphisms within the *NLRP3* gene were found to be associated with increased risk of sepsis and multiple organ dysfunction syndrome in patients with major trauma.[21] In an animal model of burn injury, early inflammasome activation has been detected in a variety of immune cells (NK cells, CD4/CD8 T cells, and B cells), as determined by the assessment of caspase 1 cleavage by flow cytometry.[22] Further, inhibition of caspase 1 activity in vivo results in increased burn mortality, suggesting that inflammasome activation may play an unanticipated protective role in the host response to injury that may be linked to increased production of specific cytokines. In addition to the NLRP3 inflammasome, there are numerous other NLRP sensors that are capable of detecting a diverse range of molecular targets. Among them are those endogenous molecules that are released as a consequence of tissue injury and cellular stress (hypoxia/hypoperfusion).

C-Type Lectin Receptors. Macrophages and dendritic cells possess receptors that detect molecules released from damaged or dying cells in order to retrieve and process antigens from cell corpses for T-cell presentation. A key family of receptors that directs this process is the CLR family that includes the selectin and the mannose receptor families and that binds carbohydrates in a calcium-dependent fashion. Best described for their sensing of PAMPs, particularly fungal antigens, the CLRs can also act to promote the endocytosis and clearance of cell corpses. More recent work has demonstrated, however, that a subset of CLR receptors such as dendritic cell-NK lectin group receptor-1 (DNGR-1) and macrophage-inducible C-type lectin receptor (Mincle) recognize DAMPS of intracellular origin, such as F-actin and the ribonucleoprotein SAP-130.[23] Ligation and activation of Mincle promotes its interaction with an Fcγ receptor, which contains immunoreceptor tyrosine-based activation motifs. This leads to proinflammatory cytokine, chemokine, and nitric oxide production, in addition to neutrophil recruitment. In this way, Mincle may contribute to local inflammation at sites of tissue injury.

Soluble Pattern Recognition Molecules: The Pentraxins. Soluble pattern recognition molecules (PRMs) are a molecularly diverse group of molecules that share a conserved mode of action that is defined by complement activation, agglutination and neutralization, and opsonization. The best described of the PRMs are the **pentraxins**. PRMs can be synthesized at sites of injury and inflammation by macrophages and dendritic cells, while neutrophils can store PRMs and can release them rapidly following activation. In addition, epithelial tissues (the liver in particular) serve as a reservoir source for systemic mass release. The short pentraxin, **C-reactive protein** (CRP), was the first PRM to be identified. Serum amyloid protein (SAP), which has 51% sequence similarity to human CRP, also contains the pentraxin molecular signature. CRP and SAP plasma levels are low (≤3 mg/L) under normal circumstances. However, CRP is synthesized by the liver in response to IL-6, increasing serum levels more than a 1000-fold. Thus, CRP is considered part of the **acute-phase protein response** in humans. For this reason, CRP has been studied as a marker of the proinflammatory response in many clinical settings, including appendicitis, vasculitis, and ulcerative colitis. CRP and SAP are ancient immune molecules that share many functional properties with antibodies: they bind bacterial polysaccharides, ECM components, apoptotic cells, and nuclear materials, as well as all three classes of Fcγ receptors (FcγR). Both molecules also participate in the activation and regulation of complement pathways. In this way, short pentraxins can link immune cells to the complement system.[24]

Finally, significant data support a role for pentraxin 3 (PTX3), a long pentraxin family member, in the "sterile"

inflammatory response associated with cellular stress. While CRP is produced solely in the liver, PTX3 is produced by various cells in peripheral tissues, including immune cells. PTX3 plasma concentrations increase rapidly in various inflammatory conditions, including sepsis. Further, in a recent prospective study of polytraumatized patients, serum PTX3 concentrations were highly elevated, peaking at 24 hours. In addition, PTX3 concentrations at admission were associated with injury severity, whereas higher PTX3 serum concentrations 24 hours after admission correlated with lower probability for survival.[25]

Pattern Recognition Receptor Signaling: Toll-Like Receptors and the Inflammasome

As noted earlier, members of the TLR family respond to endogenous molecules released from damaged or stressed cells. In animal models, activation of TLRs in the absence of bacterial pathogens correlates with the development of critical illness including "sterile inflammation." What we know about TLR signaling events has largely been derived from the TLR-mediated response to bacterial pathogens. However, it is likely that the intracellular adaptors required for signal transmission by TLRs in response to exogenous ligands are conserved and used for "damage" sensing of endogenous ("self") ligands as well. The intracellular domain structure of TLRs is highly conserved and is characterized by a cytoplasmic toll/IL-1R homology (TIR) domain. Binding of ligand to the receptor results in a receptor dimer, either a homodimer (e.g., TLR4/TLR4) or heterodimer (e.g., TLR2/TLR1), which recruits a number of adaptor proteins to the TIR domains, through TIR-TIR interaction.[26] With one exception (TLR3), the universal adaptor protein central to the TLR signaling complex is myeloid differentiation factor 88 (MyD88), a member of the IL-1 receptor subfamily. MyD88 works through the recruitment of a second TIR-containing adaptor, MyD88 adaptor-like protein (Mal), in the context of TLR4 and TLR2 signaling, which serves as a bridge between MyD88 and activated TLRs to initiate signal transduction. It is interesting that Mal's adaptor function requires cleavage of the carboxy-terminal portion of the protein by **caspase 1,** a key effector of the inflammasome.[27] This finding suggests an important synergy between TLRs and NLRs that may potentiate TLR-mediated signaling. There are three other TIR domain-containing adaptor proteins that are also important to TLR-signaling events; these are TIR-domain-containing adapter-inducing INF-β (TRIF), TRIF-related adaptor molecule (TRAM), and sterile α- (SAM) and HEAT/armadillo (ARM) motif-containing protein (SARM). Two of these, TRIF and TRAM, are involved in the *MyD88-independent* signaling pathways, which are activated by TLR3 and TLR4.

Signaling through the MyD88-dependent pathway results in the activation of numerous cytoplasmic protein kinases including IL-1 receptor–associated kinases (IRAK-1 and IRAK-4), resulting in an interaction with TNF receptor–associated factor 6 (TRAF6). TRAF6, an E3 ubiquitin ligase, forms a complex with two other proteins, which together activate the complex that subsequently phosphorylates IκB kinase (IKK)-β and the MAP kinases (MAPKs). Ultimately, the phosphorylation of IκB by the IKK complex and NEMO (NF-κB essential modulator) leads to its degradation, which frees NF-κB and allows its translocation to the nucleus and the transcription of **NF-κB target genes**. Simultaneously, MAPK activation is critical for activation of the activator protein-1 (AP-1) transcription factor, and thus production of **inflammatory cytokines**. The MyD88-independent pathway acts through TRIF to activate NF-κB, similar to the MyD88-dependent pathway. However, TRIF can also recruit other signaling molecules to phosphorylate interferon-regulatory factor 3 (IRF3), which induces expression of type I IFN genes.[26]

Signaling from the Inflammasome. As discussed earlier, activation and assembly of the inflammasome in response to DAMP sensing result in the cleavage of pro-caspase 1 into two products. This event is pivotal to all known inflammasome signaling pathways. The caspase 1 products assemble to form the **IL-1 converting enzyme** (ICE), which cleaves the IL-1 cytokines, IL-1β, IL-18, and IL-33. This final step is required for activation and secretion of the cytokines from the cell.[20] IL-1β and IL-18 are potent proinflammatory cytokines that promote key immune responses that are essential to host defense. Thus, the synthesis, processing, and secretion of these cytokines are tightly regulated, as successful cytokine release requires a two-step process. The first signal, which is typically TLR-mediated, initiates the synthesis and storage of the inactive cytokine precursors in the cytoplasm. The second signal, which is inflammasome-mediated, initiates proteolytic cleavage of the procytokine, which is a requirement for its activation and secretion from the cell. Of further interest, evidence has demonstrated that both IL-1β and IL-18 lack a signal sequence, which is usually necessary for those proteins that are destined for cellular export. These signal peptides target proteins to the endoplasmic reticulum (ER) and to the Golgi complex, where they are packaged for secretion from the cell through the classical secretory pathway. More than 20 proteins in addition to IL-1β and IL-18 undergo **unconventional protein secretion** independent of the ER and Golgi complex.[28] The list includes signaling molecules involved in inflammatory, cell survival, and repair responses, such as HMGB1, IL-1α, galectins 1 and 3, and FGF2. Currently, the mechanisms responsible for unconventional protein secretion are not understood; however, the process is also evident in yeast under conditions of cellular stress. It makes evolutionary sense that a mechanism for rapid secretion of stored proteins essential to the stress response is highly conserved.

CENTRAL NERVOUS SYSTEM REGULATION OF INFLAMMATION IN RESPONSE TO INJURY

The central nervous system (CNS) communicates with the body through ordered systems of sensory and motor neurons, which receive and integrate information to generate a coordinated response. Rather than being an immune-privileged organ, recent work indicates that the CNS receives information with regard to injury-induced inflammation both via soluble mediators as well as direct neural projections that transmit information to regulatory areas in the brain (Fig. 2-2). How does the CNS sense inflammation? DAMPs and inflammatory molecules convey stimulatory signals to the CNS via multiples routes. For example, soluble inflammatory signaling molecules from the periphery can reach neurons and glial cells directly through the fenestrated endothelium of the circumventricular organs (CVO) or via a leaky blood brain barrier in pathologic settings such as may occur following a traumatic brain injury.[29] In addition, inflammatory stimuli can interact with receptors located on the brain endothelial cells to generate a variety of proinflammatory mediators (cytokines, chemokines, adhesion molecules, proteins of the complement system, and immune receptors) that directly impact the brain parenchyma. Not surprising, this

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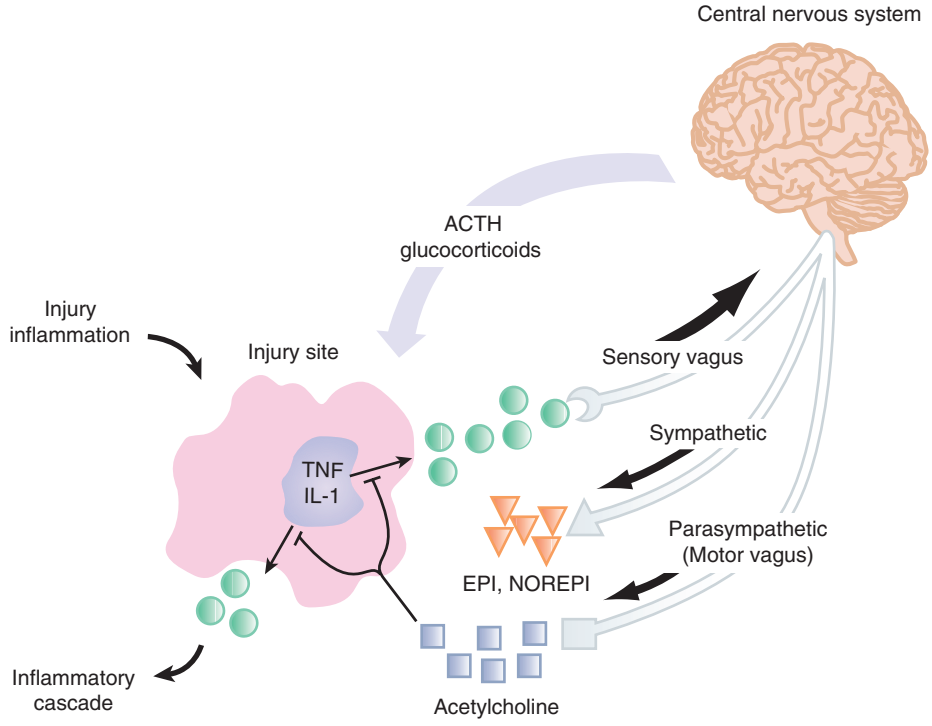

Figure 2-2. Neural circuit relaying messages of localized injury to the brain (nucleus tractus solitarius). The brain follows with a hormone release (adrenocorticotropic hormone [ACTH], glucocorticoids) into the systemic circulation and by sympathetic response. The vagal response rapidly induces acetylcholine release directed at the site of injury to curtail the inflammatory response elicited by the activated immunocytes. This vagal response occurs in real time and is site specific. EPI = epinephrine; IL-1 = interleukin-1; NOREPI = norepinephrine; TNF = tumor necrosis factor. *(Adapted and re-created with permission from Macmillan Publishers Ltd. Tracey KJ. The inflammatory reflex.* Nature. *2002;420:853. Copyright © 2002.)*

response is countered by potent anti-inflammatory signaling, a portion of which is provided by the hypothalamic-pituitary-adrenal (HPA) axis and the release of systemic glucocorticoids. Inflammatory stimuli in the CNS result in behavioral changes, such as increased sleep, lethargy, reduced appetite, and the most common feature of infection, fever.

Information regarding peripheral inflammation and tissue damage can also be signaled to the brain via afferent neural fibers, particularly those of the vagus nerve.[30] These afferent fibers can interconnect with neurons that project to the hypothalamus to modulate the HPA axis. In addition, afferent vagal nerve impulses modulate cells in the brain stem, at the dorsal motor nucleus of the vagus, from which efferent preganglionic parasympathetic impulses originate. Axons from these cells, which comprise the visceromotor component of the vagus nerve, form an "inflammatory reflex" that feeds back to the periphery to regulate inflammatory signaling events.[31] Although the mechanisms by which cholinergic signals from the CNS regulate immune cells in the periphery are incompletely understood, recent evidence has provided some mechanistic insight. The first line of evidence to support this idea is the observation that vagal stimulation reduces proinflammatory cytokine production from the spleen in several experimental models systems.[32] This effect is dependent on both the vagal efferent signals and, in part, splenic catecholaminergic nerve fibers that originate in the celiac plexus and that terminate in a T-cell–rich area of the spleen. Interestingly, these signals propagated by adrenergic nerves result in measurable increases in acetylcholine (ACh) levels in the spleen. In addition, the resident immune cells in the spleen require the expression of cholinergic receptors, specifically α7 nicotinic acetylcholine receptors (α7nAChR), for the suppression of cytokine synthesis.[33] How is this effect mediated? The apparent source of ACh is choline-acetyltransferase–expressing T cells, which compose 2% to 3% of $CD4^+$ T cells in the spleen and are capable of ACh production. Data also indicate that the vagus nerve may regulate inflammation in tissues that it directly innervates.

Neuroendocrine Response to Injury

Traumatic injury results in complex neuroendocrine signaling from the brain that serves to enhance immune defense and rapidly mobilize substrates necessary to meet essential energy and structural needs. The two principle neuroendocrine pathways that orchestrate the host response are the **hypothalamic-pituitary-adrenal (HPA) axis**, which results in the release of glucocorticoid hormones, and the **sympathetic nervous system**, which results in release of the catecholamines, epinephrine, and norepinephrine. Virtually every hormone of the HPA axis influences the physiologic response to injury and stress (Table 2-3), but some with direct influence on the inflammatory response or immediate clinical impact are highlighted here, including growth hormone (GH), macrophage inhibitory factor (MIF), aldosterone, and insulin.

The Hypothalamic-Pituitary-Adrenal Axis. One of the main mechanisms by which the brain responds to injury-associated stress is through activation of the HPA axis. Following injury, corticotrophin-releasing hormone (CRH) is secreted from the paraventricular nucleus (PVN) of the hypothalamus. This action is mediated in part by circulating cytokines produced as

Table 2-3

Hormones regulated by the hypothalamus, pituitary, and autonomic system

Hypothalamic Regulation
Corticotropin-releasing hormone
Thyrotropin-releasing hormone
Growth hormone–releasing hormone
Luteinizing hormone–releasing hormone
Anterior Pituitary Regulation
Adrenocorticotropic hormone
Cortisol
Thyroid-stimulating hormone
Thyroxine
Triiodothyronine
Growth hormone
Gonadotrophins
Sex hormones
Insulin-like growth factor
Somatostatin
Prolactin
Endorphins
Posterior Pituitary Regulation
Vasopressin
Oxytocin
Autonomic System
Norepinephrine
Epinephrine
Aldosterone
Renin-Angiotensin System
Insulin
Glucagon
Enkephalins

a result of the innate immune response to injury. These include TNF-α, IL-1β, IL-6, and the type I IFNs (IFN-α/β). Cytokines that are produced as a result of the adaptive immune response (IL-2 and IFN-γ) are also capable of increasing cortisol release. Direct neural input via afferent vagal fibers that interconnect with neurons projecting to the hypothalamus can also trigger CRH release. CRH acts on the anterior pituitary to stimulate the secretion of adrenocorticotropin hormone (ACTH) into the systemic circulation. Interestingly, the cytokines that act on the hypothalamus are also capable of stimulating ACTH release from the anterior pituitary so that marked elevations in ACTH and in cortisol can occur that are proportional in magnitude to the injury severity. Additionally, pain, anxiety, vasopressin, angiotensin II, cholecystokinin, vasoactive intestinal peptide, and catecholamines all contribute to ACTH release in the injured patient.

ACTH acts on the zona fasciculata of the adrenal glands to synthesize and secrete glucocorticoids (Fig. 2-3). Cortisol is the major glucocorticoid in humans and is essential for survival during significant physiologic stress. The resulting increase in cortisol levels following trauma have several important anti-inflammatory actions.

Cortisol elicits its many actions through a cytosolic receptor, the glucocorticoid receptor (GR). Because it is lipid soluble, cortisol can diffuse through the plasma membrane to interact with its receptor, which is sequestered in the cytoplasm in a complex with heat shock proteins (Fig. 2-4). Upon ligand binding, the GR is activated and can employ a number of mechanisms to modulate proinflammatory gene transcription and signaling events, with a "net" anti-inflammatory effect.[34] For example, the activated GR complex can interact with transcription factors to sequester them in the cytoplasm, promote their degradation, or inhibit them through other mechanisms. Affected target genes include proinflammatory cytokines, growth factors, adhesion molecules, and nitric oxide. In addition, glucocorticoids can negatively affect the access of the transcription factor, NF-κB,

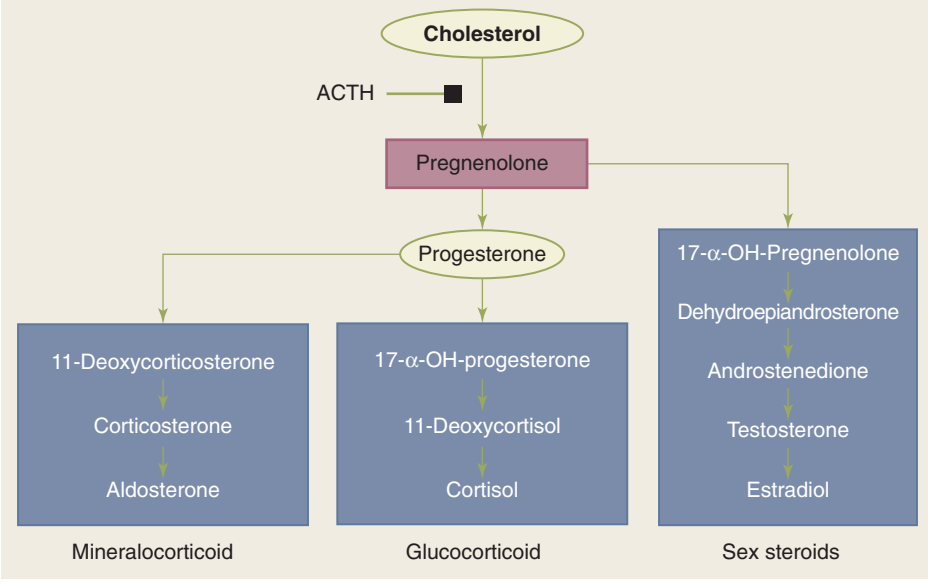

Figure 2-3. Steroid synthesis from cholesterol. Adrenocorticotropic hormone (ACTH) is a principal regulator of steroid synthesis. The end products are mineralocorticoids, glucocorticoids, and sex steroids.

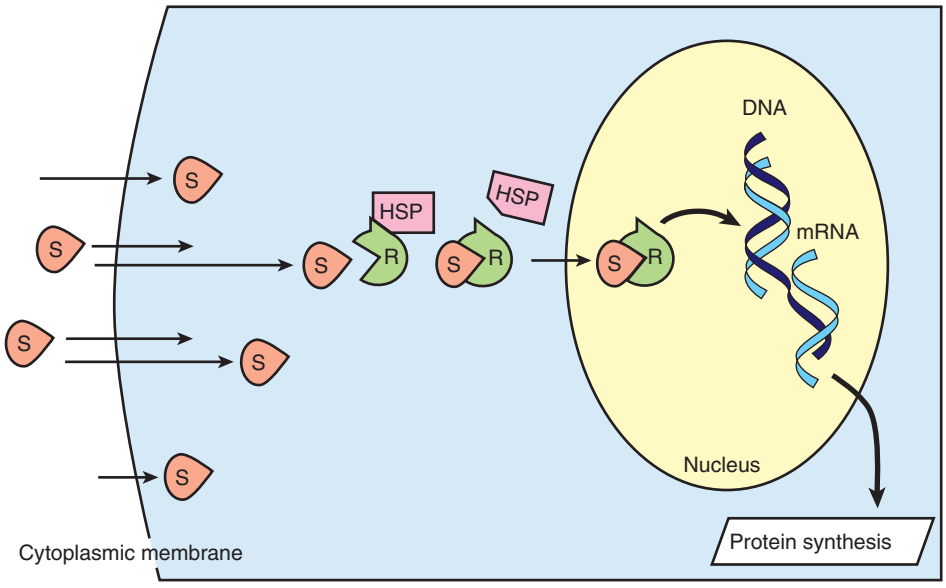

Figure 2-4. Simplified schematic of steroid transport into the nucleus. Steroid molecules (S) diffuse readily across cytoplasmic membranes. Intracellularly, the receptors (R) are rendered inactive by being coupled to heat shock protein (HSP). When S and R bind, HSP dissociates, and the S-R complex enters the nucleus, where the S-R complex induces DNA transcription, resulting in protein synthesis. mRNA = messenger RNA.

to the promoter regions of its target genes via a mechanism that involves histone deacetylase 2. In this way, glucocorticoids can inhibit a major mechanism by which TLR ligation induces proinflammatory gene expression.[35] The GR complex can also bind to specific nucleotide sequences (termed glucocorticoid response elements) to promote the transcription of genes that have anti-inflammatory functions. These include IL-10 and IL-1 receptor antagonist. Further, GR complex activation can indirectly influence TLR activity via an interaction with signaling pathways such as the mitogen-activated protein kinase and transforming growth factor–activated kinase-1 (TAK1) pathways. Finally, a recent report demonstrated that the GR complex can target both suppressor of cytokine signaling 1 (SOCS1) and type 1 IFNs to regulate TLR-induced STAT1 activation.[36]

Adrenal insufficiency represents a clinical syndrome highlighted largely by inadequate amounts of circulating cortisol and aldosterone. Classically, adrenal insufficiency is described in patients with atrophic adrenal glands caused by exogenous steroid administration who undergo a stressor such as surgery. These patients subsequently manifest signs and symptoms such as tachycardia, hypotension, weakness, nausea, vomiting, and fever. Critical illness may be associated with a **relative adrenal insufficiency** such that the adrenal gland cannot mount an effective cortisol response to match the degree of injury. More recently, investigators have determined that critical illness-associated cortisol insufficiency in trauma patients occurs more frequently than previously thought.[37] It has a bimodal presentation in which the patient is at increased risk both early following the injury-associated inflammatory response and in a delayed fashion, with sepsis being the initiating event. Laboratory findings in adrenal insufficiency include hypoglycemia from decreased gluconeogenesis, hyponatremia from impaired renal tubular sodium resorption, and hyperkalemia from diminished kaliuresis. Rigorous testing to establish the diagnosis includes monitoring of basal and ACTH-stimulated cortisol levels, both of which are lower than normal during adrenal insufficiency. Treatment strategies remain controversial; however, they include low-dose steroid supplementation.[38]

Macrophage Inhibitory Factor Modulates Cortisol Function. Macrophage inhibitory factor (MIF) is a proinflammatory cytokine expressed by a variety of cells and tissues, including the anterior pituitary, macrophages, and T lymphocytes. Several important functions of MIF in innate and adaptive immune responses and in inflammation have been described, supporting the idea that MIF may function to counteract the anti-inflammatory activity of glucocorticoids.[39] For example, MIF has been reported to play a central role in the exacerbation of inflammation associated with acute lung injury, where it has been detected in the affected lungs and in alveolar macrophages. MIF has also been reported to upregulate the expression of TLR4 in macrophages.[40] Finally, an early increase in plasma MIF has been detected in severely injured patients and was found to correlate with NF-κB translocation and respiratory burst in polymorphonuclear lymphocytes (PMNs) derived from severely injured patients. Further, nonsurvivors were shown to have higher serum MIF concentrations early after injury than survivors.[41] These data suggest that targeting MIF after injury may be beneficial in preventing early PMN activation and subsequent organ failure in severely injured patients.

Growth Hormone, Insulin-Like Growth Factor, and Ghrelin. Growth hormone (GH) is a neurohormone expressed primarily by the pituitary gland that has both metabolic and immunomodulatory effects. GH promotes protein synthesis and insulin resistance and enhances the mobilization of fat stores. GH secretion is upregulated by hypothalamic GH-releasing hormone and downregulated by somatostatin. GH primarily exerts its downstream effects through direct interaction with GH receptors and through the enhanced hepatic synthesis of insulin-like growth factor (IGF)-1, an anabolic growth factor that is known to improve the metabolic rate, gut mucosal function, and protein loss after traumatic injury. Less than 5% of IGF-1 circulates free in the plasma, with the remainder bound principally to one of six IGF-binding proteins (IGFBPs), the majority to IGFBP-3. In the liver, IGF stimulates protein synthesis and glycogenesis; in adipose tissue, it increases glucose uptake and lipid utilization; and in skeletal muscles, it mediates glucose uptake and protein synthesis. In addition to its effects on cellular metabolism, GH enhances phagocytic activity of immunocytes through increased lysosomal superoxide production. It also increases the

proliferation of T-cell populations.[42] The catabolic state that follows severe injury has been linked to the suppression of the GH-IGF-IGFBP axis, as critical illness is associated with decreased circulating IGF levels. Not surprising, the administration of exogenous recombinant human GH (rhGH) has been studied in a prospective, randomized trial of critically ill patients where it was associated with increased mortality, prolonged ventilator dependence, and increased susceptibility to infection.[43] More recently, circulating GH levels were examined on admission in 103 consecutive critically ill adult patients. In this study, circulating GH levels were about seven-fold increased in the 24 nonsurvivors when compared with survivors, and GH level was an independent predictor of mortality, along with the APACHE II/SAPS II scores. In distinct contrast, the effect of rhGH administration in severely burned children, both acutely and following prolonged treatment, has been proven to be beneficial. Pediatric burn patients receiving rhGH demonstrated markedly improved growth and lean body mass, whereas hypermetabolism was significantly attenuated.[44] This finding was associated with significant increases in serum GH, IGF-1, and IGFBP-3.

Ghrelin, a natural ligand for the GH-secretagogue receptor 1a (GHS-R1a), is an appetite stimulant that is secreted by the stomach. GHS-R1a is expressed in a variety of tissues in different concentrations including the immune cells, B and T cells, and neutrophils. Ghrelin seems to play a role in promoting GH secretion and in glucose homeostasis, lipid metabolism, and immune function. In a rodent gut ischemia/reperfusion model, ghrelin administration inhibited proinflammatory cytokine release, reduced neutrophil infiltration, ameliorated intestinal barrier dysfunction, attenuated organ injury, and improved survival. It is interesting that this effect was dependent on an intact vagus nerve and that intracerebroventricular injection of ghrelin was also protective.[45] These data suggest that the effect of ghrelin is mediated via the CNS, most likely through the "cholinergic anti-inflammatory pathway." More recently, high ghrelin levels were demonstrated in critically ill patients as compared to healthy controls, independent of the presence of inflammatory markers. Moreover, the high ghrelin levels were a positive predictor of intensive care unit survival in septic patients, matching previous results from animal models.

The Role of Catecholamines in Postinjury Inflammation. Injury-induced activation of the sympathetic nervous system results in secretion of ACh from the preganglionic sympathetic fibers innervating the adrenal medulla. The adrenal medulla is a special case of autonomic innervation and is considered a **modified postganglionic neuron**. Thus, ACh signaling to the resident chromaffin cells ensures that a surge of epinephrine (EPI) and norepinephrine (NE) release into the circulation takes place in a ratio that is tightly regulated by both central and peripheral mechanisms. Circulating levels of EPI and NE are three- to four-fold elevated, an effect that persists for an extended time. The release of EPI can be modulated by transcriptional regulation of phenylethanolamine *N*-methyltransferase (PNMT), which catalyzes the last step of the catecholamine biosynthesis pathway methylating NE to form EPI. PNMT transcription, a key step in the regulation of EPI production, is activated in response to stress and tissue hypoxia by hypoxia-inducible factor 1α (HIF1A).

Catecholamine release almost immediately prepares the body for the "fight or flight" response with well-described effects on the cardiovascular and pulmonary systems and on metabolism. These include increased heart rate, myocardial contractility, conduction velocity, and blood pressure; the redirection of blood flow to skeletal muscle; increased cellular metabolism throughout the body; and mobilization of glucose from the liver via glycogenolysis, gluconeogenesis, lipolysis, and ketogenesis. To compound the resulting hyperglycemia, insulin release is decreased mainly through the stimulation of α-adrenergic pancreatic receptors. Hyperglycemia, as will be discussed later, contributes to the proinflammatory response and to further mitochondrial dysfunction.

The goal of this well-orchestrated catecholamine response is to re-establish and maintain the systems' homeostasis, including the innate immune system. Circulating catecholamines can directly influence inflammatory cytokine production.[46] Data indicate that basal EPI levels condition the activity and responsiveness of cytokine-secreting cells, which may explain large interindividual variability in innate cytokine profiles observed following injury. Epinephrine infusion at higher doses has been found to inhibit production of TNF-α in vivo and to enhance the production of the anti-inflammatory cytokine IL-10.[47] Additionally, *in vitro* studies indicate that stress levels of glucocorticoids and EPI, acting in concert, can inhibit production of IL-12, a potent stimulator of Th1 responses. Further, they have been shown in vitro to decrease Th1 cytokine production and increase Th2 cytokine production to a significantly greater degree compared to either adrenal hormone alone. Thus, catecholamines secreted from the adrenal gland, specifically EPI, play a role in both innate proinflammatory cytokine regulation and adaptive Th responses, and may act in concert with cortisol during the injury response to modulate cytokine activity.[48]

How are these effects explained? It is well established that a variety of human immune cells (e.g., mononuclear cells, macrophages, granulocytes) express adrenergic receptors that are members of the family of G-protein–coupled receptors that act through the activation of intracellular second messengers such as cyclic adenosine monophosphate (cAMP) and calcium ion influx (discussed in more detail later). These second messengers can regulate a variety of immune cell functions, including the release of inflammatory cytokines and chemokines.

The sympathetic nervous system also has direct immune-modulatory properties via its innervation of lymphoid tissues that contain resting and activated immune cells. With stimulation of these postganglionic nerves, NE is released where it can interact with β_2-adrenergic receptors expressed by $CD4^+$ T and B lymphocytes, many of which also express α_2-adrenergic receptors. Additionally, endogenous catecholamine expression has been detected in these cells, as has the machinery for catecholamine synthesis. For example, human peripheral blood mononuclear cells contain inducible mRNA for the catecholamine-generating enzymes, tyrosine-hydroxylase and dopamine-β-hydroxylase, and data suggest that cells can regulate their own catecholamine synthesis in response to extracellular cues. Exposure of peripheral blood mononuclear cells to NE triggers a distinct genetic profile that indicates a modulation of Th cell function. What the net effect of dopamine, NE, and EPI synthesis by circulating and resident immune cells may be relative to that secreted by the adrenal medulla is not clear and is an area that would certainly benefit from ongoing research efforts to identify novel therapeutic targets.

Aldosterone. Aldosterone is a mineralocorticoid released by the zona glomerulosa of the adrenal cortex. It binds to the mineralocorticoid receptor (MR) of principal cells in the collecting duct of the kidney where it can stimulate expression of genes involved in sodium reabsorption and potassium excretion

to regulate extracellular volume and blood pressure. MRs have also been shown to have effects on cell metabolism and immunity. For example, recent studies show aldosterone interferes with insulin signaling pathways and reduces expression of the insulin-sensitizing factors, adiponectin and peroxisome proliferator activated receptor-γ (PPAR-γ), which contribute to insulin resistance. In the immune system, mononuclear cells, such as monocytes and lymphocytes, have been shown to possess an MR that binds aldosterone with high specificity, regulating sodium and potassium flux, as well as plasminogen activator inhibitor-1 and p22 phox expression, in these cells.[49] Further, aldosterone inhibits cytokine-mediated NF-κB activation in neutrophils, which also possess a functional MR.

Insulin. Hyperglycemia and insulin resistance are hallmarks of injury and critical illness due to the catabolic effects of circulating mediators, including catecholamines, cortisol, glucagon, and GH. The increase in these circulating proglycemic factors, particularly EPI, induces glycogenolysis, lipolysis, and increased lactate production independent of available oxygen in a process that is termed "aerobic glycolysis." Although there is an increase in insulin production at the same time, severe stress is frequently associated with **insulin resistance,** leading to decreased glucose uptake in the liver and the periphery contributing to acute hyperglycemia. Insulin is a hormone secreted by the pancreas, which mediates an overall host anabolic state through hepatic glycogenesis and glycolysis, peripheral glucose uptake, lipogenesis, and protein synthesis.[50]

The insulin receptor (IR) is widely expressed and consists of two isoforms, which can form homo- or heterodimers with insulin binding. Dimerization leads to receptor autophosphorylation and activation of intrinsic tyrosine kinase activity. Downstream signaling events are dependent on the recruitment of the adaptor proteins, insulin receptor substrate (IRS-1), and Shc to the IR. Systemic insulin resistance likely results from proinflammatory signals, which modulate the phosphorylation of IRS-1 to affect its function.

Hyperglycemia during critical illness is predictive of increased mortality in critically ill trauma patients.[51] It can modulate the inflammatory response by altering leukocyte functions, and the resulting decreases in phagocytosis, chemotaxis, adhesion, and respiratory burst activities are associated with an increased risk for infection. In addition, glucose administration results in a rapid increase in NF-κB activation and proinflammatory cytokine production. Insulin therapy to manage hyperglycemia has grown in favor and has been shown to be associated with both decreased mortality and a reduction in infectious complications in select patient populations. However, the trend toward tight glycemic control in the intensive care unit failed to show benefit when examined in several reviews.[52] Thus, the ideal blood glucose range within which to maintain critically ill patients and to avoid hypoglycemia has yet to be determined.

THE CELLULAR STRESS RESPONSES

Reactive Oxygen Species and the Oxidative Stress Response

Reactive oxygen and nitrogen species (ROS and RNS, respectively) are small molecules that are highly reactive due to the presence of unpaired outer orbit electrons. They can cause cellular injury to both host cells and invading pathogens through the oxidation of cell membrane substrates. Oxygen radicals are produced as a by-product of oxygen metabolism in the mitochondria as well as by processes mediated by cyclooxygenases, NADPH oxidase (NOX), and xanthine oxidase. The main areas of ROS production include mitochondrial respiratory chain, peroxisomal fatty acid metabolism, cytochrome P450 reactions, and the respiratory burst of phagocytic cells. In addition, protein folding in the endoplasmic reticulum can also result in the formation of ROS.[53] Potent oxygen radicals include oxygen, superoxide, hydrogen peroxide, and hydroxyl radicals. RNS include NO and nitrite. The synthesis of ROS is regulated at several checkpoints and via several signaling mechanisms, including Ca^{2+} signaling, phosphorylation, and small G protein activation, which influence both the recruitment of the molecules required for NOX function and the synthesis of ROS in the mitochondria. NOX activation is triggered by a number of inflammatory mediators (e.g., TNF, chemokines, lysophospholipids, complement, and leukotrienes). Host cells are protected from the damaging effects of ROS through a number of mechanisms. The best described of these is via the upregulation and/or activation of endogenous antioxidant proteins. However, pyruvate kinase also provides negative feedback for ROS synthesis, as do molecules that react nonenzymatically with ROS. Under normal physiologic conditions, ROS production is balanced by these antioxidative strategies. In this context, ROS can act effectively as signaling molecules through their ability to modulate cysteine residues by oxidation and thus influence the functionality of target proteins.[54] This has recently been described as a mechanism in the regulation of phosphatases. ROS can also contribute to transcription activity both indirectly, through its effects on transcription factor lifespan, and directly, through the oxidation of DNA. An important role for ROS has been well described in phagocytes, which use these small molecules for pathogen killing. Recent data, however, indicate that ROS may mediate inflammasome activation by diverse agonists.[55] In addition, ROS appear to be involved in adaptive immunity. They have been described as a prime source of phosphatase activation in both B and T lymphocytes, which can regulate the function of key receptors and intracellular signaling molecules in these cells by affecting phosphorylation events.

The Heat Shock Response

Heat shock proteins (HSPs) are a group of intracellular proteins that are increasingly expressed during times of stress, such as burn injury, inflammation, oxidative stress, and infection. HSPs are expressed in the cytoplasm, nucleus, endoplasmic reticulum, and mitochondria, where they function as molecular chaperones that help monitor and maintain appropriate protein folding.[56] HSPs accomplish this task through the promotion of protein refolding, the targeting of misfolded proteins for degradation, and the assistance of partially folded proteins to appropriate membrane compartments. HSPs bind also bind foreign proteins and thereby function as intracellular chaperones for ligands such as bacterial DNA and endotoxin. HSPs are presumed to protect cells from the effects of traumatic stress and, when released by damaged cells, alert the immune system of the tissue damage. However, depending on their location and the type of immune cell in which they are expressed, HSPs may exert proinflammatory immune activating signals or anti-inflammatory immune dampening signals (Table 2-4).[57]

The Unfolded Protein Response

Secreted, membrane-bound, and organelle-specific proteins fold in the lumen of the endoplasmic reticulum (ER) where they also

TABLE 2-4

The immunomodulatory functions of heat shock proteins (HSPs)

	CELL LOCATION	RECOGNIZED AS DAMP?	IMMUNOMODULATORY FUNCTION
HSP90	Cytoplasm, endoplasmic reticulum Can function both inside and outside the cell	May act as DAMP chaperone to activate innate immune response	Binds and optimizes RNA polymerase II action to regulate gene transcription Stabilizes glucocorticoid receptor in the cytoplasm Important for processing and membrane expression of TLR Chaperones include IKK Facilitates antigen presentation to dendritic cells
HSP70	Can function both inside and outside the cell Endoplasmic reticulum homolog is BiP	Exogenous HSP70 elicits cellular calcium flux, NF-κB activation, cytokine production	Can have anti-inflammatory actions when expression is increased Inhibits TLR-mediated cytokine production via NF-κB Reduces dendritic cell capacity for T-cell stimulation BiP sequesters proteins important to the unfolded protein response
HSP60	Mitochondria	Exogenous HSP60 inhibits NF-κB activation	Plays a role in intracellular protein trafficking Modulates cytokine synthesis

BiP = binding immunoglobulin protein; DAMP = damage-associated molecular pattern; IKK = IκB kinase; NF-κB, nuclear factor-κB; TLR = toll-like receptor

receive their posttranslational modifications. Millimolar calcium concentrations are required to maintain the normal cellular protein folding capacity. Cellular stress decreases calcium concentration in the ER, disrupting the machinery required for this process and leading to the accumulation of misfolded or unfolded proteins. These occurrences are sensed by a highly conserved array of signaling proteins in the ER, including inositol requiring enzyme 1 (IRE1), protein kinase RNA (PKR)–like ER kinase (PERK), and activating transcription factor 6 (ATF6). Together, this complex generates the **unfolded protein response** (UPR), a mechanism by which ER distress signals are sent to the nucleus to modulate transcription in an attempt to restore homeostasis. Prolongation of the UPR, indicative of irreversible cellular damage, can result in cell death. Genes activated in the UPR result not only in the inhibition of translation, but also other potentially immunomodulatory events including induction of the acute-phase response, activation of NF-κB, and the generation of antibody-producing B cells.[58]

Burn injury leads to the marked reduction in ER calcium levels and activation of UPR sensing proteins. Moreover, recent data in a series of burn patients strongly link the UPR to insulin resistance and hyperglycemia in these patients.[59] Thus, a better understanding of the UPR, which is triggered by severe inflammation, may allow the identification of novel therapeutic targets for injury-associated insulin resistance.

Autophagy

Under normal circumstances, cells need to have a way of disposing of damaged organelles and debris aggregates that are too large to be managed by proteasomal degradation. In order to accomplish this housekeeping task, cells use a process referred to as "macroautophagy" (**autophagy**), which is thought to have originated as a stress response.[60] The steps of autophagy include the engulfment of cytoplasm/organelle by an "isolation membrane," which is also called a phagophore. The edges of the phagophore then fuse to form the autophagosome, a double-membraned vesicle that sequesters the cytoplasmic material and that is a characteristic feature of autophagy. The autophagosome then fuses with a lysosome to form an autolysosome where the contents, together with the inner membrane, are degraded. This process is controlled by numerous autophagy-specific genes and by the specific kinase, mammalian target of rapamycin (mTOR).

As noted earlier, autophagy is a normal cellular process that occurs in quiescent cells for cellular maintenance. However, under conditions of hypoxia and low cellular energy, autophagy is induced in an attempt to provide additional nutrients for energy production. The induction of autophagy promotes a shift from aerobic respiration to glycolysis and allows cellular components of the autophagosome to be hydrolyzed to energy substrates. Increased levels of autophagy are typical in activated immune cells and are a mechanism for the disposal of ROS and phagocytosed debris.

Recent data support the idea that autophagy may also play an important role in the immune response.[61] Autophagy is stimulated by Th1 cytokines and with activation of TLR in macrophages, but is inhibited by Th2 cytokines. It is also recognized as an important regulator of cytokine secretion, particularly those cytokines of the IL-1 family that are dependent on inflammasome processing for activation. For example, autophagosomes can sequester and degrade pro-IL-1β and inflammasome components. In animal models of sepsis, inhibition of autophagy results in increased proinflammatory cytokine levels that correlate with increased mortality.[62] These data suggest that autophagy is a protective mechanism whereby the cell can regulate the levels of cytokine production.

Apoptosis

Apoptosis (regulated cell death) is an energy-dependent, organized mechanism for clearing senescent or dysfunctional cells, including macrophages, neutrophils, and lymphocytes, without promoting an inflammatory response. This contrasts with cellular necrosis that results in disorganized intracellular molecule release with subsequent immune activation and inflammatory response. Systemic inflammation modulates apoptotic signaling in active immunocytes, which subsequently influences the inflammatory response through the loss of effector cells.

Apoptosis proceeds primarily through two pathways: the extrinsic pathway and the intrinsic pathway. The extrinsic

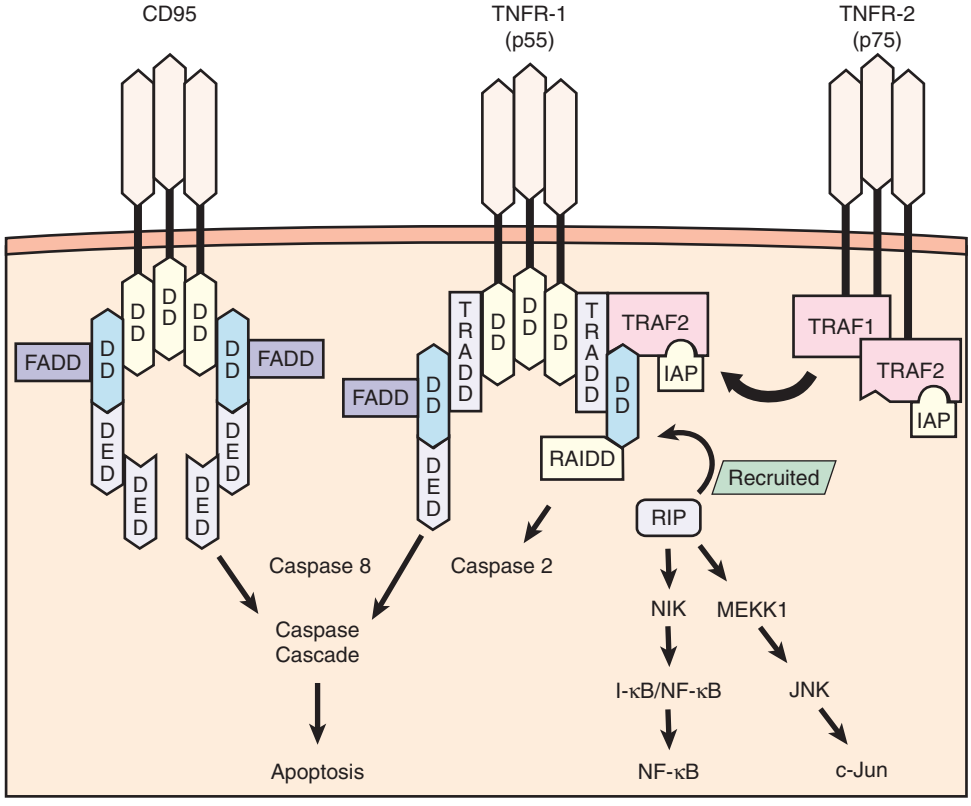

Figure 2-5. Signaling pathway for tumor necrosis factor receptor 1 (TNFR-1) (55 kDa) and TNFR-2 (75 kDa) occurs by the recruitment of several adapter proteins to the intracellular receptor complex. Optimal signaling activity requires receptor trimerization. TNFR-1 initially recruits TNFR-associated death domain (TRADD) and induces apoptosis through the actions of proteolytic enzymes known as *caspases,* a pathway shared by another receptor known as *CD95 (Fas).* CD95 and TNFR-1 possess similar intracellular sequences known as *death domains (DDs),* and both recruit the same adapter proteins known as *Fas-associated death domains (FADDs)* before activating caspase 8. TNFR-1 also induces apoptosis by activating caspase 2 through the recruitment of receptor-interacting protein (RIP). RIP also has a functional component that can initiate nuclear factor-κB (NF-κB) and c-Jun activation, both favoring cell survival and proinflammatory functions. TNFR-2 lacks a DD component but recruits adapter proteins known as TNFR-associated factors 1 and 2 (TRAF1, TRAF2) that interact with RIP to mediate NF-κB and c-Jun activation. TRAF2 also recruits additional proteins that are antiapoptotic, known as inhibitor of apoptosis proteins (IAPs). DED = death effector domain; I-κB = inhibitor of κB; I-κB/NF-κB = inactive complex of NF-κB that becomes activated when the I-κB portion is cleaved; JNK = c-Jun N-terminal kinase; MEKK1 = mitogen-activated protein/extracellular regulatory protein kinase kinase kinase-1; NIK = NF-κB–inducing kinase; RAIDD = RIP-associated interleukin-1b-converting enzyme and ced-homologue-1–like protein with death domain, which activates proapoptotic caspases. *(Adapted with permission from Lin E, Calvano SE, Lowry SF. Tumor necrosis factor receptors in systemic inflammation. In: Vincent J-L (series ed), Marshall JC, Cohen J, eds.* Update in Intensive Care and Emergency Medicine: Vol. 31: Immune Response in Critical Illness. *Berlin: Springer-Verlag; 2002:365. With kind permission from Springer Science + Business Media.)*

pathway is activated through the binding of death receptors (e.g., Fas, TNFR), which leads to the recruitment of Fas-associated death domain protein and subsequent activation of caspase 3 (Fig. 2-5). On activation, caspases are the effectors of apoptotic signaling because they mediate the organized breakdown of nuclear DNA. The intrinsic pathway proceeds through protein mediators (e.g., Bcl-2, Bcl-2–associated death promoter, Bcl-2–associated X protein, Bim) that influence mitochondrial membrane permeability. Increased membrane permeability leads to the release of mitochondrial cytochrome C, which ultimately activates caspase 3 and thus induces apoptosis. These pathways do not function in a completely autonomous manner, because there is significant interaction and crosstalk between mediators of both extrinsic and intrinsic pathways. Apoptosis is modulated by several regulatory factors, including inhibitor of apoptosis proteins and regulatory caspases (e.g., caspases 1, 8, 10).

Apoptosis during sepsis may influence the ultimate competency of the acquired immune response. In a murine model of peritoneal sepsis, increased lymphocyte apoptosis was associated with mortality, which may be due to a resultant decrease in IFN-γ release. In postmortem analysis of patients who expired from overwhelming sepsis, there was an increase in lymphocyte apoptosis, whereas macrophage apoptosis did not appear to be affected. Clinical trials have observed an association between the degree of lymphopenia and disease severity in sepsis. In addition, after the phagocytosis of apoptotic cells by macrophages, anti-inflammatory mediators such as IL-10 are released that may exacerbate immune suppression during sepsis. Neutrophil apoptosis is inhibited by inflammatory products, including TNF, IL-1, IL-3, IL-6, granulocyte-macrophage colony-stimulating factor (GM-CSF), and IFN-γ. This retardation in regulated cell death may prolong and exacerbate secondary injury through neutrophil free radical release as the clearance of senescent cells is delayed.[63]

Necroptosis

Cellular necrosis refers to the premature uncontrolled death of cells in living tissue typically caused by accidental exposure

to external factors, such as ischemia, inflammation, or trauma, which result in extreme cellular stress. Necrosis is characterized by the loss of plasma membrane integrity and cellular collapse with extrusion of cytoplasmic contents, but the cell nuclei typically remain intact. Recent data have defined a process by which necrosis occurs through a series of well-described steps that are dependent on a signaling pathway that involves the receptor-interacting protein kinase (RIPK) complex. Termed "necroptosis," it occurs in response to specific stimuli, such as TNF- and TLR-mediated signals.[64] For example, ligation of the TNF receptor 1 (TNFR1) under conditions in which caspase 8 is inactivated (e.g., by pharmacologic agents) results in the overgeneration of ROS and a metabolic collapse. The net result is programmed necrosis (necroptosis). The effect of cell death by necroptosis on the immune response is not yet known. However, it is likely that the "DAMP" signature that occurs in response to necroptotic cell death is an important contributor to the systemic inflammatory response. Evidence to support this concept was provided by investigators who examined the role of necroptosis in murine models of sepsis. They demonstrated that *Ripk3*$^{-/-}$ mice were capable of recovering body temperature better, exhibited lower circulating DAMP levels, and survived at higher rates than their wild-type littermates.[65] These data suggest that the cellular damage that occurs with programmed necrosis exacerbates the sepsis-associated systemic inflammatory response.

MEDIATORS OF INFLAMMATION

Cytokines

Cytokines are a class of protein signaling compounds that are essential for both innate and adaptive immune responses. Cytokines mediate a broad sequence of cellular responses, including cell migration, DNA replication, cell turnover, and immunocyte proliferation (Table 2-5). When functioning locally at the site of injury and infection, cytokines mediate the eradication of invading microorganisms and also promote wound healing. However, an exaggerated proinflammatory cytokine response to inflammatory stimuli may result in hemodynamic instability (i.e., septic shock) and metabolic derangements (i.e., muscle wasting). Anti-inflammatory cytokines also are released, at least in part, as an opposing influence to the proinflammatory cascade. These anti-inflammatory mediators may also result in immunocyte dysfunction and host immunosuppression. Cytokine signaling after an inflammatory stimulus can best be represented as a finely tuned balance of opposing influences and should not be oversimplified as a "black and white" proinflammatory/anti-inflammatory response. A brief discussion of the important cytokine molecules is included.

5▶

Tumor Necrosis Factor-α. TNF-α is a cytokine that is rapidly mobilized in response to stressors such as injury and infection and is a potent mediator of the subsequent inflammatory response. TNF is primarily synthesized by immune cells, such as macrophages, dendritic cells, and T lymphocytes, but nonimmune cells have also been reported to secrete low amounts of the cytokine.

TNF is generated in a precursor form called transmembrane TNF that is expressed as a trimer on the surface of activated cells. After being processed by the metalloproteinase TNF-α–converting enzyme (TACE; also known as ADAM-17), a smaller, soluble form of TNF is released, which mediates its biologic activities through type 1 and 2 TNF receptors (TNFR1; TNFR2).[66] Transmembrane TNF-α also binds to TNFR1 and TNFR2, but its biologic activities are likely mediated through TNFR2. While the two receptors share homology in their ligand binding regions, there are distinct differences that regulate their biologic function. For example, TNFR1 is expressed by a wide variety of cells but is typically sequestered in the Golgi complex. Following appropriate cell signaling, TNFR1 is mobilized to the cell surface, where it sensitizes cells to TNF, or it can be cleaved from the surface in the form of a soluble receptor that can neutralize TNF.[67] In contrast, TNFR2 expression is confined principally to immune cells where it resides in the plasma membrane. Both TNF receptors are capable of binding intracellular adaptor proteins that lead to activation of complex signaling processes and mediate the effects of TNF.

Although the circulating half-life of soluble TNF is brief, it acts upon almost every differentiated cell type, eliciting a wide range of important cellular responses. In particular, TNF elicits many metabolic and immunomodulatory activities. It stimulates muscle breakdown and cachexia through increased catabolism, insulin resistance, and redistribution of amino acids to hepatic circulation as fuel substrates. TNF also mediates coagulation activation, cell migration, and macrophage phagocytosis, and enhances the expression of adhesion molecules, prostaglandin E_2, platelet-activating factor, glucocorticoids, and eicosanoids. Recent studies indicate that a significant early TNF response after trauma may be associated with improved survival in these patients.[68]

Interleukin-1. IL-1α and IL-1β, which are encoded by two distinct IL-1 genes, were the first described members of the IL-1 cytokine family. Currently, the family has expanded to 11 members, with the three major forms being IL-1α, IL-1β, and IL-1 receptor antagonist (IL-1Rα). IL-1α and IL-1β share similar biologic functions, but have limited sequence homology. They use the same cell surface receptor, termed IL-1 receptor type 1 (IL-1R1), which is present on nearly all cells. Although IL-1Rα is synthesized and released in response to the same stimuli that lead to IL-1 production, it lacks the necessary domain to form a bioactive complex with the IL-1 receptor when bound. Thus, IL-1Rα serves as a competitive antagonist for the receptor. IL-1R activation initiates signaling events, which result in the synthesis and release of a variety of inflammatory mediators.

The IL-1α precursor is constitutively expressed and stored in a variety of healthy cells, including epithelium, endothelium, and platelets. Both the precursor and mature forms of IL-1α are active. With appropriate signals, IL-1α moves to the cell membrane where it can act on adjacent cells bearing the IL-1 receptor. It can also be released directly from injured cells. In this way, IL-1α is believed to function as a DAMP, which promotes the synthesis of inflammatory mediators, such as chemokines and eicosanoids. These mediators attract neutrophils to the injured site, facilitate their exit from the vasculature, and promote their activation. Once they have reached their target, neutrophil lifespan is extended by the presence of IL-1α.[69]

IL-1β, a multifunctional proinflammatory cytokine, is not detectable in healthy cells. Rather, its expression and synthesis occur in a more limited number of cells, such as monocytes, tissue macrophages, and dendritic cells, following their activation. IL-1β expression is tightly regulated at multiple levels (e.g., transcription, translation, and secretion), although the rate-limiting step is its transcription. IL-1β is synthesized and released in response to inflammatory stimuli, including cytokines

Table 2-5

Cytokines and their sources

CYTOKINE	SOURCE	COMMENT
TNF	*Macrophages/monocytes* Kupffer cells Neutrophils NK cells Astrocytes Endothelial cells T lymphocytes Adrenal cortical cells Adipocytes Keratinocytes Osteoblasts Mast cells Dendritic cells	Among earliest responders after injury; half-life <20 min; activates TNF receptors 1 and 2; induces significant shock and catabolism
IL-1	*Macrophages/monocytes* B and T lymphocytes NK cells Endothelial cells Epithelial cells Keratinocytes Fibroblasts Osteoblasts Dendritic cells Astrocytes Adrenal cortical cells Megakaryocytes Platelets Neutrophils Neuronal cells	Two forms (IL-1 α and IL-1 β); similar physiologic effects as TNF; induces fevers through prostaglandin activity in anterior hypothalamus; promotes β-endorphin release from pituitary; half-life <6 min
IL-2	*T lymphocytes*	Promotes lymphocyte proliferation, immunoglobulin production, gut barrier integrity; half-life <10 min; attenuated production after major blood loss leads to immunocompromise; regulates lymphocyte apoptosis
IL-3	*T lymphocytes* Macrophages Eosinophils Mast cells	
IL-4	*T lymphocytes* Mast cells Basophils Macrophages B lymphocytes Eosinophils Stromal cells	Induces B-lymphocyte production of IgG4 and IgE, mediators of allergic and anthelmintic response; downregulates TNF, IL-1, IL-6, IL-8
IL-5	*T lymphocytes* Eosinophils Mast cells Basophils	Promotes eosinophil proliferation and airway inflammation
IL-6	*Macrophages* B lymphocytes Neutrophils Basophils Mast cells Fibroblasts Endothelial cells Astrocytes	Elicited by virtually all immunogenic cells; long half-life; circulating levels proportional to injury severity; prolongs activated neutrophil survival

(*Continued*)