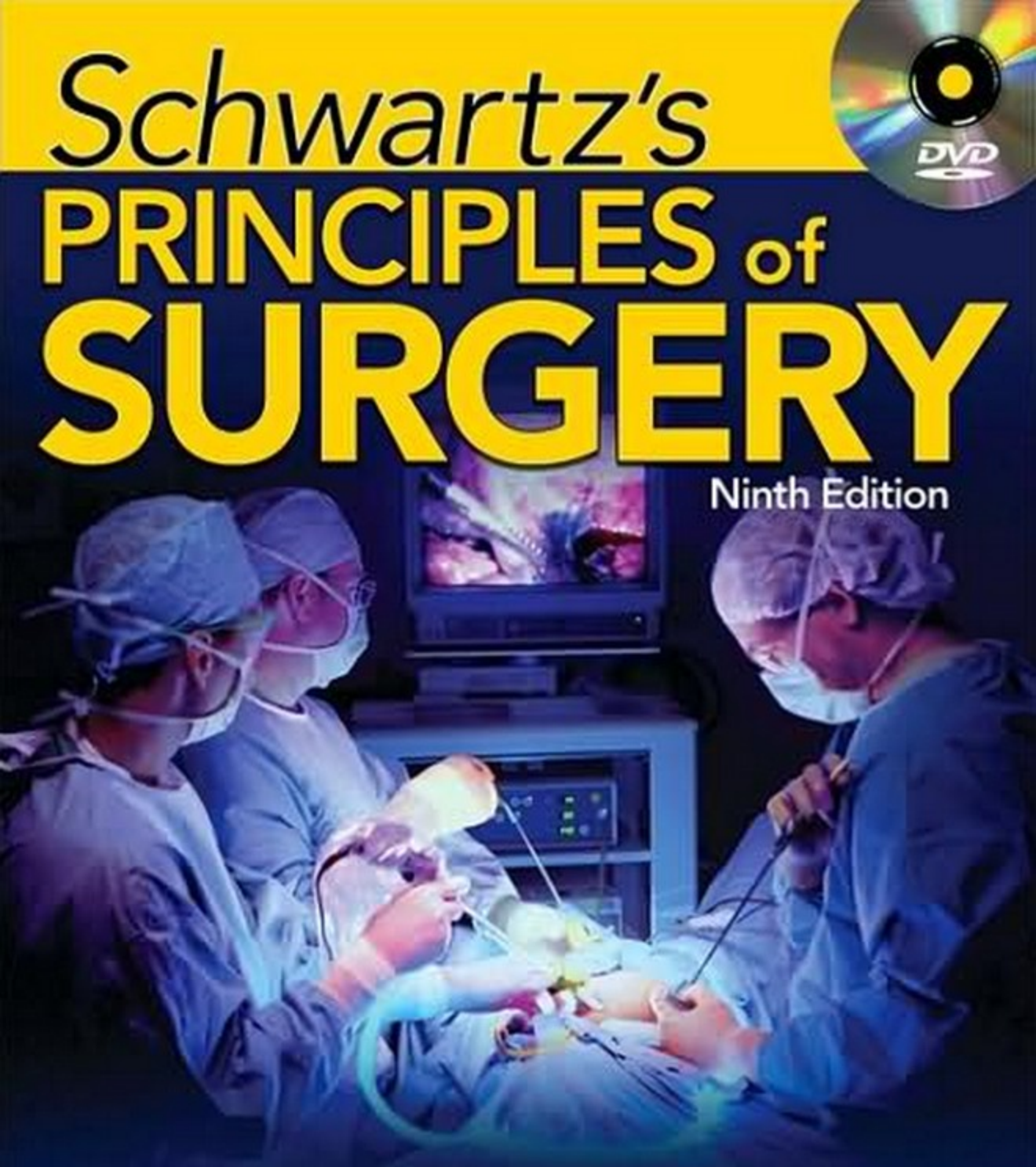
Schwartz's PRINCIPLES of SURGERY

Ninth Edition



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Preface

When I was asked to serve as editor-in-chief of this historic textbook of surgery, my goal was to preserve its excellent reputation, honoring the commitment of Dr. Seymour Schwartz and previous co-editors and contributors who upheld the highest standard for seven prior editions. I would like to thank all who helped achieve this goal, namely the outstanding contributions by the individual chapter authors and the meticulous dedication of the editorial board, all of whom share a passion for patient care, teaching, and surgery.

It is this shared passion that has been channeled now into the creation of this new ninth edition; updating, improving, and finetuning it to secure its place as a leading international textbook of surgery. Each chapter has either been fastidiously updated or created anew by leaders in their respective surgical fields to ensure the highest quality of surgical teaching. Additionally, each chapter has been outfitted with quick-reference key points; highlighted evidenced-based references; and full-color illustrations, images, and information tables. Two new chapters have been added to this edition: *Accreditation Council for Graduate Medical Core Competencies* and *Ethics, Palliative Care, and Care at the End of Life*.

One new component of this edition is the inclusion of a digital video disc of surgical videos. Many students already augment their more traditional classroom and practical education through the breadth of information available in the electronic realm, such as that available on AccessSurgery.com. This collection of operative and instructional videos, generously provided by chapter authors and editors, provides accurate visual instruction and technique to round out students' surgical training. It is the sincere hope of all who have contributed to this textbook that the knowledge of craft contained within will provide a solid foundation for the acquisition of skill, a haven for the continuation of education, and motivation for the pursuit of excellence.

I wish to thank all of those responsible for the publication of this new edition, including the newest member of the editorial board, Dr. Jeffrey Matthews, as well as those who fearlessly signed on as contributors to our newly established international editorial board to provide regional perspective and commentary. I extend many thanks and gratitude to Marsha Loeb, Christie Naglieri, and all at McGraw-Hill for their guidance and knowledge throughout this process. I wish to thank Katie Elsbury for her dedication to the organization and editing of this textbook. I would also like to thank our families, whose love and support *continue* to make this book possible.

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Laparoscopic Splenectomy

Marlon Guerrero, MD
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Bilateral Exploration Parathyroidectomy

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Laparoscopic Sleeve Gastrectomy
Laparoscopic Adjustable Gastric and Hiatal Hernia Repair

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Open Surgical Treatment of Extent IV Thoracoabdominal Aortic Aneurysms

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Robotic-Assisted Laparoscopic Partial Nephractomy
Robotic-Assisted Laparoscopic Radial Prostatectomy

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Right-Lobe Living Donor Liver Transplantation

Jeffrey B. Matthews, MD, FACS
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Laparoscopic Cystogastrostomy for Pancreatic Pseudocyst

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Schwartz's Principles of Surgery, 9e

F. Charles Brunicardi, Dana K. Andersen, Timothy R. Billiar, David L. Dunn, John G. Hunter, Jeffrey B. Matthews, Raphael E. Pollock

KEY POINTS

1. The Accreditation Council for Graduate Medical Education (ACGME) Outcomes Project changes the focus of graduate medical education from how programs are *potentially* educating residents to how programs are *actually* educating residents through assessment of competencies.

2. The six core competencies are patient care, medical knowledge, practice-based learning and improvement, interpersonal and communication skills, professionalism, and systems-based practice.

3. The Residency Review Committee recognizes the importance of simulators for technical training and mandated that all training programs have a skills laboratory by July 2008. A Surgical Skills Curriculum Task Force has developed a National Skills Curriculum to assist programs with training and assessing competency through simulators.

4. The ACGME has developed a professional development tool called the *ACGME Learning Portfolio.* This interactive web-based portfolio can be used as a tool for residents, faculty, and programs directors to allow for reflection, competency assessment, and identification of weaknesses.

5. There is much to be learned still, and programs should continue to share their experiences to identify benchmark programs.

ACCREDITATION COUNCIL FOR GRADUATE MEDICAL EDUCATION OUTCOMES PROJECT

Technologic and molecular advances have fundamentally changed the way medicine is practiced. The Internet has revolutionized the way both physicians and patients learn about diseases. In addition, political and economic pressures have altered the way society views and reimburses medical care. The end result of these changes is that access to medical care, access to information about medical care, and the very nature of the doctor-patient relationship has changed.[1] In response to this situation, the Accreditation Council for Graduate Medical Education (ACGME) Outcomes Project was developed. Dr. Leach stated that this initiative was based on three principles: (1) whatever we measure we tend to improve; (2) focusing on outcomes instead of processes allows programs flexibility to adapt based on their needs and resources; and (3) the public deserves to have access to data demonstrating that graduating physicians are competent.[2] This initiative changed the focus of graduate medical education from how programs were *potentially* educating residents by complying with the accreditation requirements to how programs are *actually* educating residents through assessment of the program's outcomes. In 1999, the Outcomes Project identified six core competencies that would provide a conceptual framework to train residents to competently and compassionately treat patients in today's changing health care system. The six core competencies as

designated by the ACGME are patient care, medical knowledge, practice-based learning and improvement, interpersonal and communication skills, professionalism, and systems-based practice (Table 1-1).[3] Starting in July 2001, the ACGME implemented a 10-year timeline to implement these concepts into medical education. The timeline was divided into four phases, allowing flexibility for individual programs to meet these goals (Table 1-2).[4]

Table 1-1 Accreditation Council for Graduate Medical Education Core Competencies

Core Competency	Description
Patient care	To be able to provide compassionate and effective health care in the modern-day health care 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 health care 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 health care delivery system and to be able to use the system to support patient care

Table 1-2 Accreditation Council for Graduate Medical Education Timeline

Phase	Dates	Program Focus	Accreditation Focus
1. Forming an initial response to changes in requirements	July 2001–June 2002	• Define objectives for residents to demonstrate learning the competencies • Review current approaches to evaluation of resident learning • Begin integrating the teaching and learning of competencies into residents' didactic and clinic experience	• Develop operational definitions of compliance • Provide constructive citations and recommendations with no consequences
2. Sharpening the focus	July 2002–June 2006	• Provide learning opportunities in all six competencies • Improve evaluation process	• Review evidence that programs are teaching and assessing the competencies • Provide constructive citations early

Phase	Dates	Program Focus to obtain accurate resident performance on the six core competencies • Provide aggregated resident performance data for the program's GMEC internal review	Accreditation Focus in the phase and transition to citations with consequences later • Review evidence that GMECs' internal reviews of programs include consideration of aggregated performance data
3. Full integration	July 2006–June 2011	• Use resident performance data as basis for improvement and provide evidence for accreditation review • Use external measures to verify resident and program performance levels	• Review evidence that programs are making data-driven improvements • Review external program performance measures and input from GMECs as evidence for achieving educational goals
4. Expansion	July 2011–beyond	—	• Identify benchmark programs • Adapt and adopt generalizable information about models of excellence • Invoke community about building knowledge about good graduate medical education

GMEC = graduate medical education committee.

CORE COMPETENCIES

The core competencies include six specific areas that have been designated as critical for general surgery resident training. Each surgical training program must provide an environment that is conducive to learning the core competencies, establish a curriculum that addresses each of the competencies, and assess that learning has taken place (see Table 1-1). The six core competencies are as follows[5]:

1. Patient Care. Residents must be able to provide patient care that is compassionate, appropriate, and effective for the treatment of health problems and the promotion of health. Residents:

a. Will demonstrate manual dexterity appropriate for their level;

b. Will develop and execute patient care plans appropriate for the resident's level, including management of pain;

c. Will participate in a program that must document a clinical curriculum that is sequential, comprehensive, and organized from basic to complex. The clinical assignments should be carefully structured to ensure that graded levels of responsibility, continuity in patient care, a balance between education and service, and progressive clinical experience are achieved for each resident.

2. Medical Knowledge. Residents must demonstrate knowledge of established and evolving biomedical, clinical, epidemiological, and social-behavioral sciences, as well as the application of this knowledge to patient care. Residents:

a. Will critically evaluate and demonstrate knowledge of pertinent scientific information, and

b. Will participate in an educational program that should include the fundamentals of basic science as applied to clinical surgery, including applied surgical anatomy and surgical pathology; the elements of wound healing; homeostasis, shock and circulatory physiology; hematologic disorders; immunobiology and transplantation; oncology; surgical endocrinology; surgical nutrition, fluid and electrolyte balance; and the metabolic response to injury, including burns.

3. Practice-Based Learning and Improvement. Residents must demonstrate the ability to investigate and evaluate their care of patients, to appraise and assimilate scientific evidence, and to continuously improve patient care based on constant self-evaluation and life-long learning. Residents are expected to develop skills and habits to be able to meet the following goals:

a. Identify strengths, deficiencies, and limits in one's knowledge and expertise;

b. Set learning and improvement goals;

c. Identify and perform appropriate learning activities;

d. Systematically analyze practice using quality improvement methods, and implement changes with the goal of practice improvement;

e. Incorporate formative evaluation feedback into daily practice;

f. Locate, appraise, and assimilate evidence from scientific studies related to their patients' health problems;

g. Use information technology to optimize learning;

h. Participate in the education of patients, families, students, residents and other health professions;

i. Participate in mortality and morbidity conferences that evaluate and analyze patient care outcomes; and

j. Utilize an evidence-based approach to patient care.

4. Interpersonal and Communication Skills. Residents must demonstrate interpersonal and communication skills that result in effective exchange of information and collaboration with patients, their families, and health professionals. Residents are expected to:

a. Communicate effectively with patients, families, and the public, as appropriate, across a broad range of socioeconomic and cultural backgrounds;

b. Communicate effectively with physicians, other health professionals, and health related agencies;

c. Work effectively as a member or leader of a health care team or other professional group;

d. Act in a consultative role to other physicians and health professionals;

e. Maintain comprehensive, timely, and legible medical records, if applicable.

f. Counsel and educate patients and families; and

g. Effectively document practice activities.

5. Professionalism. Residents must demonstrate a commitment to carrying out professional responsibilities and an adherence to ethical principles. Residents are expected to demonstrate:

a. Compassion, integrity, and respect for others;

b. Responsiveness to patient needs that supersedes self-interest;

c. Respect for patient privacy and autonomy;

d. Accountability to patients, society and the profession;

e. Sensitivity and responsiveness to a diverse patient population, including but not limited to diversity in gender, age, culture, race, religion, disabilities, and sexual orientation;

f. High standards of ethical behavior; and

g. A commitment to continuity of patient care.

6. Systems-Based Practice. Residents must demonstrate an awareness of and responsiveness to the larger context and system of health care, as well as the ability to call effectively on other resources in the system to provide optimal health care. Residents are expected to:

a. Work effectively in various health care delivery settings and systems relevant to their clinical specialty;

b. Coordinate patient care within the health care system relevant to their clinical specialty;

c. Incorporate considerations of cost awareness and risk-benefit analysis in patient and/or population-based care as appropriate;

d. Advocate for quality patient care and optimal patient care systems;

e. Work in inter-professional teams to enhance patient safety and improve patient care quality;

f. Participate in identifying system errors and implementing potential systems solutions;

g. Practice high quality, cost effective patient care;

h. Demonstrate knowledge of risk-benefit analysis; and

i. Demonstrate an understanding of the role of different specialists and other health care professionals in

overall patient management.

The goal of any surgical training program is to train physicians to provide the highest quality of patient care. The core competency mandates have set into motion changes in education that result in measurable outcome-based training. The challenge of the surgical educator is to develop innovative and focused learning techniques to accomplish this mandate within an 80-hour work week.

Patient Care

Patient care is the foundation for the practice of clinical medicine and must be addressed early and continuously during residency. Historically, patient care has been taught by an apprenticeship model; in other words, by the residents' spending time with attending physicians on the wards or in the operating rooms.[6] However, this training method has to be re-evaluated as a result of the ever-increasing constraints and changes in our health care system. Increasing public awareness of medical legal errors has resulted in heightened scrutiny with regard to patient safety issues.[1] In addition, there are increasing concerns related to the perceived financial setback and medical-legal impact of resident training in the operating room.[7] Even with the inherent flexibility provided by the ACGME, all of these factors, coupled with the work hour restrictions,[8] make surgical training in the modern health care system an especially challenging endeavor. Not only must educators impart the medical knowledge of caring for patients and new advances in patient care, but they must also impart the technical skills necessary to perform complex surgical procedures.

One of the subcompetencies under patient care is that residents "will demonstrate manual dexterity appropriate for their level."[5] Traditionally, the operating room has been used to train residents in the technical aspects of patient care by "see one, do one, and teach one." A study by Velmahos and colleagues evaluated the knowledge and technical skills of residents who were randomly assigned either to training using the traditional approach or to training in a surgical skills laboratory using the principles of cognitive task analysis. This study revealed that the residents who trained using the laboratory approach had improved medical knowledge and technical skills.[9] Multiple studies like the one previously mentioned have revealed improved performance with simulators and advocated their use in technical skills training.[10–12] Having recognized the importance of incorporating simulation training into today's residency, the Residency Review Committee (RRC) mandated that all surgery programs be required to have a surgical skills laboratory by July 2008 to maintain their accreditation.[13] To assist programs, the Surgical Skills Curriculum Task Force, a joint project of the American College of Surgeons (ACS) and the Association of Program Directors in Surgery, developed a standardized skills curriculum.[14,15] This curriculum was developed in three phases (Table 1-3): phase I with modules for junior residents, phase II for senior residents, and phase III for team training. Another resource that programs may use in developing a surgical skills curriculum is the Fundamentals of Laparoscopic Surgery (FLS) program. This program is endorsed by the ACS and the Society of Gastrointestinal and Endoscopic Surgeons. The FLS consists of a comprehensive curriculum with hands-on skills training and an assessment tool designed to teach and assess the fundamentals of laparoscopic surgery.[16] Future goals for surgical education include a method to ensure that residents are "certified" and deemed competent to perform a procedure in a simulator environment before allowing residents to perform that particular procedure in the operating room.[17]

Table 1-3 National Skills Curriculum Phases and Launch Dates		
Phase		Dates
I	Basic/core skills and tasks	July 2007
II	Advanced procedures	January 2008
III	Team-based skills	July 2008

The RRC has mandated that all residency programs develop a surgical skills laboratory, and the majority of program directors feel that this is an important part of residency training. However, a study by Korndorffer and associates just before the mandate was issued revealed that only 55% of the 162 programs that replied to the survey had a surgical skills laboratory facility.[18] The average cost to develop a laboratory has been reported as $133,000 to $450,000, but the cost can range from $300 to $3 million.[18,19] Kapadia and colleagues surveyed 40 programs with surgical skills laboratories in place and found that funding came from industry (68%), surgery departments (64%), hospitals (46%), and other sources (29%). They also found a wide variation in the size of the facility, location, availability of simulators, protected time for skills training, and curriculum. This study also revealed that 65% of the programs believed that it was somewhat difficult to recruit faculty members to staff the laboratory; however, this could be related to the fact that 69% of the laboratories did not offer any faculty incentive to teach.[19] These studies suggest that although most surgical educators believe that surgical skills laboratories are important for resident education, there is still much room for improvement and standardization.

In addition to technical competency, residents are expected to "develop and execute patient care plans appropriate for the resident's level, including management of pain."[5] This can be reinforced during attendance at rounds and integrated into many of the conferences that are currently available in many surgery programs, such as grand rounds and the morbidity and mortality conference.[20,21] Prince and others demonstrated in an institutional study that use of an interactive format for the morbidity and mortality conference improved the educational value of the conference for residents at all levels.[22] Rosenfeld restructured the morbidity and mortality conference to make it more competence based. For example, each patient case was further divided into separate categories such as patient communication, ethical dilemmas, system problems, and practice-based improvement to enhance patient care.[20] Stiles and associates developed a morning report conference after the implementation of the night float system to improve patient sign-out procedures. They found that this forum not only helped to improve communication but also allowed for teaching, discussion of patient care plans, and direct evaluation of resident competence.[23]

Medical Knowledge

The ACGME has mandated that "residents must demonstrate knowledge of established and evolving biomedical, clinical, epidemiological, and social-behavioral sciences, as well as the application of this knowledge to patient care."[5] Surgery has undergone an exponential growth in new procedures and technology. With this explosion in medical innovation, training programs are posed with the daunting task of not only teaching the technical aspects of surgery, but also imparting the basic science and fundamentals of surgical diseases. Furthermore, development of the field of molecular biology and its application to surgical diseases has mandated that surgeons understand the basic molecular mechanisms of each disease process.[24,25] The new era of molecular biology requires understanding the complex science that can lead to

advances such as molecular fingerprinting techniques to tailor treatments that are specific for each individual patient. Other, more cognitive tools such as how to critically review literature and how to logically evaluate the relevance of a study must also be imparted to residents so that they can correctly apply findings of the latest medical studies to each individual patient.

The ACGME mandates that residents "will participate in an educational program that should include the fundamentals of basic science as applied to clinical surgery, including applied surgical anatomy and surgical pathology; the elements of wound healing; homeostasis, shock and circulatory physiology; hematologic disorders; immunobiology and transplantation; oncology; surgical endocrinology; surgical nutrition, fluid and electrolyte balance; and the metabolic response to injury, including burns."[5] The ability of a surgical program to adequately meet this educational challenge can be improved by using innovative learning techniques. Educational systems such as the SQR3 (Survey, Question, Read, Recite, and Review) system of studying,[26] the Pimsleur model,[27] and Rosetta Stone learning techniques[28] are all tools that can aid in the understanding and application of advances in a rapidly changing surgical field. The authors' surgery residency program combined adult learning principles with some of these learning techniques into a problem-based learning program that met weekly after grand rounds. This mandatory, focused curriculum for the residents incorporated both basic science and its clinical application in an interactive and collaborative format. This educational format led to high resident satisfaction and also a sustainable increase in resident American Board of Surgery In-Training Examination scores.[29,30]

Residents are also expected to "critically evaluate and demonstrate knowledge of pertinent scientific information."[5] Residents can be taught early how to critically review the literature using the format of a journal club. The journal club is a widely used technique through which to disseminate the latest in medical knowledge. Even as early as the late 1980s, a study in the *Journal of the American Medical Association* found that residents who participated in a journal club had improved reading habits and improved medical knowledge compared with their peers who did not participate in a journal club.[31] The wide use of journal clubs in surgery education can be seen as a necessary foundation for medical education. In one survey, over 65% of general surgery residency programs have a journal club that meets at least once a month to discuss relevant surgical and medical topics.[32] MacRae and others took this approach a step further by evaluating the effect of a multifaceted Internet-based journal club and found that this learning format improved the skills of the surgical residents to critically appraise the medical literature.[33] Many online resources are available for residents that provide an abundant amount of material for study, reference, and interactive learning.[34–36] In particular, AccessSurgery provides an extensive online resource with medical data and operative techniques, with a core curriculum organized around the ACGME mandates.[34] Finally, and perhaps most importantly, it must be conveyed to surgical trainees that surgery is a lifelong learning process, and the ability to continue building on one's medical knowledge is critical for a successful surgical career.

Practice-Based Learning and Improvement

The third ACGME mandate states that "residents must demonstrate the ability to investigate and evaluate their care of patients, to appraise and assimilate scientific evidence, and to continuously improve patient care based on constant self-evaluation and life-long learning."[5] This mandate comes from the increasing public demand for accountability and increased demand for data regarding outcomes for specific surgeon.[2] Practice-based learning and improvement involves a cycle of four steps: identify areas for improvement, engage in learning, apply the new knowledge and skills to a practice, and check for improvement.[37] This ability to critically and impartially analyze one's practice patterns to continually improve patient care should

start early during training, so that this behavior becomes second nature for residents when they become practicing surgeons.

In residency training, the simplest example of practice-based learning is the surgical morbidity and mortality conference. This conference traditionally allows for in-depth discussions of surgical cases and adverse patient outcomes. Complications are categorized (preventable, probably preventable, possibly preventable, and unpreventable) and areas of improvement are identified. Rosenfeld as well as Williams and Dunnington have reformatted this conference to make it more competence based by having residents assess themselves. Residents are required to fill out a practice-based improvement form and identify areas of improvement.[20,38] Another innovative modality to teach practice-based learning was described by Canal and colleagues, who developed a 6-week curriculum in continuous quality improvement for surgery residents that included a specific project. In this project, the residents identified a need for quality improvement, implemented a plan for improvement, and developed a method to measure the improvement. These residents scored significantly higher in knowledge of and experience in quality improvement after completing this curriculum and felt that it was an effective and formal way to teach them the science of practice-based improvement.[39]

Clearly, for surgeons to identify areas of improvement, there has to be some method to allow for comparison and reflection. An interesting Internet-based learning portfolio called *Computerized Obstetrics and Gynecology Automated Learning Analysis (KOALA)* was developed for the obstetrics and gynecology residents in Canada. This portfolio encouraged self-analysis and self-directed learning by allowing residents to log patient encounters, list critical events and questions derived from these events, look up data used to answer these questions, and state how their practice patterns would be altered based on their reflections. Residents who used this method to reflect and critically analyze their performance scored significantly higher on the Self-Directed Learning Readiness Scale, looked forward to learning for life, and had a strong desire to learn new things.[40] An avenue currently available for practicing surgeons and residents to analyze their outcomes is the ACS Case Log System. This system was developed to support practice-based learning and improvement by allowing surgeons to voluntarily report their own results and compare them to those of other surgeons enrolled in the system. This allows surgeons to critically evaluate their practice outcomes and identify areas that need improvement.[41]

To further improve practice patterns, the ACGME has mandated that trainees must understand the use of information technology systems to manage patient information and support clinical care. Technology is rapidly improving, and hospitals are increasing their efficiency by using electronic medical records. One of the best examples of this is the Computerized Patient Record System (CPRS) used by the Veterans Affairs (VA) hospital system. This fully computerized patient database allows easy access to all patient clinical data, including laboratory tests, radiographic studies, physician notes, and appointment times. Use of this central core information system also has allowed the VA health system to develop the National Surgical Quality Improvement Program (NSQIP).[42] Using information from the CPRS, nurse reviewers are able to gather and input information into the NSQIP system. NSQIP has been the first prospective risk-adjusted outcomes-based program for comparing and improving surgical outcomes across multiple institutions. This program has revolutionized the reporting and quality control of surgical services within the VA system.

Practice-based learning is complex and involves many components, including self-awareness, critical thinking, problem solving, self-directed learning, analysis of outcomes, use of information technology, and focus on evidence-based medicine to improve practice outcomes and patient care.[5] This competency is multifaceted, and an extensive literature review by Ogrinc and associates found little instruction on how to

impart these important skills to our residents. Much work appears to be needed before an ideal curriculum can be developed. Future plans should be made for faculty to develop these skills and for programs to continually share their experiences.[43]

Interpersonal and Communication Skills

The fourth competency mandated by the ACGME is that "residents must demonstrate interpersonal and communication skills that result in effective exchange of information and collaboration with patients, their families, and health professionals."[5] Effective communication between physicians, patients, and other health care professionals is essential to the successful and competent practice of medicine and patient care. Studies reveal that physicians with good communication and interpersonal skills have improved patient outcomes and are subject to less medical litigation.[44–46] In support of this, a root cause analysis by the Joint Commission identified breakdown in communication as the leading cause of wrong-site operations and other sentinel events.[47] The ACS has developed a Task Force on Communication and Interpersonal Skills to specifically address this issue and encourage practicing surgeons to develop these important skills.[48] The goal of this task force is to appropriately address the core competency of interpersonal skills and communication and to use novel educational techniques to improve these skills. Certain areas, such as palliative care and patient mortality, have not been a focus for surgeons or surgical trainees but are critical in the surgeon-patient relationship. Four areas in which surgeons can improve their communication skills have been identified in palliative care: the preoperative visit, and discussion of a poor prognosis, surgical complications, and death.[49] These are situations that all surgeons will face at some point in their careers, and the ability to communicate effectively and compassionately with patients during these stressful times is an important skill to develop. Fortunately, multiple techniques for imparting this particular skill have been described in the literature. The group at Southern Illinois University had teams of senior surgical faculty and a faculty member from the Department of Medical Humanities develop a case-based ethics curriculum that covered topics such as resource allocation, research ethics, substituted consent, competition of interests, truth telling, and communication.[17] Other methods to teach communication skills have relied on the use of standardized patients.[38,50,51] Yudkowsky and associates assessed the use of a patient-based communication skills examination. Their conclusion was that the use of a patient-based examination was able to demonstrate consistent results and that verbal feedback was beneficial for resident education on improvement of communication skills.[50] Other recommended teaching strategies include observation with real-time feedback, role modeling, self-assessment, and videotaping.[52]

Residents also are expected to "work effectively as a member or leader of a health care team or other professional group"[5] (Fig. 1-1). This is particularly important for surgeons, because caring for surgical patients requires a team approach to safely get the patient from the preoperative evaluation process, to the operating room, and through the postoperative course. Surgeons are typically the leaders of such teams; hence, it is important for residents to develop the necessary leadership skills during training. With less time spent in the hospital, the ability to learn from real-life situations is limited. Therefore, these principles need to be taught through other creative means such as didactic lectures or problem-based learning. Studies have revealed that formal leadership training not only improves communication skills[53,54] but also helps to develop conflict resolution skills.[55] Awad and colleagues instituted a formal collaborative leadership training program and found that this format significantly increased the residents' views of leadership in the areas of alignment, communication, and integrity.[56] Having recognized leadership training as a necessity for surgeons to thrive in today's medical environment, the ACS offers a course called "Surgeons as Leaders: From

Operating Room to Boardroom," whose purpose is to provide surgeons with the skills needed for effective leadership.[57]

Fig. 1-1.

Source: Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB, Pollock RE: *Schwartz's Principles of Surgery, 9th Edition:* http://www.accessmedicine.com

Establishing interpersonal and communication skills equips residents with the necessary tools to communicate effectively with both patients and health professionals.

A subcompetency under communication and interpersonal skills is to "maintain comprehensive, timely, and legible medical records."[5] Not only does communication occur in person, but physicians commonly communicate their plans and thoughts in the medical record. One of the predominant issues in health care is medical errors related to poor communication. The consequences of poor communication have been shown to cause delays in patient care, improper use of resources, and serious adverse events that lead to significant morbidity and mortality.[58] This is especially important now, as many programs have instituted the night float system to maintain compliance with the work hour restrictions. For this system to work effectively, communication is integral for safe patient care during shift changes.[59,60] One example of a creative approach to this new challenge of information transfer is a web-based system that allows for secure storage of patient information, maintenance of patient lists, access to laboratory values and vital sign data, and ability to compile this information to a sign-out list that can be passed on to a coverage team.[61] The residents that participated in the study of this system reported better sign-out quality, decreased time collecting data on prerounds, increased patient contact time, and improved continuity of care. Other medical centers also have begun to institute the use of computerized web-based systems for resident sign-out, and this format may become more widespread as the efficiency and safety of these systems become more

apparent.

Not only should surgeons be technically competent and medically knowledgeable, but interpersonal and communication skills are also vital to patient care. The inherent nature of surgery often requires the bearing of bad news, disclosure of complications, and discussion of end-of-life issues. Learning and harnessing the skill of doing these things well during residency will provide a lifelong tool to effectively and compassionately care for patients.

Professionalism

The core competency of professionalism is expressed as follows: "residents must demonstrate a commitment to carrying out professional responsibilities, adherence to ethical principles, and sensitivity to a diverse patient population."[5] The trainee should demonstrate respect, compassion, and integrity while involved in patient care. In addition, residents should understand that their patients' needs supersede their own self-interest and that they are to be held accountable to their patients, society, and the profession.[5]

The ACS endorsed the Charter of Medical Professionalism as its Code of Professional Conduct in 2002.[62,63] This model of professionalism is based on three principles. First, the physician should be dedicated to the patient's welfare. This should supersede all financial, societal, and administrative forces. Second, the physician should have respect for the patient's autonomy. This entails being honest and providing the patient with all the necessary information to make an informed decision. Third, the medical profession should promote justice in the health care system by removing discrimination due to any societal barriers.[64] The ACS also has developed a Task Force on Professionalism to address the competency of professionalism for practicing surgeons and surgical residents. In 2004, this task force stated that professionalism is not just a desirable trait for surgeons to acquire peripherally but is the "central core" of the profession of surgery. The task force has stated the principles of professionalism and defined the responsibility of surgeons to commit to excellence.[65] In addition, it also has created a multimedia program geared toward teaching residents and surgeons about the principles of professionalism through clinical vignettes and discussions.[66] Kumar and associates evaluated this learning tool and found that residents who watched the ACS DVD had improved conceptual understanding of professionalism and scored higher on tests that evaluated these concepts than their peers who had not watched the video.[67]

Professionalism also has been taught by various other methods reported in the literature. A training program at the University of Washington set out to see if professionalism was teachable, learnable, and measurable. This group defined professionalism, developed a curriculum to teach professionalism, and evaluated these traits by a previously validated tool known as the *Global Resident Competency Rating Form.* They found that, after implementation of the curriculum, residents evaluated by the faculty were given significantly higher scores for traits that demonstrate professionalism such as (a) demonstrating respect, compassion, integrity, and reliability; (b) showing commitment to ethical principles; and (c) displaying sensitivity to patient culture, age, sex, and disabilities.[68] Rosenfeld also described a curriculum for professionalism taught by leaders in the community. This 2-year course on professionalism dealt with various topics such as ethics, communication, professional development, respect, sensitivity, and health care delivery. The topics were presented in various formats via lectures, discussion panels, small groups, and videos. The residents were then assessed for competency through quizzes on clinical vignettes and 360-degree evaluations. The preliminary results revealed that residents were treating their patients and other health care workers in a more professional manner.[69] Heru described the use of role playing and instructional videotapes in teaching

professionalism to residents. The residents who were taught using this format showed an increased awareness of unprofessional behavior and increased sensitivity to others, and were able to better deal with conflict.[70] Teaching residents how to navigate through difficult situations and manage conflict is also another important aspect of professionalism, which can further promote an environment of integrity and mutual respect. Fisher and Ury have described four principles for successful conflict resolution: (a) maintain objectivity by not focusing on the participants but focusing on the problem, (b) relinquish the position of power and inflexibility to concentrate more on individual interests, (c) create outcomes in which both parties will have gains, and (d) make sure there are objective criteria for the negotiating process. All of these principles are related to maintaining an open mind and dialogue and yielding to principles, not pressure.[71] These four principles can be integrated into a curriculum through various teaching techniques to help residents deal with conflict in a nonhostile and productive manner.

The ACS has set standards on professional behavior in the Code of Professional Conduct. With these standards used as a conceptual framework, the development of professionalism should be a continuous process for any physician. Surgeons should constantly analyze and reflect on their behavior and continue to work toward actions based on integrity, honesty, respect, altruism, compassion, accountability, excellence, and leadership. This is an area in which surgical educators, acting as mentors and role models through daily interactions with their patients, residents, and peers, may be the most powerful teaching tool (Fig. 1-2).[72,73]

Fig. 1-2.

Dr. Michael E. DeBakey, a surgical pioneer and transformational health care leader, served as a mentor and role model to generations of residents and inspired professionalism and the pursuit of excellence. He is pictured here with a group of chief residents at the Baylor College of Medicine.

Systems-Based Practice

The ACGME has mandated that "residents must demonstrate an awareness of and responsiveness to the larger context and system of health care, as well as the ability to call effectively on other resources in the system to provide optimal health care."[5] In today's medical world, resources and finances are limited, and each health care provider must understand that the business aspect of medicine is closely interrelated with the effective delivery of care. As health care costs have grown, so have health care management organizations. Learning how to interact with these organizations is crucial for the improvement of health care delivery and allocation of resources. Some reports have demonstrated that surgeons feel deficient in the understanding of public health and the business aspects of surgery.[74]

The ACS has developed a Task Force on Systems-Based Practice to specifically address this particular competency.[75] Systems-based practice is not inherently integrated into the surgical curriculum; therefore, it may be more challenging to incorporate and teach. Several methods for educating residents about systems-based practice have been described in the literature. Dunnington and Williams have arranged for residents to participate in hospital committees that focus on quality improvement and patient safety. The residents keep a journal of the issues that are discussed during the meetings and reflect on how these issues will affect the way that they practice medicine in the future. Both committee members and residents have found this to be a constructive learning process.[17] Davison and colleagues described a longitudinal systems-based practice into their 3-year-long core curriculum which included group discussions (risk management, discharge planning, patient relations), didactic lectures (structure of health care, pathway to surgery, current procedural terminology, governance, contract negotiations), and hospital training sessions. Personnel with expertise in health care delivery systems and health care management were enlisted to teach some of these courses.[76] Englander and associates applied systems-based practice by involving residents in the process of cost-reduction efforts. The residents identified a project that was cost inefficient then identified key issues, devised improvement plans, and subsequently implemented them. This educational exercise saved the hospital over $500,000 per year. The authors concluded that involving residents in cost-reduction efforts helps to teach and assess the skill of systems-based practice.[77] Conferences such as grand rounds, morbidity and mortality conferences, and morning reports have also been modified to teach the principles of systems-based practice.[20,21,23]

Given today's changing health care economics, surgeons are faced with the need to understand the business aspects of medicine to care optimally for patients. This involves being able to work effectively in different health care settings, incorporating cost awareness and risk-benefit analysis in patient care, improving patient safety and quality of care, and identifying system errors and implementing solutions (Fig. 1-3).[5] Unfortunately, this has not been an inherent part of surgical training, and many physicians do not feel that they have an adequate understanding of these concepts.[74] However, there are strides in the right direction with various novel methods to incorporate systems-based practice into surgical curriculums.

Fig. 1-3.

One of the ACGME core competencies requires that residents demonstrate an awareness of and responsiveness to the larger context and system of health care, as well as the ability to call effectively on other resources in the system to provide optimal health care. The Texas Medical Center in Houston, Texas, encompasses 740 acres and 42 member institutions where residents must learn to navigate, comprehend, and utilize the larger health care system as a whole.

ASSESSMENT AND THE ACCREDITATION COUNCIL FOR GRADUATE MEDICAL EDUCATION LEARNING PORTFOLIO

The ACGME not only has mandated the teaching of the six core competencies but also has stated that residents must be evaluated to ensure that they have acquired these necessary skills. There is little doubt that, in the future, these or similar core competencies will be used to assess practicing surgeons as well. Hence, the need to document the acquisition and maintenance of these competencies is important to all surgeons, not just those in training.

Competence has been defined as "the ability to do something well measured against a standard, especially ability acquired through training."[78] Miller has described a model of competency that consists of four levels: "knows," "knows how," "shows how," and "performs." Residents, early in their training, would most likely attain the level of "knows" and "knows how." This would be comparable to a resident's understanding the pathology and clinical diagnosis of appendicitis and the appropriate treatment algorithms. The "shows how" level would be demonstrated by a resident who could demonstrate how to perform an appendectomy while

being supervised by faculty on a simulator or animal model. The "performs" level is the competence level at which the surgeon could perform this operation without any supervision or assistance in a real-life clinical situation. The levels of competency are not based on postgraduate year but are based on the ability to specifically meet a defined objective set forth by a surgical curriculum.[79]

The most pressing question is how to implement a competency-based curriculum and, perhaps even more of a challenge, how to assess the six core competencies. An assessment tool should ideally be reliable, valid, reproducible, and also practical.[80] The two most common evaluation tools in surgical programs have been the American Board of Surgery In-Training Examination (ABSITE) and the ward evaluation. The ABSITE is administered once a year and attempts to test the general medical knowledge and patient care knowledge of surgical trainees. A direct linear correlation has been described between the ABSITE score and the American Board of Surgery Qualifying Examination score,[81] which emphasizes the need to perform at an adequate level on the ABSITE. ABSITE scores also have been found to be higher in programs that have instituted mandatory reading programs and focused problem-based learning education programs.[29,82] Overall, the ABSITE remains a tried and true method of assessing the basic medical knowledge of surgical trainees.

The second method of evaluation has been the ward evaluation. These evaluations are typically performed at the end of the rotation and are subject to biases related to factors such as memory and the general impression of the surgery faculty of the given resident. These evaluations often consist of subjective terms that globally define the residents, for example, *excellent, good,* and *very good.* However, these ratings do not provide any objective data on competence.[83] Even though the ward evaluation provides general information on achievement of educational goals, the new ACGME mandates will require either revising these evaluations to make them more competence based or developing new methods for measuring outcomes.

A number of programs have instituted novel evaluation tools to assess for competency in patient care and medical knowledge. The Operative Performance Rating System (OPRS) is an innovative tool used to assess the competence of patient care that was developed by Larson and colleagues. It is an Internet-based system for evaluating sentinel procedures performed by residents that assesses not only technical skills but also the intraoperative decision-making process. They found this to be a feasible and reliable method. The authors concluded that this may be a way to evaluate competence in patient care, track the development of surgical skills, identify problems early on, and certify competence in a particular procedure.[84] Schell and Flynn described a web-based program for teaching and assessing medical knowledge and patient care. Residents were allowed to follow a self-paced curriculum by viewing a CD-ROM didactic lesson and participating in a minimally invasive skills laboratory to assess competency in the basics of minimally invasive surgery. They found that residents showed significant improvement in their surgical skills, and the trainees described a high satisfaction with this program and felt that it should be an integral component of their education.[10] The Objective Structured Assessment of Technical Skills (OSATS) test was developed at the University of Toronto to assess technical competency. The test is administered in stations that simulate tasks performed in the operating room, such as a small-bowel anastomosis, placement of a T tube, control of inferior vena cava hemorrhage, and so on. The participants are graded by a surgical evaluator who completes two standardized grading forms for each station. One grading form covers the specific steps and technical points of the station (i.e., correct suture, use of forceps, etc), whereas the second form is a global rating scale that evaluates the flow of operation and more subjective but important aspects of an operation. The authors concluded that this method has high reliability and construct validity for assessing competency in technical skills.[85] Furthermore, the OSATS examination has been validated in a number of studies as accurately representing the technical

skills of a surgical trainee when compared with performance in carrying out a procedure on a live patient.[86,87] Virtual simulators have also been used effectively to teach and assess surgical skills, medical knowledge, and practice-based learning and improvement in a controlled environment.[12,88]

Other competencies, such as communication and professionalism, may require a more interactive and direct means for true assessment. The methods most described in the literature involve standardized patients and the 360-degree evaluations. Yudkowsky and colleagues described a method to assess communication and interpersonal skills, patient care, and professionalism known as the *Communication and Interpersonal Skills Objective Structured Clinical Assessment (CIS-OSCE) examination.* This examination was administered to residents in multiple specialties at the University of Illinois at Chicago and consisted of resident interaction with standardized patients on various matters such as obtaining informed consent, relaying bad news, and discussing domestic violence. They found this method of evaluation to be valid and feasible.[50] The Patient Assessment and Management Examination (PAME) to access competencies such as patient care, communication and interpersonal skills, and professionalism has also been described. This examination consists of six stations with standardized patients. It entails an initial assessment, ordering and interpretation of test, discussion of the findings with the patient, and evaluation of a higher level of thinking with implementation of a treatment plan. These interactions are observed by a staff physician, which allows for direct assessment of competencies.[38,51] The 360-degree evaluation to assess communication and professionalism has been described for various specialties. This process involves evaluation of the resident by various people who have had interactions with the resident, including patients as well as nurses and other ancillary staff. The resident's ability to communicate effectively and behave in a professional manner is evaluated based on a scale. This method has been found to be a valid and reliable method to assess for the competencies; however, it can be difficult to carry out.[89–91]

Practice-based learning and systems-based practice have been assessed through existing conferences. Rosenfeld as well as Williams and Dunnington revised their morbidity and mortality conference to allow for assessment of practice-based learning by having residents fill out a practice-based learning log. This allowed staff to determine whether the residents were able to identify key issues and implement improved practice patterns.[20,38] Stiles and associates developed a competency-based morning report format and felt that this was an ideal environment in which to directly assess many of the core competencies, including systems-based practice and practice-based learning, through direct interactions with the residents.[23]

In 2004, the Association of Program Directors and the ACS worked together to develop a web-based system to evaluate all of the core competencies at the end of residents' rotations. This evaluation system was studied throughout multiple institutions and found to be both a reliable and valid method to assess the core competencies.[92] In addition, the ACGME has developed a professional developmental tool called the *ACGME Learning Portfolio.* This portfolio is an interactive web-based portfolio that allows residents to record, organize, and reflect back on their learning experiences. Residents, faculty, and program directors can use this portfolio as a tool to allow for constructive feedback, to monitor a resident's progress, and to identify areas of weakness. It will also enable program directors to evaluate the quality of their curriculums and isolate deficiencies that require improvement.[93] Both of these tools use the web for data collection and evaluation, which allows for centralization and ease in interpretation of the data, permits use of real-time data to identify strengths and weaknesses, and may allow programs to provide competency-based performance data for the RRC. The number of assessment tools for the core competencies continues to increase as programs learn from trial and error. Programs should continue to share their work through

publications to identify programs with models of excellence that can be adopted at other institutions (see Table 1-2).

CONCLUSION

The goal of the ACGME core competency mandate has been to ensure that patient care continues to improve into the twenty-first century with the development of benchmark programs and best educational practices. The goal of the modern surgical educator is to develop a better means to ensure that the material is properly taught and, even more importantly, truly learned. The defined core competencies provide an excellent framework for surgical education. This supplies an exciting foundation for the introduction of new educational initiatives and the development of novel educational programs through collaboration. These innovations should serve to move surgical education forward and allow for improved training of the surgeons of the future.

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KEY POINTS

1. Systemic inflammation is characterized by exaggerated immune responses to either a sterile or infectious process. The cause of inflammatory activation needs to be addressed to resolve the dysregulated immune state.

2. An understanding of the signaling mechanisms and pathways underlying systemic inflammation can help guide therapeutic interventions in injured and/or septic patients.

3. Management of such patients is optimized with the use of evidence-based and algorithm-driven therapy.

4. Nutritional assessments, whether clinical or laboratory guided, and intervention should be considered at an early juncture in all surgical and critically ill patients.

5. Excessive feeding should be avoided in an effort to limit complications, including ventilator dependency, aspiration events, and infections.

SYSTEMIC RESPONSE TO INJURY AND METABOLIC SUPPORT: INTRODUCTION

The immune system has developed to respond to and neutralize pathogenic micro-organisms as well as coordinate tissue repair. The inflammatory response to injury or infection involves cell signaling, cell migration, and mediator release. Minor host insults instigate a local inflammatory response that is transient and in most cases beneficial. Major host insults may propagate reactions that can become amplified, resulting in systemic inflammation and potentially detrimental responses. This topic is highly relevant because systemic inflammation is a central feature[1] 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 increasing incidence of over 900,000 cases per year. Trauma is the leading cause of mortality and morbidity for individuals under 50 years of age.

This chapter reviews the autonomic, cellular, and hormonal responses to injury. These facets of the inflammatory response to injury and infection are discussed in reference to the specific response being considered.

SYSTEMIC INFLAMMATORY RESPONSE SYNDROME

The systemic inflammatory response syndrome (SIRS) is characterized by a sequence of host phenotypic and metabolic responses to systemic inflammation that includes changes in heart rate, respiratory rate, blood pressure, temperature regulation, and immune cell activation (Table 2-1). The systemic inflammatory response includes two

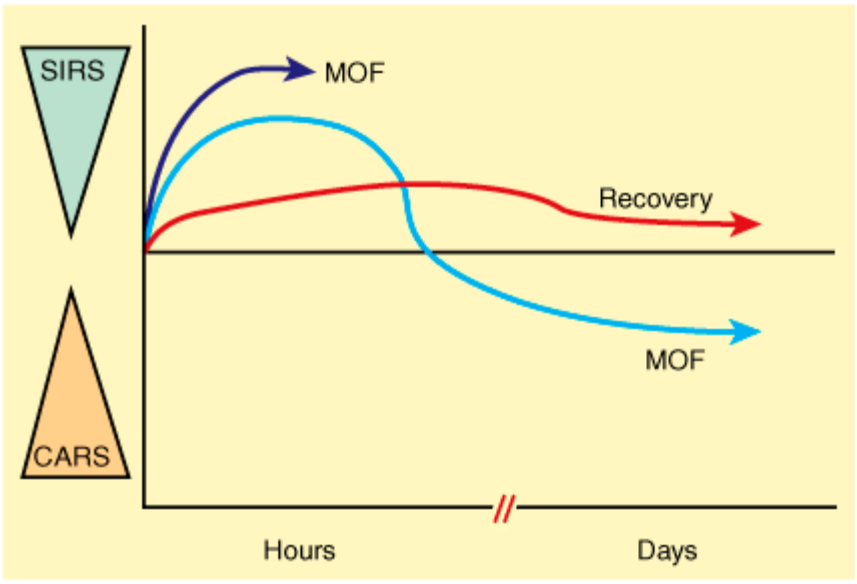
general phases: (1) an acute proinflammatory state resulting from innate immune system recognition of ligands, and (2) an anti-inflammatory phase that may serve to modulate the proinflammatory phase. Under normal circumstances, these coordinated responses direct a return to homeostasis[2] (Fig. 2-1).

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 ≥38C (100.4F) or ≤36C (96.8F)	
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.

Fig. 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*).

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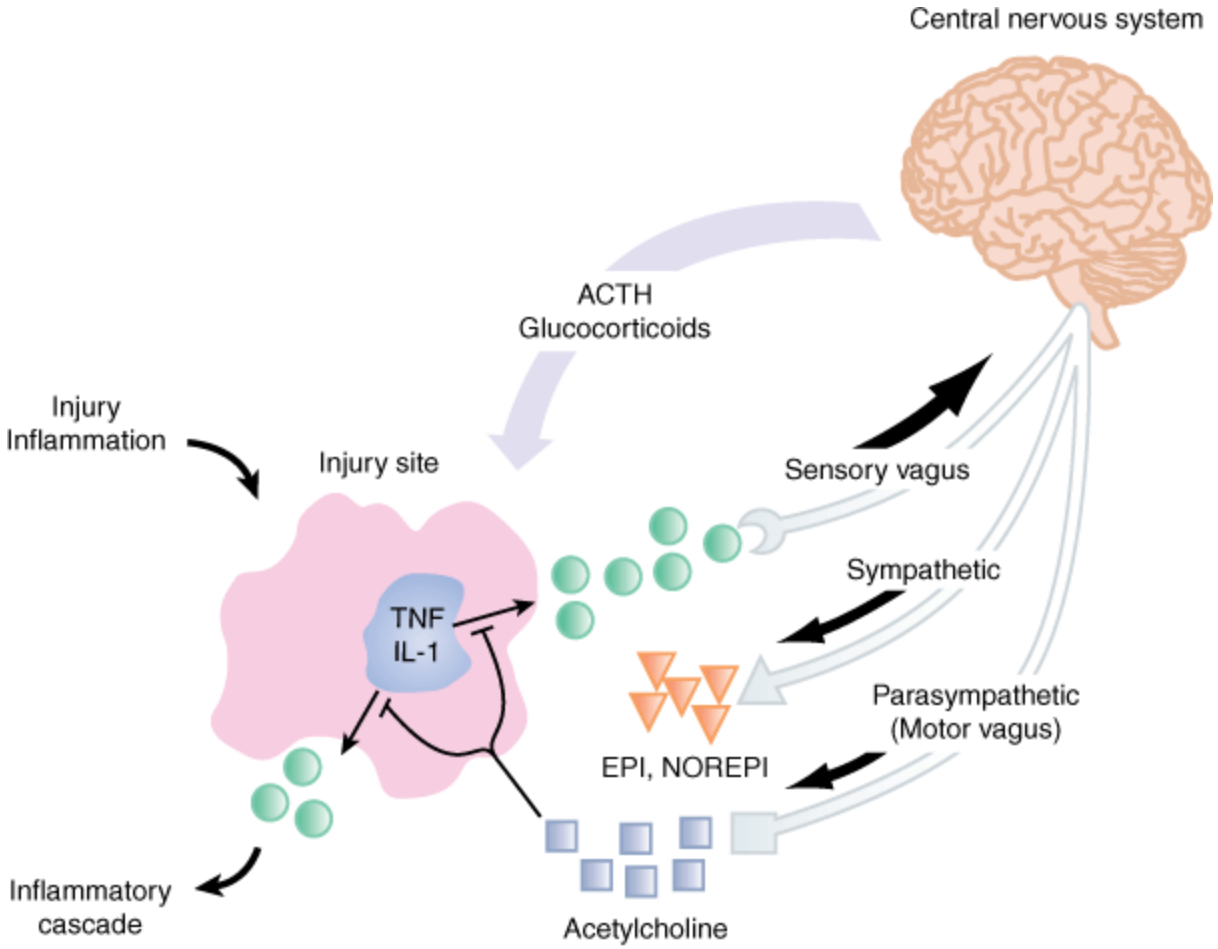
CENTRAL NERVOUS SYSTEM REGULATION OF INFLAMMATION

Afferent Signals to the Brain

The central nervous system (CNS) plays a key role in orchestrating the inflammatory response. The CNS influences multiple organs through both neurohormonal and endocrine signals. Injury or infection signals are recognized by the CNS through afferent signal pathways (Fig. 2-2). The CNS may respond to peripheral inflammatory stimuli through both circulatory and neuronal pathways. Inflammatory mediators activate CNS receptors and establish phenotypic responses such as fever and anorexia. The vagus nerve has been described as highly influential in mediating afferent sensory input to the CNS.[3]

Fig. 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* 420:853, 2002. Copyright 2002.)

Cholinergic Anti-Inflammatory Pathways

The vagus nerve exerts several homeostatic influences, including enhancing gut motility, reducing heart rate, and regulating inflammation. Central to this pathway is the understanding of neurally controlled anti-inflammatory pathways of the vagus nerve. Parasympathetic nervous system activity transmits vagus nerve efferent signals primarily through the neurotransmitter acetylcholine. This neurally mediated anti-inflammatory pathway allows for a rapid response to inflammatory stimuli and also for the potential regulation of early proinflammatory mediator release, specifically tumor necrosis factor (TNF).[4] Vagus nerve activity in the presence of systemic inflammation may inhibit cytokine activity and reduce injury from disease processes such as pancreatitis, ischemia and

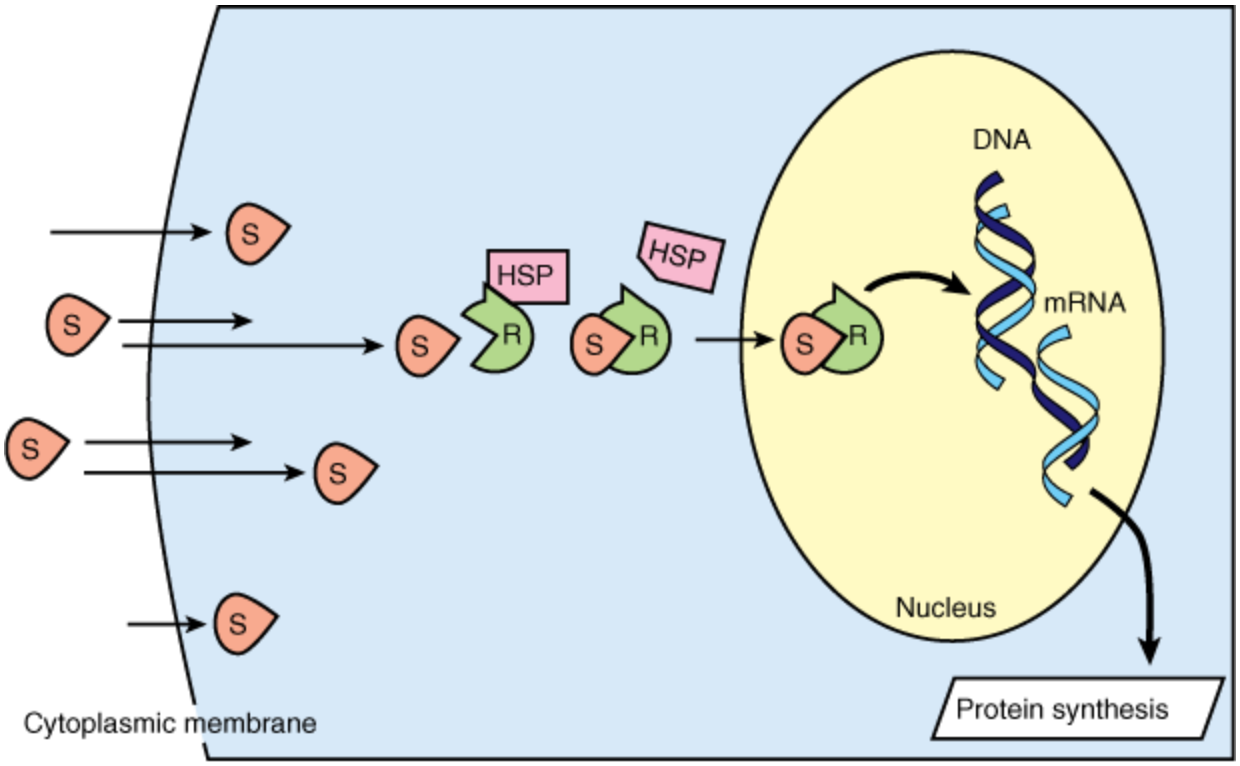
reperfusion, and hemorrhagic shock. This activity is primarily mediated through nicotinic acetylcholine receptors on immune mediator cells such as tissue macrophages. Furthermore, enhanced inflammatory profiles are observed after vagotomy, during stress conditions.[4] Experimental trials have studied this pathway to develop therapeutic interventions. Specifically, nicotine, which also activates nicotinic acetylcholine receptors on immune cells, has been shown to reduce cytokine release after endotoxemia in animal models.[5]

HORMONAL RESPONSE TO INJURY

Hormone Signaling Pathways

Hormones are chemical signals that are released to modulate the function of target cells. Humans release hormones in several chemical categories, including polypeptides (e.g., cytokines, glucagon, and insulin), amino acids (e.g., epinephrine, serotonin, and histamine), and fatty acids (e.g., glucocorticoids, prostaglandins, and leukotrienes). Hormone receptors are present on or within the target cells and allow signal transduction to progress intracellularly mostly through three major pathways: (1) receptor kinases such as insulin and insulin-like growth factor (IGF) receptors, (2) guanine nucleotide-binding or G-protein receptors such as neurotransmitter and prostaglandin receptors, and (3) ligand-gated ion channels that permit ion transport when activated. On activation, the signal is then amplified through the action of secondary signaling molecules. Intracellular signaling leads to downstream effects such as protein synthesis and further mediator release. Protein synthesis is mediated through intracellular receptor binding either by hormone ligands or through subsequently released secondary signaling molecules. These, together with the targeted DNA sequences, activate transcription. The prototype of the intracellular hormone receptor is the glucocorticoid receptor (Fig. 2-3). This receptor is regulated by the stress-induced protein known as *heat shock protein (HSP),* which maintains the glucocorticoid receptor in the cytosol; however, on ligand binding, HSP is released, and the receptor-ligand complex is transported to the nucleus for DNA transcription.[6]

Fig. 2-3.



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.

Virtually every hormone of the hypothalamic-pituitary-adrenal axis influences the physiologic response to injury and stress (Table 2-2), but some with direct influence on the inflammatory response or immediate clinical impact are highlighted here.

Table 2-2 Hormones Regulated by the Hypothalamus, Pituitary, and Autonomic System

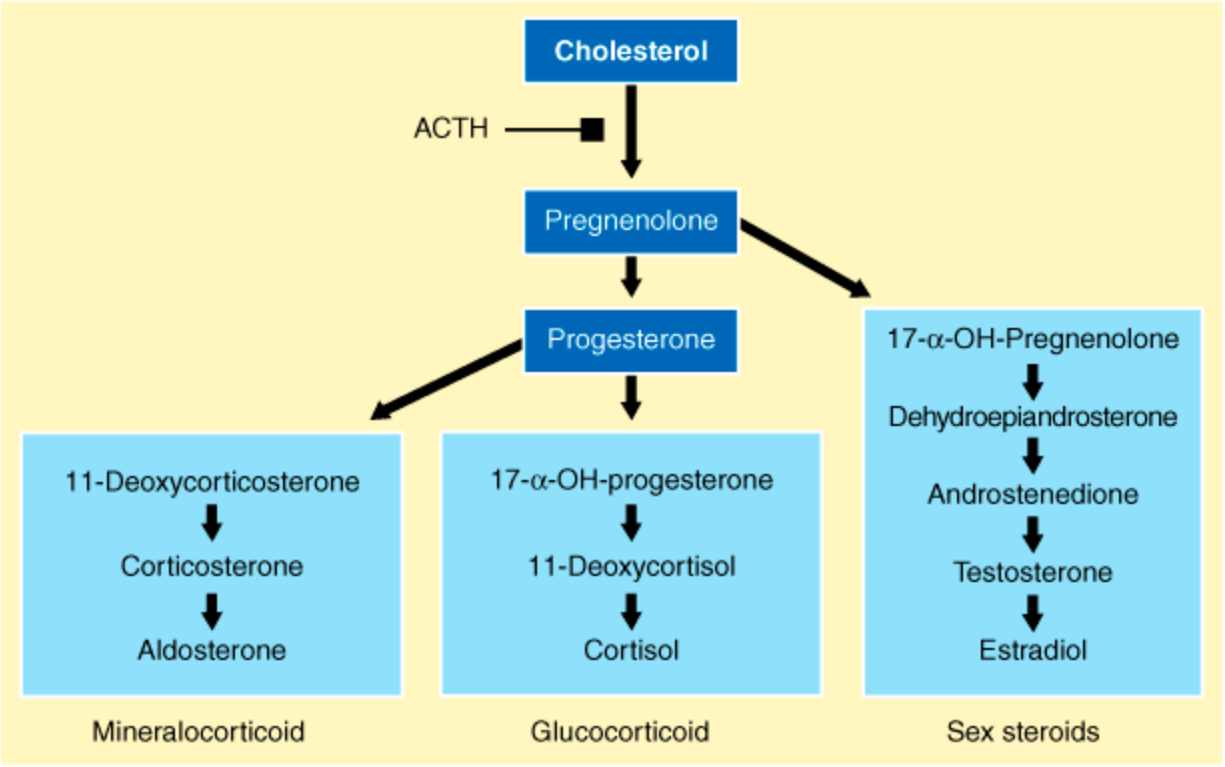
Hypothalamic Regulation
Corticotropin-releasing hormone
Thyrotropin-releasing hormone
Growth hormone–releasing hormone
Luteinizing hormone–releasing hormone
Anterior Pituitary Regulation
Adrenocorticotropic hormone
Cortisol
Thyroid-stimulating hormone
Thyroxine
Triiodothyronine
Growth hormone

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

Adrenocorticotropic Hormone

Adrenocorticotropic hormone (ACTH) is a polypeptide hormone released by the anterior pituitary gland. ACTH binds with receptors in the zona fasciculata of the adrenal gland, which mediate intracellular signaling and subsequent cortisol release. ACTH release follows circadian rhythms in healthy humans; however, during times of stress this diurnal pattern becomes blunted because ACTH release is elevated in proportion to the severity of injury. Several important stimuli for ACTH release are present in the injured patient, including corticotropin-releasing hormone, pain, anxiety, vasopressin, angiotensin II, cholecystokinin, vasoactive intestinal polypeptide, catecholamines, and proinflammatory cytokines. Within the zona fasciculata of the adrenal gland, ACTH signaling activates intracellular pathways that lead to glucocorticoid production (Fig. 2-4). Conditions of excess ACTH stimulation result in adrenocortical hypertrophy.[7]

Fig. 2-4.



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

Cortisol and Glucocorticoids

Cortisol is a glucocorticoid steroid hormone released by the adrenal cortex in response to ACTH. Cortisol release is increased during times of stress and may be chronically elevated in certain disease processes. For example, burn-injured patients may exhibit elevated levels for 4 weeks.

Metabolically, cortisol potentiates the actions of glucagon and epinephrine that manifest as hyperglycemia. Cortisol acts on liver enzymes by decreasing glycogenesis, while increasing gluconeogenesis. In skeletal muscle, cortisol facilitates the breakdown of protein and amino acids, and mediates the release of lactate. Subsequently, these substrates are used by the liver for gluconeogenesis. In adipose tissue cortisol stimulates the release of free fatty acids, triglycerides, and glycerol to increase circulating energy stores. Wound healing also is impaired, because cortisol reduces transforming growth factor beta (TGF-β) and insulin-like growth factor I (IGF-I) in the wound. This effect can be partially ameliorated by the administration of vitamin A.

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. Laboratory findings in adrenal insufficiency include hypoglycemia from decreased gluconeogenesis, hyponatremia from impaired renal tubular sodium resorption, and hyperkalemia from diminished kaliuresis. Diagnostic tests include baseline cortisol levels and ACTH-stimulated cortisol levels, both of which are lower than normal during adrenal insufficiency. Treatment strategies are controversial; however, they include low-dose steroid supplementation.[8]

Glucocorticoids have immunosuppressive properties that have been used when needed, as in organ transplantation. Immunologic changes associated with glucocorticoid administration include thymic involution, depressed cell-mediated immune responses reflected by decreases in T-killer and natural killer cell function, T-lymphocyte blastogenesis, mixed lymphocyte responsiveness, graft-versus-host reactions, and delayed hypersensitivity responses. In addition glucocorticoids inhibit leukocyte migration to sites of inflammation by inhibiting the expression of adhesion molecules. In monocytes, glucocorticoids inhibit intracellular killing while maintaining chemotactic and phagocytic properties. Glucocorticoids inhibit neutrophil superoxide reactivity, suppress chemotaxis, and normalize apoptosis signaling mechanisms but maintain neutrophil phagocytic function. In clinical settings manifested by hypoperfusion, such as septic shock, trauma, and coronary artery bypass grafting, glucocorticoid administration is associated with attenuation of the inflammatory response.

Macrophage Migration–Inhibiting Factor

Macrophage migration–inhibiting factor (MIF) is a neurohormone that is stored and secreted by the anterior pituitary and by intracellular pools within macrophages. MIF is a counterregulatory mediator that potentially reverses the anti-inflammatory effects of cortisol. During times of stress, hypercortisolemia, and host immunosuppression, MIF may modulate the inflammatory response by inhibiting the immunosuppressive effect of cortisol on immunocytes and thereby increasing their activity against foreign pathogens.[9]

Growth Hormones and Insulin-Like Growth Factors

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 secondarily through the enhanced hepatic synthesis of IGF-I. IGF circulates primarily bound to various IGF-binding proteins and also has anabolic effects, including increased protein synthesis and lipogenesis. 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. Critical illness is associated with an acquired GH resistance and contributes to decreased levels of IGF. This effect in part mediates the overall catabolic phenotype manifested during critical illness. In addition, GH enhances phagocytic activity of immunocytes through increased lysosomal superoxide production. GH also increases the proliferation of T-cell populations.[10] Exogenous GH administration has been studied in critically ill patients and may be associated with worse outcomes, including increased mortality, prolonged ventilator dependence, and increased susceptibility to infection.[11] The mechanisms through which GH is associated with these outcomes are unclear, although GH-induced insulin resistance and hyperglycemia may contribute.

Catecholamines

Catecholamines are hormones secreted by the chromaffin cells of the adrenal medulla and function as neurotransmitters in the CNS. The most common catecholamines are epinephrine, norepinephrine, and dopamine,

which have metabolic, immunomodulatory, and vasoactive effects. After severe injury, plasma catecholamine levels are increased threefold to fourfold, with elevations lasting 24 to 48 hours before returning toward baseline levels.

Catecholamines act on both alpha and beta receptors, which are widely distributed on several cell types, including vascular endothelial cells, immunocytes, myocytes, adipose tissue, and hepatocytes. Epinephrine has been shown to induce a catabolic state and hyperglycemia through hepatic gluconeogenesis and glycogenolysis as well as by peripheral lipolysis and proteolysis. In addition epinephrine promotes insulin resistance in skeletal muscle. Catecholamines also increase the secretion of thyroid hormone, parathyroid hormones, and renin, but inhibit the release of aldosterone.

Epinephrine also has immunomodulatory properties mediated primarily through the activation of $beta_2$ receptors on immunocytes. Epinephrine has been shown to inhibit the release of inflammatory cytokines, including TNF, interleukin-1, and interleukin-6, while also enhancing the release of the anti-inflammatory mediator interleukin-10.[12] Similar to cortisol, epinephrine increases leukocyte demargination with resultant neutrophilia and lymphocytosis. The immunomodulatory sequelae of catecholamines in patients during septic shock have yet to be clearly elucidated.

Catecholamines exert several hemodynamic effects, including increased cardiac oxygen demand, vasoconstriction, and increased cardiac output. Catecholamines are used to treat systemic hypotension during septic shock. Because of the increased cardiac stress induced by catecholamines, however, cardioprotective strategies, including beta blockade for patients undergoing surgery, have shown significant benefit in reducing cardiac-related deaths.

Aldosterone

Aldosterone is a mineralocorticoid released by the zona glomerulosa of the adrenal cortex. Aldosterone increases intravascular volume by acting on the renal mineralocorticoid receptor of the distal convoluted tubules to retain sodium and eliminate potassium and hydrogen ions. Aldosterone secretion is stimulated by ACTH, angiotensin II, decreased intravascular volume, and hyperkalemia. Aldosterone deficiency is manifested by hypotension and hyperkalemia, whereas aldosterone excess is manifested by edema, hypertension, hypokalemia, and metabolic alkalosis.

Insulin

Hyperglycemia and insulin resistance are hallmarks of critical illness due to the catabolic effects of circulating mediators, including catecholamines, cortisol, glucagon, and growth hormone. Insulin is secreted by the islets of Langerhans in the pancreas. Insulin mediates an overall host anabolic state through hepatic glycogenesis and glycolysis, peripheral glucose uptake, lipogenesis, and protein synthesis.[13]

Hyperglycemia during critical illness has immunosuppressive effects, including glycosylation of immunoglobulins and decreased phagocytosis and respiratory burst of monocytes, and thus is associated with an increased risk for infection. 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, caution should be exercised to avoid the deleterious sequelae of hypoglycemia from overaggressive glycemic control.[14] The ideal blood glucose range within which to maintain critically ill patients and avoid hypoglycemia has yet to be determined.

ACUTE PHASE PROTEINS

Acute phase proteins are a class of proteins produced by the liver that manifest either increased or decreased

plasma concentration in response to inflammatory stimuli such as traumatic injury and infection. Specifically, C-reactive protein has been studied as a marker of proinflammatory response in many clinical settings, including appendicitis, vasculitis, and ulcerative colitis. Importantly, C-reactive protein levels do not show diurnal variations and are not modulated by feeding. Acute phase protein levels may be unreliable as an index of inflammation in the setting of hepatic insufficiency.

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 2-3). When functioning locally at the site of injury and infection, cytokines mediate the eradication of invading micro-organisms 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).

Table 2-3 Cytokines and Their Sources

TNF
Macrophages/monocytes
Among earliest responders after injury; half-life <20 min; activates TNF receptors 1 and 2; induces significant shock and catabolism
Kupffer cells
Neutrophils
NK cells
Astrocytes
Endothelial cells
T lymphocytes
Adrenal cortical cells
Adipocytes
Keratinocytes
Osteoblasts
Mast cells
Dendritic cells
IL-1
Macrophages/monocytes
Two forms (IL-1α and IL-1β); similar physiologic effects as TNF; induces fevers through prostaglandin activity in anterior hypothalamus; promotes β-endorphin release from pituitary; half-life <6 min
B and T lymphocytes
NK cells
Endothelial cells
Epithelial cells
Keratinocytes
Fibroblasts
Osteoblasts
Dendritic cells
Astrocytes
Adrenal cortical cells

Megakaryocytes
Platelets
Neutrophils
Neuronal cells
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
Induces B-lymphocyte production of IgG4 and IgE, mediators of allergic and anthelmintic response; downregulates TNF, IL-1, IL-6, IL-8
Mast cells
Basophils
Macrophages
B lymphocytes
Eosinophils
Stromal cells
IL-5
T lymphocytes
Promotes eosinophil proliferation and airway inflammation
Eosinophils
Mast cells
Basophils
IL-6
Macrophages
Elicited by virtually all immunogenic cells; long half-life; circulating levels proportional to injury severity; prolongs activated neutrophil survival
B lymphocytes
Neutrophils
Basophils
Mast cells
Fibroblasts
Endothelial cells
Astrocytes
Synovial cells
Adipocytes
Osteoblasts
Megakaryocytes
Chromaffin cells
Keratinocytes
IL-8
Macrophages/monocytes
Chemoattractant for neutrophils, basophils, eosinophils, lymphocytes

T lymphocytes
Basophils
Mast cells
Epithelial cells
Platelets
IL-10
T lymphocytes
Prominent anti-inflammatory cytokine; reduces mortality in animal sepsis and ARDS models
B lymphocytes
Macrophages
Basophils
Mast cells
Keratinocytes
IL-12
Macrophages/monocytes
Promotes T_H 1 differentiation; synergistic activity with IL-2

Neutrophils
Keratinocytes
Dendritic cells
B lymphocytes
IL-13
T lymphocytes
Promotes B-lymphocyte function; structurally similar to IL-4; inhibits nitric oxide and endothelial activation
IL-15
Macrophages/monocytes
Anti-inflammatory effect; promotes lymphocyte activation; promotes neutrophil phagocytosis in fungal infections
Epithelial cells
IL-18
Macrophages
Similar to IL-12 in function; levels elevated in sepsis, particularly gram-positive infections; high levels found in cardiac deaths
Kupffer cells
Keratinocytes
Adrenal cortical cells
Osteoblasts
IFN-γ
T lymphocytes
Mediates IL-12 and IL-18 function; half-life of days; found in wounds 5–7 d after injury; promotes ARDS
NK cells
Macrophages
GM-CSF
T lymphocytes
Promotes wound healing and inflammation through activation of leukocytes
Fibroblasts
Endothelial cells
Stromal cells
IL-21
T lymphocytes

Preferentially secreted by T_H 2 cells; structurally similar to IL-2 and IL-15; activates NK cells, B and T lymphocytes; influences adaptive immunity

HMGB1
Monocytes/lymphocytes
High mobility group box chromosomal protein; DNA transcription factor; late (downstream) mediator of inflammation (ARDS, gut barrier disruption); induces "sickness behavior"

Cytokine	Source	Comment

ARDS = acute respiratory distress syndrome; GM-CSF = granulocyte-macrophage colony-stimulating factor; IFN = interferon; Ig = immunoglobulin; IL = interleukin; NK = natural killer; T_H 1 = helper T cell subtype 1; T_H 2 = helper T cell subtype 2; TNF = tumor necrosis factor.

Anti-inflammatory cytokines also are released, at least in part as an opposing influence to the proinflammatory cascade. These anti-inflammatory mediators also may result in immunocyte dysfunction and host immunosuppression. Cytokine signaling after an inflammatory stimulus is manifested by a fluctuating and counterregulated balance of opposing influences and should not be oversimplified into dichotomic proinflammatory and anti-inflammatory responses.[2]

Heat Shock Proteins

Heat shock proteins (HSPs) are a group of intracellular proteins that are increasingly expressed during times of stress, such as burn injury, inflammation, and infection. HSPs participate in many physiologic processes, including protein folding and protein targeting. The formation of HSPs requires gene induction by the heat shock transcription factor. HSPs bind both autologous and foreign proteins and thereby function as intracellular chaperones for ligands such as bacterial DNA and endotoxin. HSPs are presumed to protect cells from the deleterious effects of traumatic stress[15] and, when released by damaged cells, alert the immune system of the tissue damage.

Reactive Oxygen Species

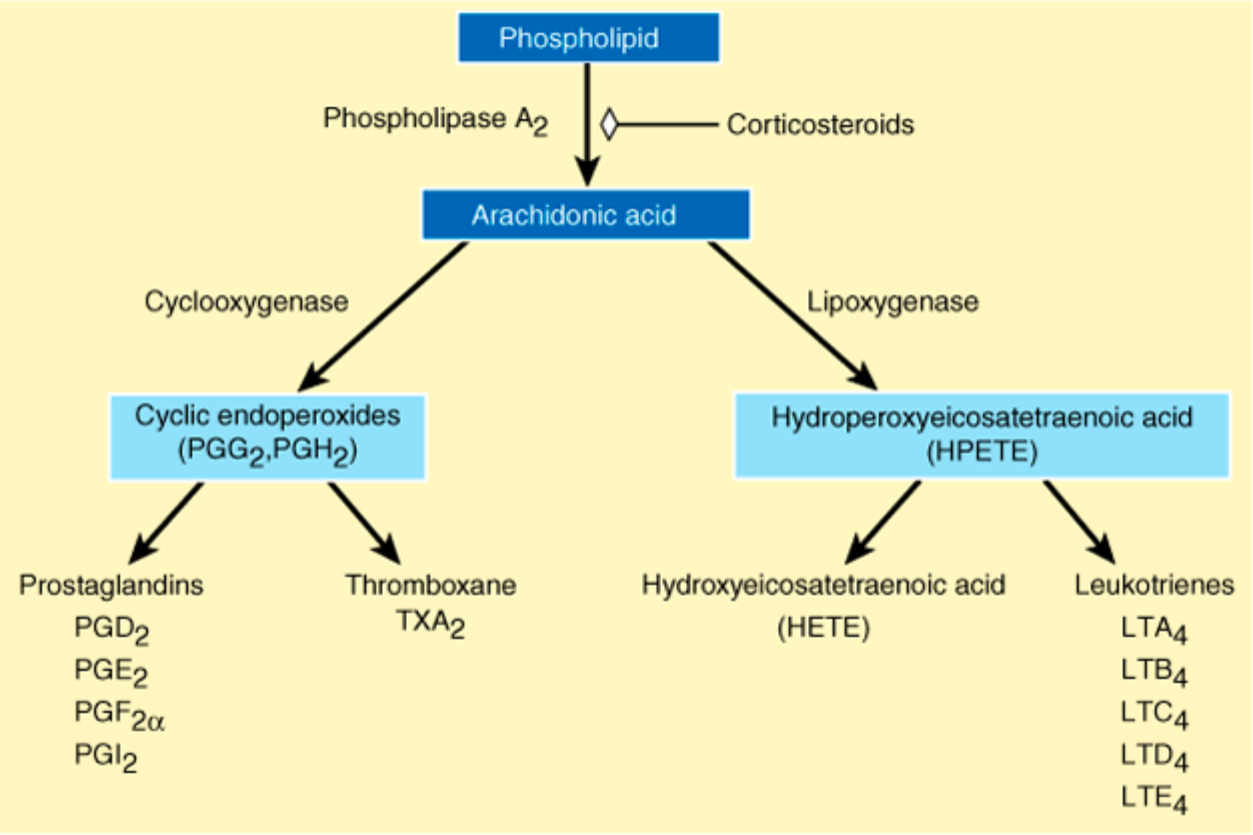
Reactive oxygen species (ROS) are small molecules that are highly reactive due to the presence of unpaired outer orbit electrons. They can cause cellular injury to both host cells and invading pathogens through the oxidation of unsaturated fatty acids within cell membranes.

Oxygen radicals are produced as a by-product of oxygen metabolism as well as by anaerobic processes. Potent oxygen radicals include oxygen, superoxide, hydrogen peroxide, and hydroxyl radicals. The main areas of ROS production include mitochondrial electron transport, peroxisomal fatty acid metabolism, cytochrome P-450 reactions, and the respiratory burst of phagocytic cells. Host cells are protected from the damaging effects of ROS through the activity of endogenous antioxidants such as superoxide dismutase, catalase, and glutathione peroxidase. Under normal physiologic conditions ROS are balanced by antioxidative enzymes. During times of stress or ischemia, however, enzymatic clearance mechanisms are consumed, and on restoration of perfusion, the unbalanced production of ROS leads to reperfusion injury.[16]

Eicosanoids

Eicosanoids are derived primarily by oxidation of the membrane phospholipid arachidonic acid (eicosatetraenoic acid) and are composed of subgroups, including prostaglandins, prostacyclins, hydroxyeicosatetraenoic acids (HETEs), thromboxanes, and leukotrienes. The synthesis of arachidonic acid from phospholipids requires the enzymatic activation of phospholipase A2 (Fig. 2-5). Products of the COX pathway include all of the prostaglandins and thromboxanes. The lipoxygenase pathway generates leukotrienes and HETE. Eicosanoids are not stored within cells but are instead generated rapidly in response to many stimuli, including hypoxic injury, direct tissue injury, endotoxin (lipopolysaccharide, or LPS), norepinephrine, vasopressin, angiotensin II, bradykinin, serotonin, acetylcholine, cytokines, and histamine. Eicosanoid pathway activation also leads to the formation of the anti-inflammatory compound lipoxin, which inhibits chemotaxis and nuclear factor κB (NF-κB) activation. Glucocorticoids, NSAIDs, and leukotriene inhibitors block the end products of eicosanoid pathways.

Fig. 2-5.



Schematic diagram of arachidonic acid metabolism. LT = leukotriene; PG = prostaglandin; TXA_2 = thromboxane A_2 .

Eicosanoids have a broad range of physiologic roles, including neurotransmission, vasomotor regulation, and immune cell regulation (Table 2-4). Eicosanoids mostly generate a proinflammatory response with deleterious host

effects and are associated with acute lung injury, pancreatitis, and renal failure. Leukotrienes are potent mediators of capillary leakage as well as leukocyte adherence, neutrophil activation, bronchoconstriction, and vasoconstriction. Experimental models of sepsis have shown a benefit to inhibiting eicosanoid production. However, human sepsis trials have failed to show a mortality benefit using NSAIDs.[17]

Table 2-4 Systemic Stimulatory and Inhibitory Actions of Eicosanoids

Pancreas
Glucose-stimulated insulin secretion
12-HPETE
PGE2
Glucagon secretion
PGD_2 , PGE2

Liver
Glucagon-stimulated glucose production
PGE2
Fat
Hormone-stimulated lipolysis
PGE2
Bone
Resorption
PGE2 , PGE-m, 6-K-PGE1 , PGF_1 , PGI2

Pituitary
Prolactin
PGE1
Luteinizing hormone
PGE1 , PGE2 , 5-HETE
Thyroid-stimulating hormone
PGA_1 , PGB_1 , PGE1 , PGE1

Growth hormone
PGE1
Parathyroid
Parathyroid hormone
PGE2
PGF_2

Lung
Bronchoconstriction
PGF_2 TXA_2 , LTC_4 , LTD_4 , LTE_4

PGE2
Kidney
Stimulation of renin secretion
PGE2 , PGI2
Gastrointestinal system
Cytoprotective effect

PGE2
Immune response
Suppression of lymphocyte activity
PGE2
Hematologic system
Platelet aggregation
TXA_2

PGI2

Organ/Function	Stimulator	Inhibitor

5-HETE = 5-hydroxyeicosatetraenoic acid; 12-HPETE = 12-hydroxyperoxyeicosatetraenoic acid; 6-K-PGE1 = 6-keto-prostaglandin E1 ; LT = leukotriene; PG = prostaglandin; PGE-m = 13,14-dihydro-15-keto-PGE2 (major urine metabolite of PGE_2); TXA_2 = thromboxane A_2 .

Eicosanoids also have several recognized metabolic effects. Cyclooxygenase pathway products inhibit pancreatic β-cell release of insulin, whereas lipoxygenase pathway products stimulate β-cell activity. Prostaglandins such as prostaglandin E2 can inhibit gluconeogenesis through the binding of hepatic receptors and also can inhibit hormone-stimulated lipolysis.[18]

Fatty Acid Metabolites

Fatty acid metabolites function as inflammatory mediators and as such have significant roles in the inflammatory response. As previously discussed, eicosanoids participate in inflammatory signaling; however, dietary omega-3 and omega-6 fatty acids also influence inflammation. Eicosanoids are produced primarily through two major pathways: (1) with arachidonic acid (omega-6 fatty acid) as substrate and (2) eicosapentaenoic acid (omega-3 fatty acid) as substrate. Many lipid preparations are soy based and are primarily composed of omega-6 fatty acids. Nutritional supplementation with either omega-6 or omega-3 fatty acid can significantly modulate the inflammatory response, because omega-6 substrate is associated with increased downstream mediator production. Omega-3 fatty acids have specific anti-inflammatory effects, including inhibition of NF-κB activity, TNF release from hepatic Kupffer cells, as well as leukocyte adhesion and migration. The anti-inflammatory effects of omega-3 fatty acids on chronic autoimmune diseases such as rheumatoid arthritis, psoriasis, and lupus have been documented in both animals and humans. In experimental models of sepsis, omega-3 fatty acids inhibit inflammation, ameliorate weight loss, increase small-bowel perfusion, and may increase gut barrier protection. In human studies, omega-3 supplementation is associated with decreased production of TNF, interleukin-1β, and interleukin-6 by endotoxin-stimulated monocytes. In a study of surgical patients, preoperative supplementation with omega-3 fatty acid was associated with reduced need for mechanical ventilation, decreased hospital length of stay, and decreased mortality with a good safety profile.[19]

Kallikrein-Kinin System

The kallikrein-kinin system is a group of proteins that contribute to inflammation, blood pressure control, coagulation, and pain responses. Prekallikrein is activated by stimuli such as Hageman factor, trypsin, plasmin, factor XI, glass surfaces, kaolin, and collagen to produce the serine protease kallikrein, which subsequently plays a role in the coagulation cascade. High molecular weight kininogen is produced by the liver and is metabolized by kallikrein to form bradykinin.

Kinins mediate several physiologic processes, including vasodilation, increased capillary permeability, tissue edema, pain pathway activation, inhibition of gluconeogenesis, and increased bronchoconstriction. They also increase renal vasodilation and consequently reduce renal perfusion pressure. Decreased renal perfusion leads to activation of the renin-angiotensin-aldosterone system, which acts on the nephron to actively resorb sodium and subsequently increase intravascular volume.

Bradykinin and kallikrein levels are increased during gram-negative bacteremia, hypotension, hemorrhage, endotoxemia, and tissue injury. The degree of elevation in the levels of these mediators has been associated with the magnitude of injury and mortality. Clinical trials using bradykinin antagonists have shown some benefit in patients with gram-negative sepsis.[20]

Serotonin

Serotonin is a monoamine neurotransmitter (5-hydroxytryptamine) derived from tryptophan. Serotonin is synthesized by neurons in the CNS as well as by enterochromaffin cells of the GI tract and platelets. This neurotransmitter stimulates vasoconstriction, bronchoconstriction, and platelet aggregation. Serotonin also increases cardiac inotropy and chronotropy through nonadrenergic cyclic adenosine monophosphate (cAMP) pathways. Serotonin receptors are located in the CNS, GI tract, and monocytes.[21] Ex vivo study has shown that serotonin receptor blockade is associated with decreased production of TNF and interleukin-1 in endotoxin-treated monocytes. Serotonin is released at sites of injury, primarily by platelets; however, its role in inflammatory modulation has yet to be clearly defined.

Histamine

Histamine is synthesized by the decarboxylation of the amino acid histidine. Histamine is either rapidly released or stored in neurons, skin, gastric mucosa, mast cells, basophils, and platelets. There are four histamine receptor (H) subtypes with varying physiologic roles. H_1 binding mediates vasodilation, bronchoconstriction, intestinal motility, and myocardial contractility. H_2 binding stimulates gastric parietal cell acid secretion. H_3 is an autoreceptor found on presynaptic histamine-containing nerve endings and leads to downregulation of histamine release. H_4 is expressed primarily in bone marrow, eosinophils, and mast cells. H_4 binding interactions have not been fully delineated but have been associated with eosinophil and mast cell chemotaxis. Increased histamine release has been documented in hemorrhagic shock, trauma, thermal injury, endotoxemia, and sepsis.[22]

CYTOKINE RESPONSE TO INJURY

Tumor Necrosis Factor

Tumor necrosis factor alpha (TNF) 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 macrophages, monocytes, and T cells, which are abundant in peritoneum and splanchnic tissues. Although the circulating half-life of TNF is brief, the activity of TNF elicits many metabolic and immunomodulatory activities. TNF stimulates muscle breakdown and cachexia through increased catabolism, insulin resistance, and redistribution of amino acids to hepatic circulation as fuel substrates. In addition, TNF also mediates coagulation activation, cell migration, and macrophage phagocytosis, and enhances the expression of adhesion molecules, prostaglandin E2 , platelet-activating factor, glucocorticoids, and eicosanoids.[23]

Tumor necrosis factor receptors (TNFRs) are composed of two subtypes: TNFR-1 and TNFR-2. TNFR-1 is ubiquitously expressed in most tissues and, on ligand binding, mediates apoptosis through proteolytic caspases.

TNFR-2 is expressed primarily on immunocytes and, on ligand binding, leads to NF-κB activation and subsequent amplification of the inflammatory signal. TNFRs exist in both transmembrane and soluble form. In response to inflammatory stimuli such as injury and infection, TNFRs are proteolytically cleaved from cell membranes and are readily detectable in soluble form. This may represent a mechanism of inflammatory regulation, because soluble TNFRs maintain their affinity for TNF and thereby compete with and limit the activation of transmembrane TNFR.[24]

Interleukin-1

Interleukin-1 (IL-1) is represented by two active subtypes, IL-1α and IL-1β. IL-1α is primarily membrane associated and functions through cellular contact. IL-1β is readily detectable in soluble form and mediates an inflammatory sequence similar to that of TNF. IL-1 is primarily synthesized by monocytes, macrophages, endothelial cells, fibroblasts, and epidermal cells. IL-1 is released in response to inflammatory stimuli, including cytokines (TNF, IL-2, interferon-γ [IFN-γ]) and foreign pathogens, and requires the formation of the inflammasome in the cell for processing and release. High doses of either IL-1 or TNF are associated with profound hemodynamic compromise. Interestingly, low doses of both IL-1 and TNF combined elicit hemodynamic events similar to those elicited by high doses of either mediator, which suggests a synergistic effect. IL-1 is an endogenous pyrogen because it acts on the hypothalamus by stimulating prostaglandin activity and thereby mediates a febrile response.

IL-1 is autoregulated by endogenous IL-1 receptor antagonists, which are released in response to inflammatory stimuli and compete with IL-1 at receptor binding sites. There are two primary receptor types for IL-1: IL-1R1 and IL-1R2. IL-1R1 is widely expressed and mediates inflammatory signaling on ligand binding. IL-1R2 is proteolytically cleaved from the membrane surface to soluble form on activation and thus serves as another mechanism for competition and regulation of IL-1 activity.[25]

Interleukin-2

Interleukin-2 (IL-2) is upregulated in response to IL-1 and is primarily a promoter of T-lymphocyte proliferation and differentiation, immunoglobulin production, and gut barrier integrity. IL-2 binds to IL-2 receptors, which are expressed on leukocytes. Partly due to its short half-life of <10 minutes, IL-2 is not readily detectable after acute injury. IL-2 receptor blockade induces immunosuppressive effects and can be pharmacologically used for organ transplantation. Attenuated IL-2 expression observed during major injury or blood transfusion may contribute to the relatively immunosuppressed state of the surgical patient.[26]

Interleukin-4

Interleukin-4 (IL-4) is released by activated helper T cells and stimulates the differentiation of T cells, and also stimulates T-cell proliferation and B-cell activation. It is also important in antibody-mediated immunity and in antigen presentation. IL-4 induces class switching of differentiating B lymphocytes to produce predominantly immunoglobulin G4 and immunoglobulin E, which are important immunoglobulins in allergic and antihelmintic responses. IL-4 has anti-inflammatory effects on macrophages, exhibited by an attenuated response to proinflammatory mediators such as IL-1, TNF, interleukin-6, and interleukin-8. In addition, IL-4 appears to increase macrophage susceptibility to the anti-inflammatory effects of glucocorticoids.

Interleukin-6

Interleukin-6 (IL-6) release by macrophages is stimulated by inflammatory mediators such as endotoxin, TNF, and IL-1. IL-6 is increasingly expressed during times of stress, as in septic shock. After injury, IL-6 levels in the circulation are detectable by 60 minutes, peak between 4 and 6 hours, and can persist for as long as 10 days. Plasma levels of IL-6 are proportional to the degree of injury during surgery. Interestingly, IL-6 has

counterregulatory effects on the inflammatory cascade through the inhibition of TNF and IL-1. IL-6 also promotes the release of soluble tumor necrosis factor receptors and IL-1 receptor antagonists, and stimulates the release of cortisol. High plasma IL-6 levels have been associated with mortality during intra-abdominal sepsis.[27]

Interleukin-8

Interleukin-8 (IL-8) is synthesized by macrophages as well as other cell lines such as endothelial cells. Critical illness as manifested during sepsis is a potent stimulus for IL-8 expression. IL-8 stimulates the release of IFN-γ and functions as a potent chemoattractant for neutrophils. Elevated plasma IL-8 also has been associated with disease severity and end organ dysfunction during sepsis.[28]

Interleukin-10

Interleukin-10 (IL-10) is an anti-inflammatory cytokine synthesized primarily by monocytes; however, it is also released by other lymphocytes. IL-10 is increasingly expressed during times of systemic inflammation, and its release is specifically enhanced by TNF and IL-1. IL-10 inhibits the secretion of proinflammatory cytokines, including TNF and IL-1, partly through the downregulation of NF-κB and thereby functions as a negative feedback regulator of the inflammatory cascade. Experimental models of inflammation have shown that neutralization of IL-10 increases TNF production and mortality, whereas restitution of circulating IL-10 reduces TNF levels and subsequent deleterious effects. Increased plasma levels of IL-10 also have been associated with mortality and disease severity after traumatic injury. IL-10 may significantly contribute to the underlying immunosuppressed state during sepsis through the inhibition and subsequent anergy of immunocytes.[29]

Interleukin-12

Interleukin-12 (IL-12) has been described as a regulator of cell mediated immunity. IL-12 is released by activated phagocytes, including monocytes, macrophages, neutrophils, and dendritic cells, and is increasingly expressed during endotoxemia and sepsis. IL-12 stimulates lymphocytes to increase secretion of IFN-γ with the costimulus of interleukin-18 and also stimulates natural killer cell cytotoxicity and helper T cell differentiation. IL-12 release is inhibited by IL-10. IL-12 deficiency inhibits phagocytosis in neutrophils. In experimental models of inflammatory stress, IL-12 neutralization conferred a mortality benefit in mice during endotoxemia. However, in a cecal ligation and puncture model of intraperitoneal sepsis, IL-12 blockade was associated with increased mortality. Furthermore, later studies of intraperitoneal sepsis observed no difference in mortality with IL-12 administration; however, IL-12 knockout mice exhibited increased bacterial counts and inflammatory cytokine release, which suggests that IL-12 may contribute to an antibacterial response. IL-12 administration in chimpanzees is capable of stimulating the release of proinflammatory mediators such as IFN-γ and also anti-inflammatory mediators, including IL-10, soluble TNFR, and IL-1 receptor antagonists. In addition, IL-12 enhances coagulation as well as fibrinolysis. Despite evidence of both proinflammatory and anti-inflammatory pathway activation, most evidence suggests that IL-12 contributes to an overall proinflammatory response.[30]

Interleukin-13

Interleukin-13 (IL-13) exerts many of the same immunomodulatory effects as does IL-4. IL-13 inhibits monocyte release of TNF, IL-1, IL-6, and IL-8, while increasing the secretion of IL-1R antagonist. However, unlike IL4, IL-13 has no identifiable effect on T lymphocytes and only has influence on selected B-lymphocyte populations. Increased IL-13 expression is observed during septic shock and mediates neutropenia, monocytopenia, and leukopenia. In addition, IL-13 inhibits leukocyte interaction with activated endothelial surfaces. Similar to IL-4 and IL-10, IL-13 has a net anti-inflammatory effect.[31]

Interleukin-15

Interleukin-15 (IL-15) is synthesized in many cell types, including macrophages and skeletal muscle after endotoxin administration. IL-15 stimulates natural killer cell activation as well as B-cell and T-cell proliferation and thus functions as a regulator of cellular immunity. IL-15 has immunomodulatory effects similar to those of IL-2, in part due to shared receptor subunits. Furthermore, IL-15 acts as a potent inhibitor of lymphocyte apoptosis by enhancing the expression of antiapoptotic molecules such as Bcl-2.[32]

Interleukin-18

Interleukin-18 (IL-18), formerly IFN-γ–inducing factor, is synthesized primarily by macrophages. IL-18 and its receptor complex are members of the IL-1 superfamily. As with IL-1, macrophages release IL-18 in response to inflammatory stimuli, including endotoxin, TNF, IL-1, and IL-6. IL-18 level also is elevated during sepsis. IL-18 activates NF-κB through an Myeloid differentiation primary response gene (88) (MyD88)-dependent pathway with subsequent proinflammatory mediator release. IL-18 regulation is in part mediated through IL-18–binding protein (IL-18BP). This molecule is not a soluble receptor isoform but rather a specific endogenous antagonist. IL-18 also mediates hepatotoxicity associated with Fas ligand and TNF. The viral skin pathogen molluscum contagiosum secretes an IL-18BP–like protein, which neutralizes IL-18 and thereby inhibits the inflammatory response. IL-18 and IL-12 act synergistically to release IFN-γ from T cells. In a murine model of systemic inflammation, IL-18 neutralization reduced lethal endotoxemia. IL-18 signaling also is associated with increased expression of intercellular adhesion molecule-1. Interestingly, in a murine model of systemic inflammation, a reversal of left ventricular dysfunction was observed with IL-18 blockade, which suggests that IL-18 may contribute to the hemodynamic compromise during septic shock.[33]

Interferons

Interferons were first recognized as soluble mediators that inhibited viral replication through the activation of specific antiviral genes in infected cells. Interferons are categorized into two major subtypes based on receptor specificity and sequence homology. Type I interferons include IFN-α, IFN-β, and IFN-ω, which are structurally related and bind to a common receptor, IFN-α receptor. Type I interferons are expressed in response to many stimuli, including viral antigens, double-stranded DNA, bacteria, tumor cells, and LPS. Type I interferons influence adaptive immune responses by inducing the maturation of dendritic cells and by stimulating class I MHC expression. IFN-α and IFN-β also enhance immune responses by increasing the cytotoxicity of natural killer cells both in culture and in vivo. In murine models, the absence of IFN-α receptor results in greater susceptibility to viral infection as well as diminished LPS-induced lethality. Furthermore, type I interferons have also been studied as therapeutic agents in hepatitis C and relapsing multiple sclerosis.

Many of the physiologic effects observed with increased levels of IL-12 and IL-18 are mediated through IFN-γ. IFN-γ is a type II interferon secreted by T lymphocytes, natural killer cells, and antigen-presenting cells in response to bacterial antigens, IL-2, IL-12, and IL-18. IFN-γ stimulates the release of IL-12 and IL-18. Negative regulators of IFN-γ include IL4, IL-10, and glucocorticoids. IFN-γ binding with a cognate receptor activates the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, leading to subsequent induction of biologic responses. Macrophages stimulated by IFN-γ demonstrate enhanced phagocytosis and microbial killing, and increased release of oxygen radicals, partly through a nicotinamideadenosine dinucleotide phosphate–dependent phagocyte oxidase. IFN-γ mediates macrophage stimulation and thus may contribute to acute lung injury after major surgery or trauma. Diminished IFN-γ level, as seen in knockout mice, is associated with increased susceptibility to both viral and bacterial pathogens. IFN-γ regulates trafficking of immunocytes to

sites of inflammation via upregulation of chemoattractants [e.g., monokine induced by IFN- (MIG), macrophage inflammatory protein 1-alpha and 1-beta] and adhesion molecules (e.g., intercellular adhesion molecule-1, vascular cell adhesion molecule-1). In addition, IFN-γ promotes differentiation of T cells to the helper T cell subtype 1 and also enhances B-cell isotype switching to immunoglobulin G.[34]

Granulocyte-Macrophage Colony-Stimulating Factor

Granulocyte-macrophage colony-stimulating factor (GM-CSF), as the name suggests, upregulates both granulocyte and monocyte cell lines from hematopoietic bone marrow stem cells. GM-CSF plasma levels are low to undetectable but rapidly increase in response to inflammatory stimuli such as TNF. GM-CSF inhibits both monocyte and neutrophilapoptosis and enhances macrophage cytokine release in response to inflammatory stimuli. GM-CSF also potentiates the release of neutrophil superoxide as well as the cytotoxicity of monocytes. Administration of GM-CSF has proven beneficial during the treatment of fungal infections in immunocompromised patients. GM-CSF may potentiate acute lung injury during critical illness, because GM-CSF blockade has been found to be associated with decreased alveolar macrophage activity and NF-κB intensity. This growth factor is effective in promoting the maturation and recruitment of functional leukocytes necessary for normal inflammatory cytokine responses and also may be effective in wound healing.[35]

High Mobility Group Box 1

High mobility group box 1 (HMGB1) is a DNA transcription factor that facilitates the binding of regulatory protein complexes to DNA. HMGB1 is actively secreted by macrophages, natural killer cells, and enterocytes. Endotoxin, TNF, and IFN-γ promote the release of HMGB1, and in a murine model of intraperitoneal sepsis, increased circulating HMGB1 was associated with increased mortality. HMGB1 also appears to have cytokine-like activities, because it promotes the release of TNF from monocytes. Interestingly, elevation of plasma HMGB1 levels after experimental induction of endotoxemia is delayed relative to that of other inflammatory mediators, with levels peaking at 16 hours and remaining elevated beyond 30 hours. This response contrasts with that of acute inflammatory mediators such as TNF, which peaks at 1 to 2 hours and becomes undetectable by 12 hours. Furthermore, HMGB1 blockade is associated with decreased mortality even when initiated 4 to 24 hours after the inflammatory stimulus.[36]

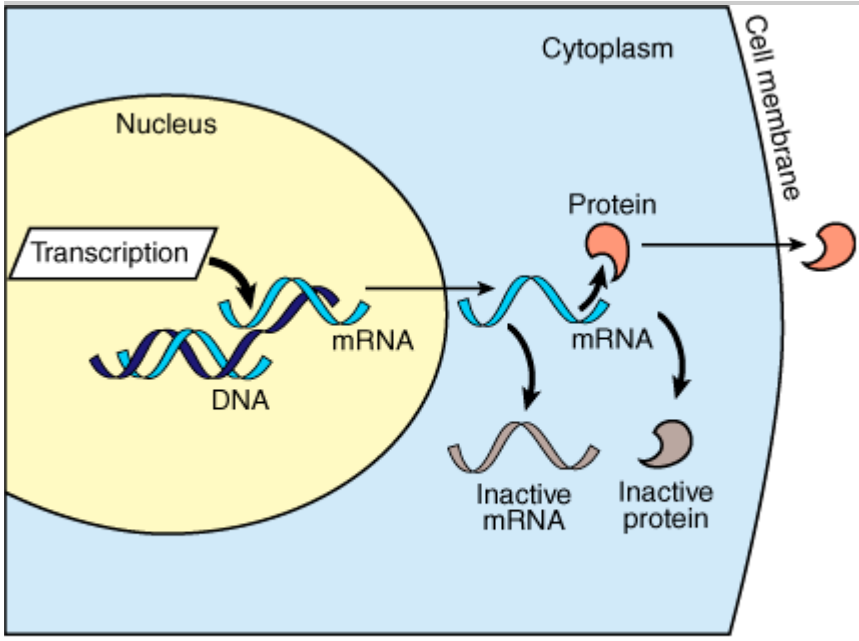
HMGB1 is passively released by necrotic cells. Thus, HMGB1 alone or in combination with other molecules may contribute to the regulation of inflammation after tissue injury. Receptors for HMGB1 are receptors for advanced glycation end products and toll-like receptor 4. Binding leads to the proinflammatory response through the activation of NF-κB. Clinical trials have demonstrated increased plasma HMGB1 during systemic inflammation, as in sepsis, hemorrhagic shock, pancreatitis, myocardial infarction, and major surgery.

CELLULAR RESPONSE TO INJURY

Gene Expression and Regulation

Many genes are regulated at the point of DNA transcription and thus influence whether messenger RNA (mRNA) and its subsequent product are expressed (Fig. 2-6). These mRNA transcripts are also regulated by modulation mechanisms, including (a) splicing, which can cleave mRNA and remove noncoding regions; (b) capping, which modifies the 5' ends of the mRNA sequence to inhibit breakdown by exonucleases; (c) and the addition of a polyadenylated tail, which adds a noncoding sequence to the mRNA, effectively increasing the half-life of the transcript. Once out of the nucleus, the mRNA can be inactivated or translated to form proteins. Many protein products are also further modified for specific function or trafficking.

Fig. 2-6.



Source: Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB, Pollock RE: *Schwartz's Principles of Surgery, 9th Edition:* http://www.accessmedicine.com

Gene expression and protein synthesis can occur within a 24-hour period. The process can be regulated at various stages: transcription, messenger RNA (mRNA) processing, or protein packaging. At each stage, it is possible to inactivate the mRNA or protein, rendering these molecules nonfunctional.

Gene expression relies on the coordinated action of transcription factors and coactivators (i.e., regulatory proteins), which are complexes that bind to highly specific DNA sequences upstream of the target gene known as the *promoter region.* Enhancer sequences of DNA mediate gene expression, whereas repressor sequences are noncoding regions that bind proteins to inhibit gene expression. During systemic inflammation, transcription factors are highly important, because regulation of cytokine gene expression may have profound effects on the clinical phenotype.

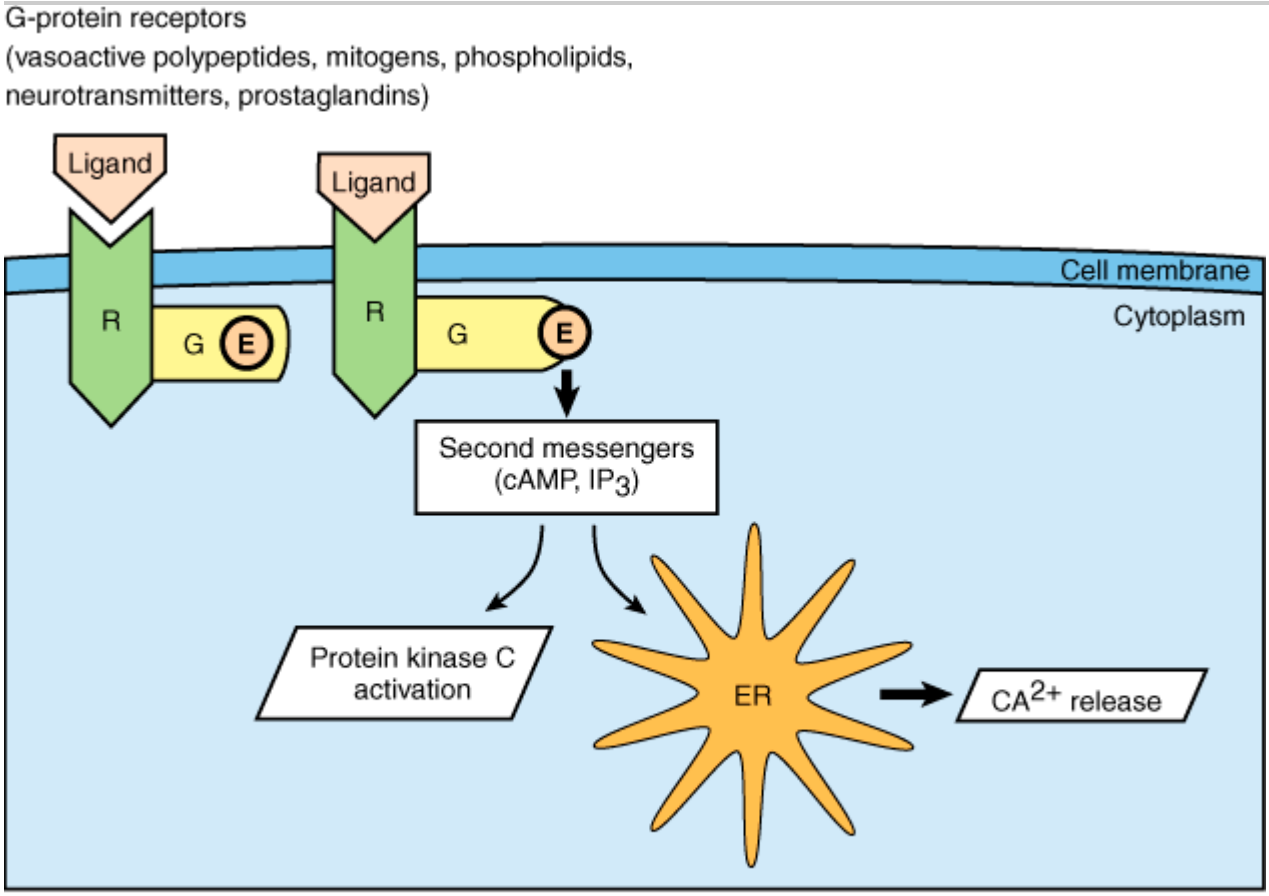
CELL SIGNALING PATHWAYS

G-Protein Receptors

G-protein receptors (GPRs) are a large family of transmembrane receptors. They bind a multitude of ligands (e.g., epinephrine, bradykinin, leukotriene) and are involved in signal transduction during the inflammatory response. Extracellular ligands bind to GPR, which result in a conformational change and activation of associated proteins. The two major second messengers of the G-protein pathway are (1) cAMP, and (2) calcium, released from the endoplasmic reticulum (Fig. 2-7). Increased intracellular cAMP can activate gene transcription through the activity of intracellular signal transducers such as protein kinase A. Increased intracellular calcium can activate the intracellular signal transducer phospholipase C with further subsequent downstream effects. GPR binding also can promote the activity of protein kinase C, which can subsequently stimulate NF-κB as well as other transcription

factors.

Fig. 2-7.



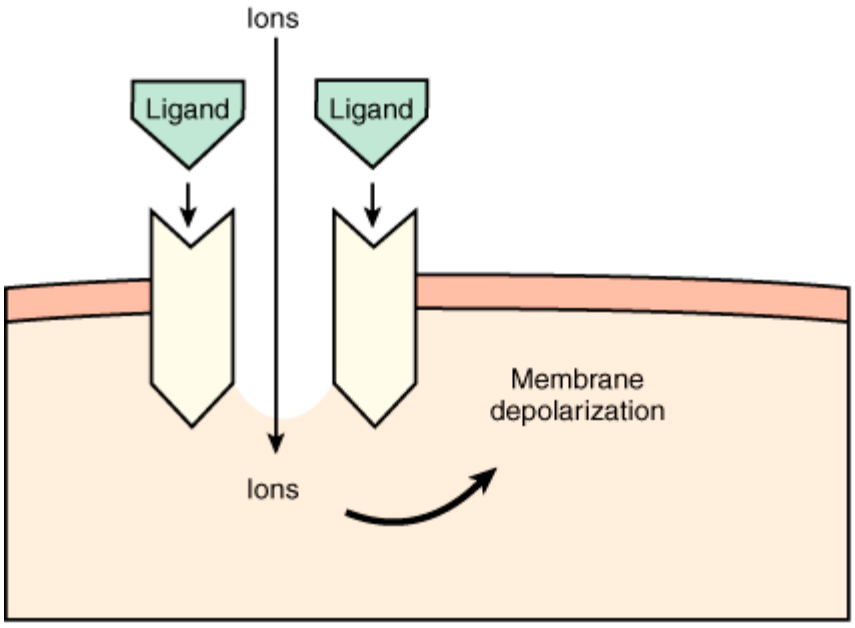
G-protein–coupled receptors are transmembrane proteins. The G-protein receptors respond to ligands such as adrenaline and serotonin. On ligand binding to the receptor (R), the G protein (G) undergoes a conformational change through guanosine triphosphate–guanosine diphosphate conversion and in turn activates the effector (E) component. The E component subsequently activates second messengers. The role of inositol triphosphate (IP_3) is to induce release of calcium from the endoplasmic reticulum (ER). cAMP = cyclic adenosine triphosphate.

Ligand-Gated Ion Channels

Ligand-gated ion channels (LGICs) are transmembrane receptors that allow the rapid influx of ions (e.g., sodium, calcium, potassium, chloride) and are central to the signal transduction of neurotransmitters. On ligand binding LGICs effectively convert a chemical signal into an electrical signal. The prototypical LGIC is the nicotinic acetylcholine receptor (Fig. 2-8).

Fig. 2-8.

Ligand-gated ion channels
(neurotransmitters, amino acids,
acetylcholine)

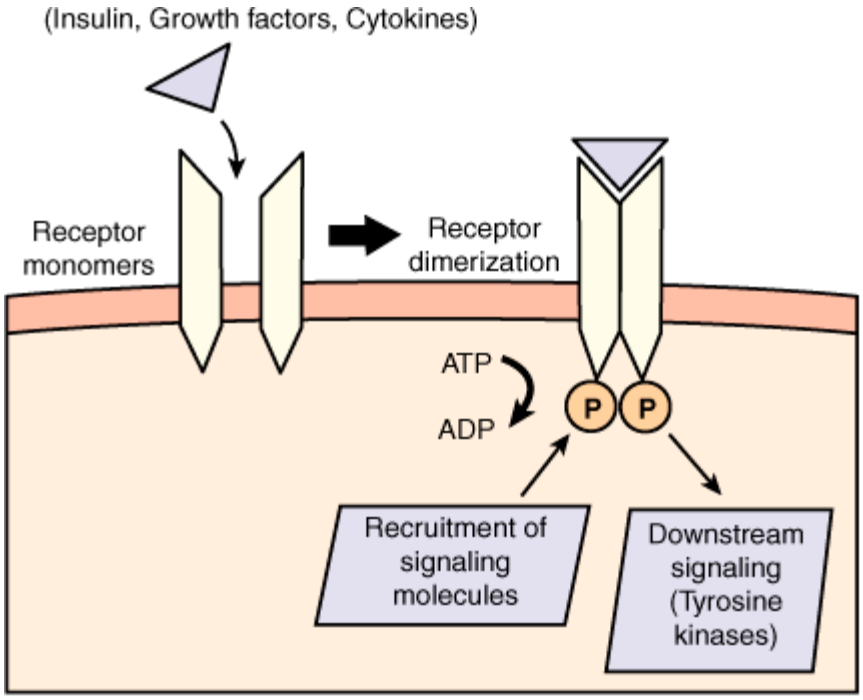


Ligand-gated ion channels convert chemical signals into electrical signals, inducing a change in cell membrane potential. On activation of the channel, millions of ions per second influx into the cell. These channels are composed of many subunits, and the nicotinic acetylcholine receptor is one such example.

Receptor Tyrosine Kinases

Receptor tyrosine kinases (RTKs) are transmembrane receptors that are involved in cell signaling for several growth factors, including platelet-derived growth factor, insulin-like growth factor, epidermal growth factor, and vascular endothelial growth factor. On ligand binding, RTKs dimerize with adjacent receptors, undergo autophosphorylation, and recruit secondary signaling molecules (e.g., phospholipase C) (Fig. 2-9). Activation of RTK is important for gene transcription as well as cell proliferation and may have influence in the development of many types of cancer.

Fig. 2-9.

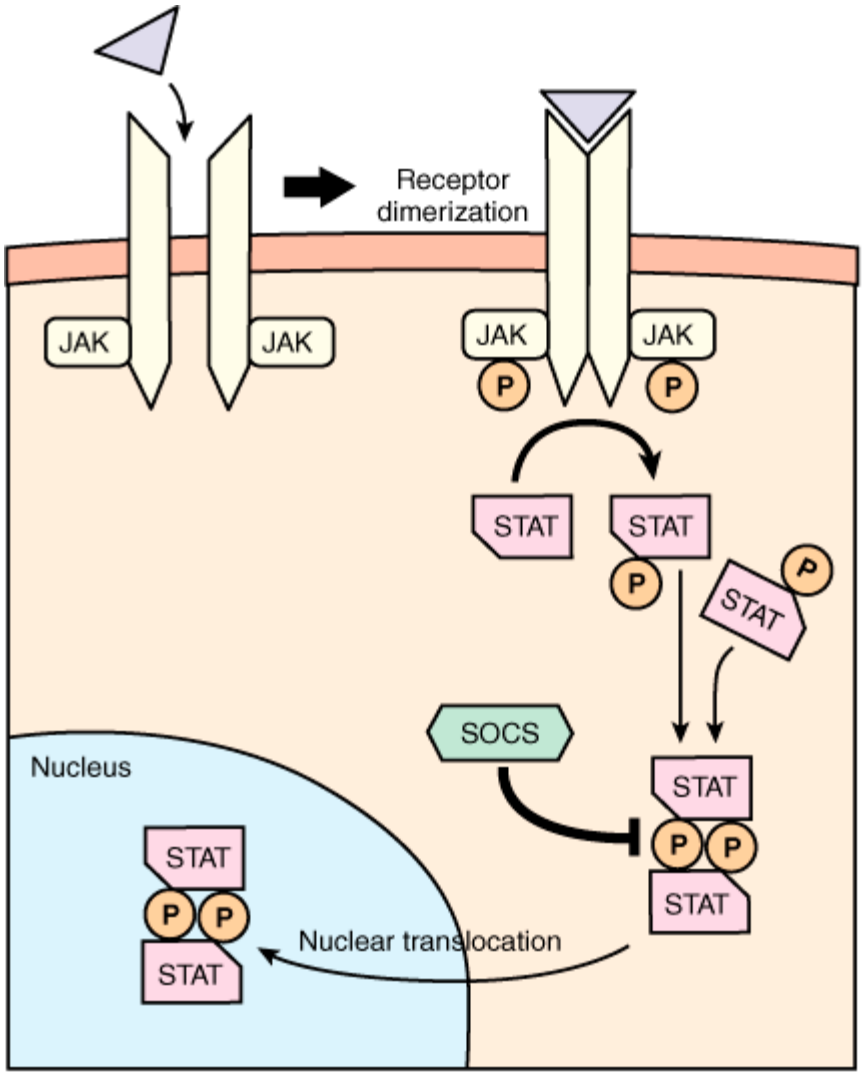


The receptor tyrosine kinase requires dimerization of monomeric units. These receptors possess intrinsic enzymatic activity that requires multiple autophosphorylation steps to recruit and activate intracellular signaling molecules. ADP = adenosine diphosphate; ATP = adenosine triphosphate; P = phosphate.

Janus Kinase/Signal Transducer and Activator of Transcription Signaling

The Janus kinases (JAKs) represent a family of tyrosine kinases that mediate signal transduction of several cytokines, including IFN-γ, IL-6, IL-10, IL-12, and IL-13. JAKs bind to cytokines, and on ligand binding and dimerization, activated JAKs recruit and phosphorylate signal transducer and activator of transcription (STAT) molecules (Fig. 2-10). Activated STAT proteins further dimerize and translocate into the nucleus and modulate the transcription of target genes. Interestingly, STAT-DNA binding can be observed within minutes of cytokine binding. The JAK/STAT system is a rapid pathway for membrane to nucleus signal transduction. The JAK/STAT pathway is inhibited by the action of phosphatase, the export of STATs from the nucleus, as well the interaction of antagonistic proteins.[37]

Fig. 2-10.



Source: Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB, Pollock RE: *Schwartz's Principles of Surgery, 9th Edition:* http://www.accessmedicine.com

The Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway also requires dimerization of monomeric units. STAT molecules possess "docking" sites that allow for STAT dimerization. The STAT complexes translocate into the nucleus and serve as gene transcription factors. JAK/STAT activation occurs in response to cytokines (e.g., interleukin-6) and cell stressors, and has been found to induce cell proliferation and inflammatory function. Intracellular molecules that inhibit STAT function, known as *suppressors of cytokine signaling (SOCSs),* have been identified. P = phosphate.

Suppressors of Cytokine Signaling

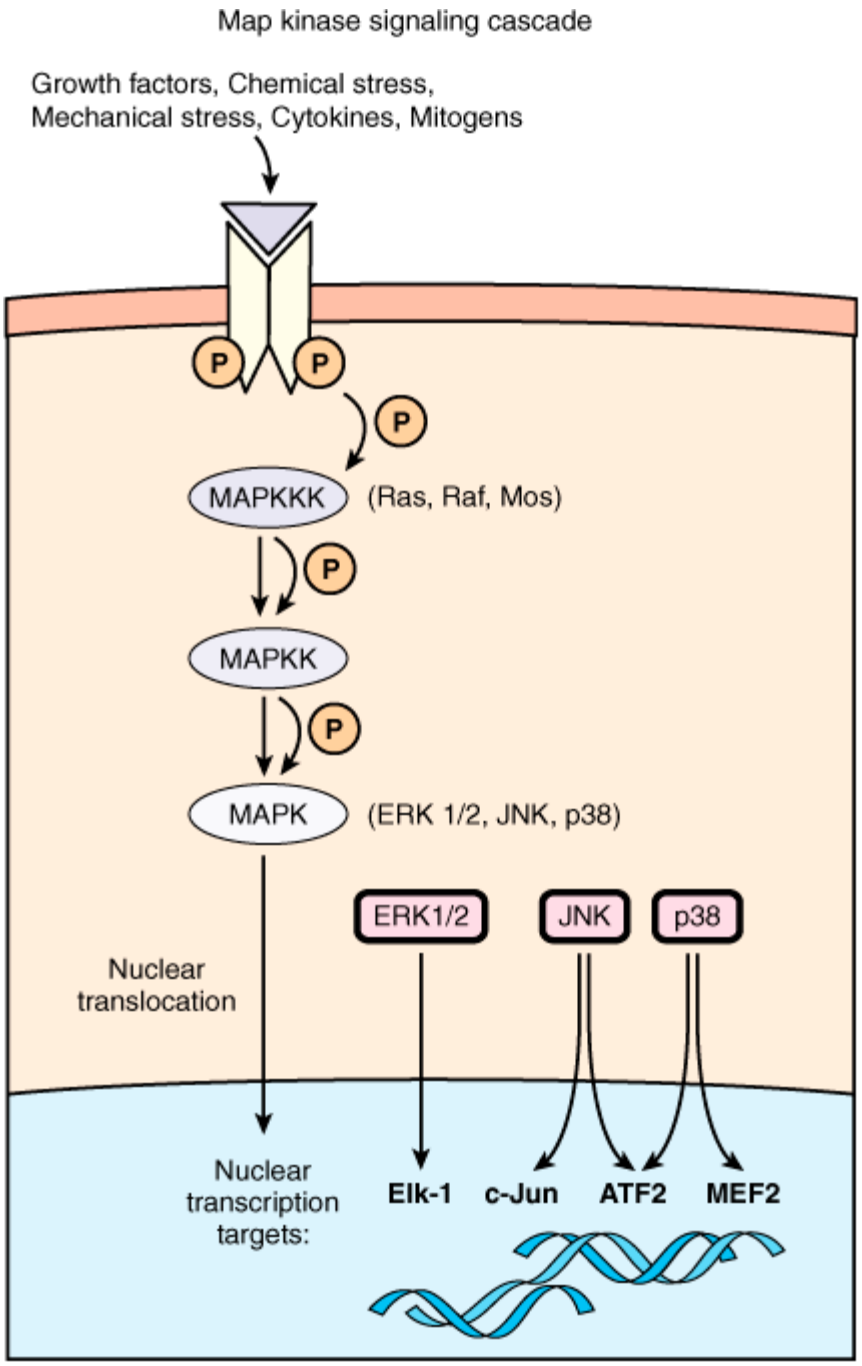
Suppressor of cytokine signaling (SOCS) molecules are a group of cytokine-induced proteins that function as a negative feedback loop by downregulating the JAK/STAT pathway. SOCSs exert an inhibitory effect partly by binding with JAK and thus competing with STAT. A deficiency of SOCS activity may render a cell hypersensitive to certain stimuli, such as inflammatory cytokines and growth hormones. Interestingly, in a murine model, SOCS knockout resulted in a lethal phenotype in part because of unregulated interferon-γ signaling. An example of this

pathway is highlighted by an attenuated IL-6 response in macrophages via suppressor of cytokine signaling 3 (SOCS-3) inhibition of signal transducer and activator of transcription 3 (STAT3).[38]

Mitogen-Activated Protein Kinases

Pathways mediated through mitogen-activated protein kinase (MAPK) contribute to inflammatory signaling and regulation of cell proliferation and cell death (Fig. 2-11). MAPK pathways involve sequential stages of mediator phosphorylation resulting in the activation of downstream effectors, including c-Jun N-terminal kinase (JNK), extracellular signal regulated protein kinase (ERK), and p38 kinase, with subsequent gene modulation. Dephosphorylation of MAPK pathway mediators inhibit their function. Activated JNK phosphorylates c-Jun, which dimerizes to form the transcription factor activated protein 1. The protein MAP/ERK kinase kinase (MEKK) has several functions, including protein kinase and ubiquitin ligase, and also has been shown to downregulate MAPK pathways. JNK is activated by TNF and IL-1 and is a regulator of apoptosis. Pharmacologic blockade of JNK was associated with decreased pulmonary injury and TNF and IL-1 secretion in an ischemia/reperfusion model. The p38 kinase is activated in response to endotoxin, viruses, IL-1, IL-2, IL-7, IL-17, IL-18, and TNF. The p38 also plays a role in immunocyte development, because p38 inactivation is a critical step in the differentiation of thymic T cells. These MAPK isoforms do not function independently but rather exhibit significant counteraction and cosignaling, which can influence the inflammatory response.[39]

Fig. 2-11.

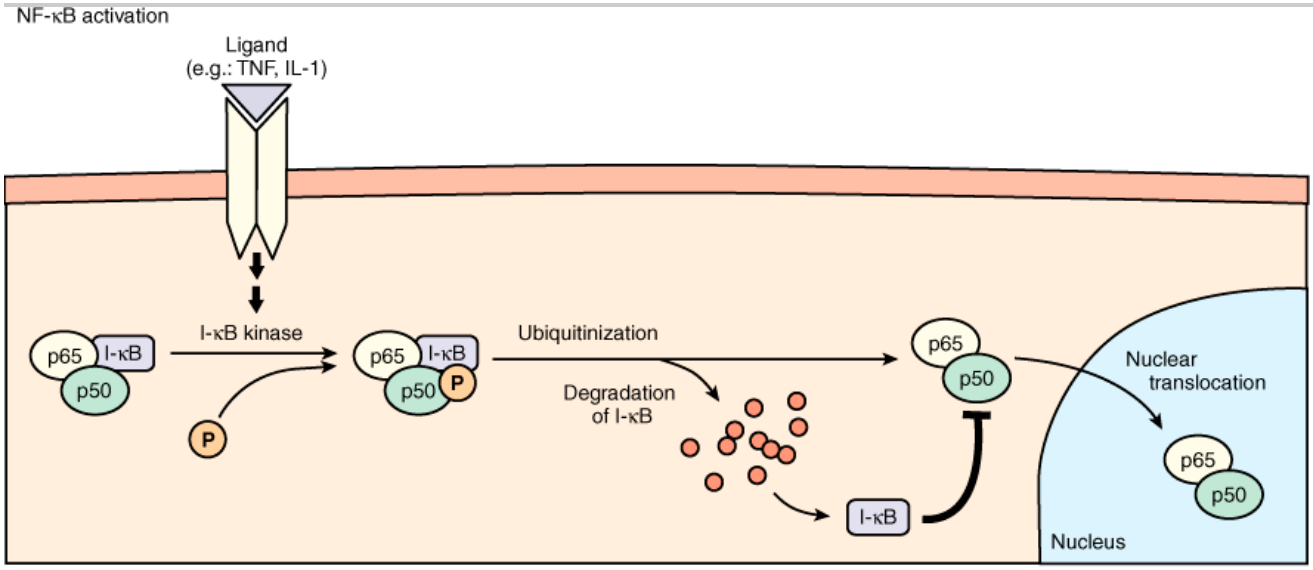


The mitogen-activated protein kinase (MAPK) signaling pathway requires multiple phosphorylation steps. Ras, Raf, and Mos are examples of the MAPK kinase kinase (MAPKKK) and are upstream molecules. Well-characterized downstream kinases are extracellular signal regulated kinases 1 and 2 (ERK 1/2), c-Jun N-terminal kinases (JNKs) or stress-activated protein kinases (SAPKs), and p38 MAPKs that target specific gene transcription sites in the nucleus. ATF2 = activating transcription factor 2; MAPKK = mitogen-activated protein kinase kinase; MEF2 = myocyte-enhancing factor 2; P = phosphate.

Nuclear Factor κB

Nuclear factor κB (NF-κB) is a transcription factor that has a central role in regulating the gene products expressed after inflammatory stimuli (Fig. 2-12). NF-κB is composed of two smaller polypeptides, p50 and p65. NF-κB resides in the cytosol in the resting state primarily through the inhibitory binding of inhibitor of κB (I-κB). In response to an inflammatory stimulus such as TNF, IL-1, or endotoxin, a sequence of intracellular mediator phosphorylation reactions leads to the degradation of I-κB and subsequent release of NF-κB. On release, NF-κB travels to the nucleus and promotes gene expression. NF-κB also stimulates the gene expression for I-κB, which results in negative feedback regulation. In clinical appendicitis, for example, increased NF-κB activity was associated with initial disease severity, and levels returned to baseline within 18 hours after appendectomy in concert with resolution of the inflammatory response.[40]

Fig. 2-12.



Source: Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB, Pollock RE: *Schwartz's Principles of Surgery, 9th Edition:* http://www.accessmedicine.com

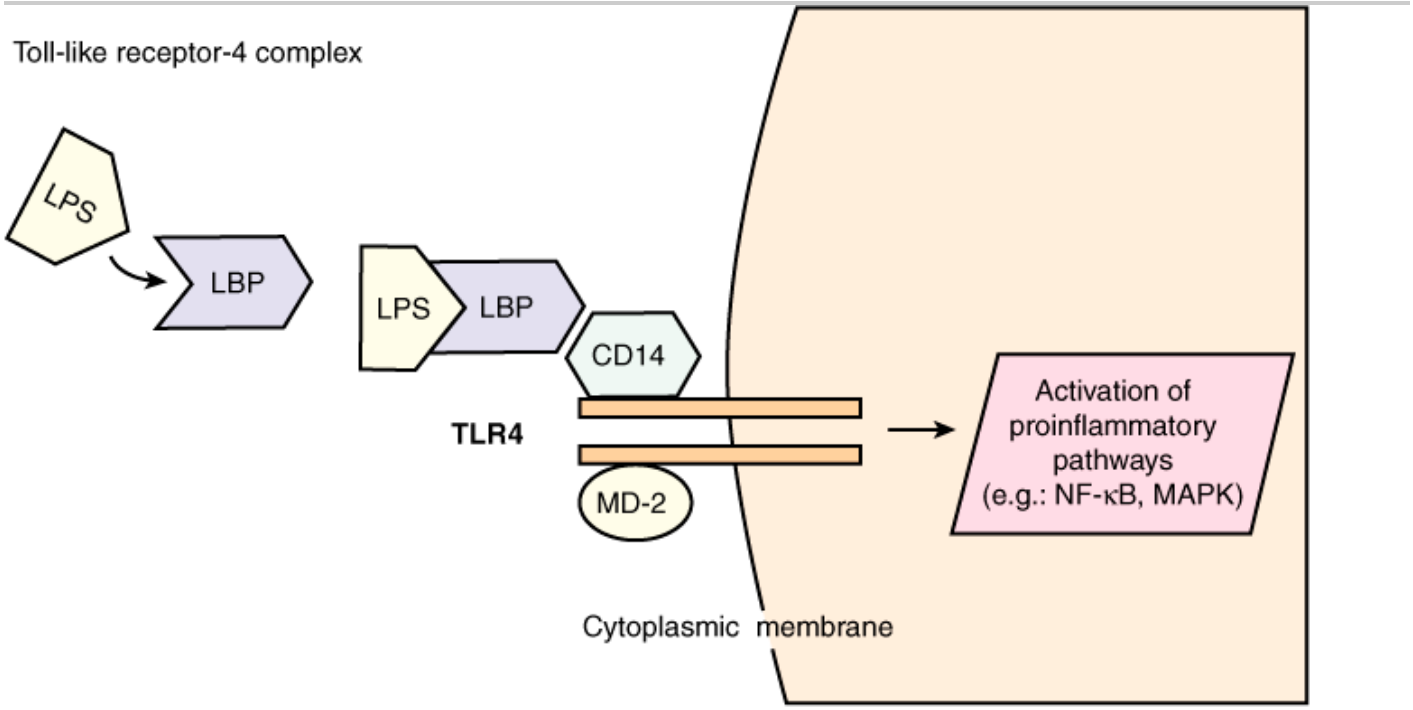
Inhibitor of κB (I-κB) binding to the p50-p65 subunits of nuclear factor κB (NF-κB) inactivates the molecule. Ligand binding to the receptor activates a series of downstream signaling molecules, of which I-κB kinase is one. The phosphorylated NF-κB complex further undergoes ubiquitinization and proteosome degradation of I-κB, activating NF-κB, which translocates into the nucleus. Rapid resynthesis of I-κB is one method of inactivating the p50-p65 complex. IL-1 = interleukin-1; P = phosphate; TNF = tumor necrosis factor.

Toll-Like Receptors and CD14

The innate immune system responds to pathogen-associated molecular patterns (PAMPs) such as microbial antigens and LPS. Toll-like receptors (TLRs) are a group of pattern recognition receptors activated by PAMPs that function as effectors of the innate immune system and belong to the IL-1 superfamily. Immunocyte recognition of LPS is mediated primarily by TLR4. LPS-binding proteins chaperone LPS to the CD14/TLR4 complex, which sets into effect cellular mechanisms that activate MAPK, NF-κB, and cytokine gene expression (Fig. 2-13). In contrast to TLR4, TLR2 recognizes PAMPs from gram-positive bacteria, including lipoproteins, lipopeptides, peptidoglycans, and

phenol-soluble modulin from *Staphylococcus* species. Interestingly, loss-of-function single nucleotide polymorphisms of TLR are associated with an increased risk of infection in susceptible critically ill patients.[41] As multiligand receptors, TLRs also bind damage-associated molecular pattern molecules (DAMPs), which are endogenous cellular products released during times of stress or injury. DAMPs include products such as HMGB1, heat shock proteins, and hyaluronic acid. Innate immune activation by DAMPs stimulates the recruitment of inflammatory cells to the site of injury and also mediates proinflammatory signaling.[42]

Fig. 2-13.



Lipopolysaccharide (LPS) recognition by immune cells is primarily by the toll-like receptor-4 (TLR4)/CD14/MD-2 complex. LPS is transported by LPS-binding protein (LBP) to the cell surface complex. Other cell surface LPS sensors include ion-gated channels, CD11b/CD18, and macrophage scavenger receptors. MAPK = mitogen-activated protein kinase; NF-κB = nuclear factor B.

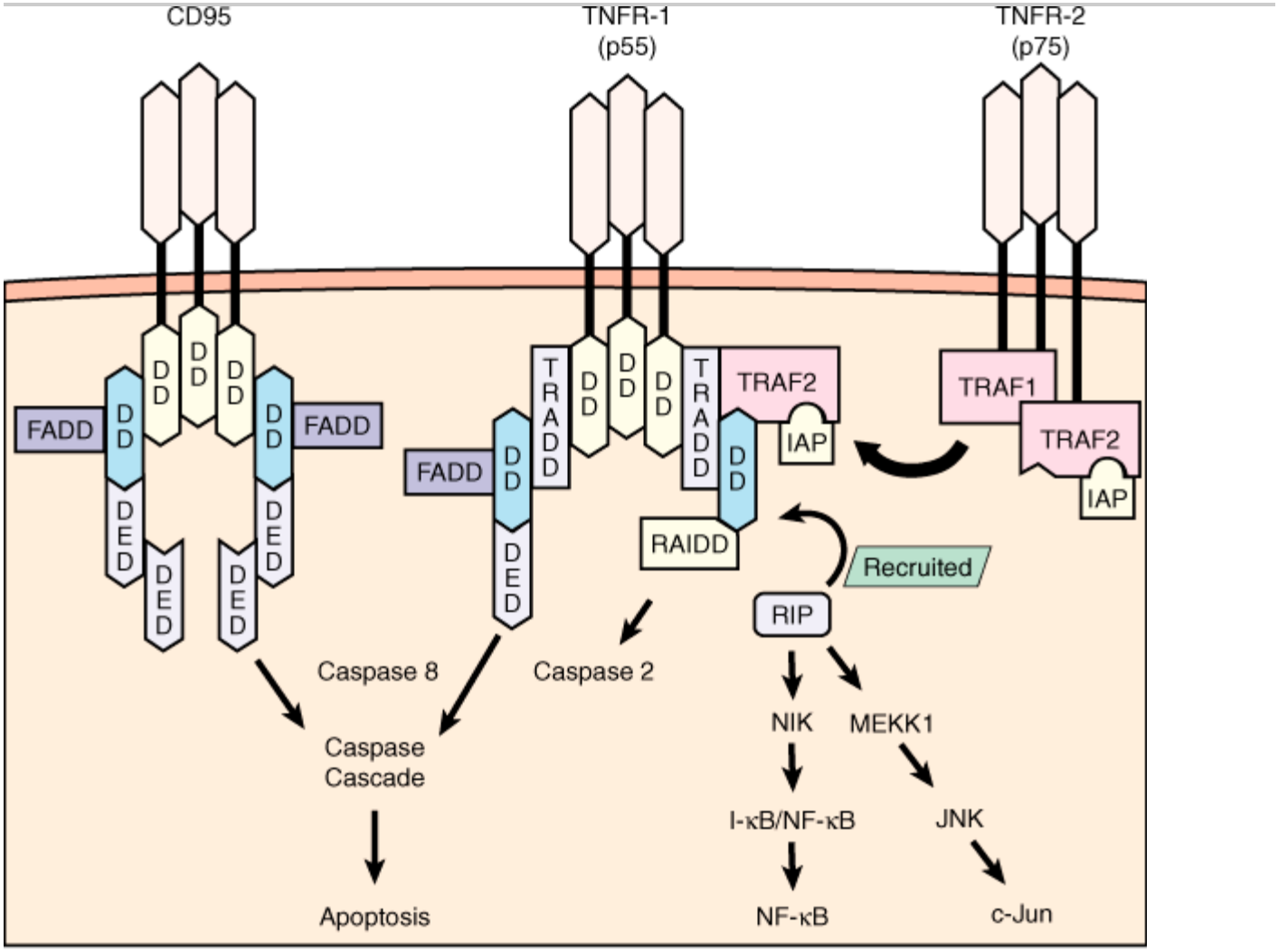
APOPTOSIS

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. Conversely, cell necrosis results in a disorganized sequence of intracellular molecular releases 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 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. 2-14). 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).

Fig. 2-14.



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, 1999, p 365. With kind permission from Springer Science + Business Media.)

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, 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.[28]

CELL-MEDIATED INFLAMMATORY RESPONSE

Platelets

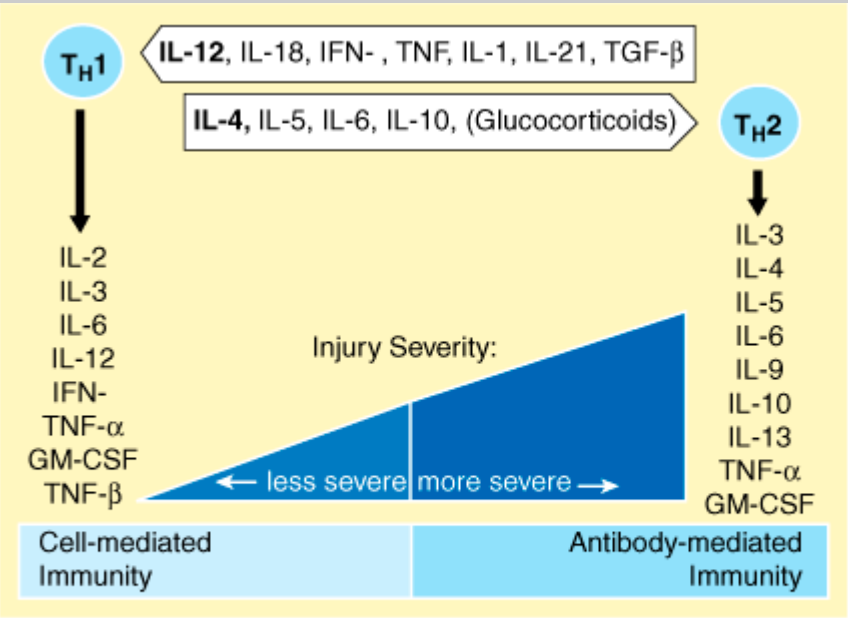
Platelets are nonnucleated structures containing both mitochondria and mediators of coagulation and inflammatory signaling. Platelets are derived from bone marrow megakaryocytes. Platelets are critically important in the hemostatic response and are activated by several factors, including exposed collagen. Activated platelets at the site of injury release inflammatory mediators that serve as the principal chemoattractant for neutrophils and monocytes. The migration of platelets and neutrophils through the vascular endothelium occurs within 3 hours of injury and is enhanced by serotonin release, platelet-activating factor, and prostaglandin E2 . Platelets are an important source of eicosanoids and vasoactive mediators. A hallmark of the septic response includes thrombocytopenia; however, the mechanism is unclear and likely multifactorial. Pharmaceutical agents such as NSAIDs inhibit platelet function through the blockade of COX.[43]

Lymphocytes and T-Cell Immunity

Lymphocytes are circulating immune cells composed primarily of B cells, T cells, and natural killer cells. As mediators of adaptive immunity, T lymphocytes are recruited to sites of injury. Helper T lymphocytes are broadly categorized into two groups: T_H 1 and T_H 2. T_H 1 cells favor cellular immune responses and secrete IFN-γ, IL-2, and IL-12, whereas T_H 2 cells favor humoral responses and produce IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13. T_H 1

activation is paramount in the defense against bacterial pathogens; however, during critical illness induced by severe trauma or sepsis, there appears to be a predominance of T_H 2 over T_H 1 cytokine responses, which may exacerbate immune dysregulation through amplified cytokine signaling (Fig. 2-15). In burn injury, T regulatory cells are associated with T-cell suppression via the release of transforming growth factor beta (TGF-β), which can downregulate T-cell function. Nutritional supplementation may confer a benefit in T-cell responses, because arginine is essential for T-cell proliferation and receptor function.[44]

Fig. 2-15.



Source: Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB, Pollock RE: *Schwartz's Principles of Surgery, 9th Edition:* http://www.accessmedicine.com

Specific immunity mediated by helper T lymphocytes subtype 1 (T_H 1) and subtype 2 (T_H 2) after injury. A T_H 1 response is favored in lesser injuries, with intact cell-mediated and opsonizing antibody immunity against microbial infections. This cell-mediated immunity includes activation of monocytes, B lymphocytes, and cytotoxic T lymphocytes. A shift toward the T_H 2 response from nave helper T cells is associated with injuries of greater magnitude and is not as effective against microbial infections. A T_H 2 response includes the activation of eosinophils, mast cells, and B-lymphocyte immunoglobulin 4 and immunoglobulin E production. (Primary stimulants and principal cytokine products of such responses are in bold characters.) Interleukin-4 (IL-4) and IL-10 are known inhibitors of the T_H 1 response. Interferon-γ (IFN-γ) is a known inhibitor of the T_H 2 response. Although not cytokines, glucocorticoids are potent stimulants of a T_H 2 response, which may partly contribute to the immunosuppressive effects of cortisol. GM-CSF = granulocyte-macrophage colony-stimulating factor; IL = interleukin; TGF = transforming growth factor; TNF = tumor necrosis factor.

(Adapted with permission from Lin E, Calvano SE, Lowry SF: Inflammatory cytokines and cell response in surgery. *Surgery* 127:117, 2000. Copyright Elsevier.)

Eosinophils

Eosinophils are immunocytes whose primary functions are antihelmintic. Eosinophils are found mostly in tissues such as the lung and GI tract, which may suggest a role in immune surveillance. Eosinophils can be activated by IL-3, IL-5, GM-CSF, chemoattractants, and platelet-activating factor. Eosinophil activation can lead to subsequent

release of toxic mediators, including reactive oxygen species, histamine, and peroxidase.[45]

Mast Cells

Mast cells are important in the primary response to injury because they are located in tissues. TNF release from mast cells has been found to be crucial for neutrophil recruitment and pathogen clearance. Mast cells are also known to play an important role in the anaphylactic response to allergens. On activation from stimuli including allergen binding, infection, and trauma, mast cells produce histamine, cytokines, eicosanoids, proteases, and chemokines, which leads to vasodilatation, capillary leakage, and immunocyte recruitment. Mast cells are thought to be important cosignaling effector cells of the immune system via the release of IL-3, IL-4, IL-5, IL-6, IL-10, IL-13, and IL-14, as well as macrophage migration–inhibiting factor.[46]

Monocytes

Monocytes are mononuclear phagocytes that circulate in the bloodstream and can differentiate into macrophages, osteoclasts, and dendritic cells on migrating into tissues. Macrophages are the main effector cells of the immune response to infection and injury, primarily through mechanisms that include phagocytosis of microbial pathogens, release of inflammatory mediators, and clearance of apoptotic cells. In humans, downregulation of monocyte and neutrophil TNFR expression has been demonstrated experimentally and clinically during systemic inflammation. In clinical sepsis, nonsurviving patients with severe sepsis have an immediate reduction in monocyte surface TNFR expression with failure to recover, whereas surviving patients have normal or near-normal receptor levels from the onset of clinically defined sepsis. In patients with congestive heart failure, there is also a significant decrease in the amount of monocyte surface TNFR expression compared with control patients. In experimental models, endotoxin has been shown to differentially regulate over 1000 genes in murine macrophages with approximately 25% of these corresponding to cytokines and chemokines. During sepsis, macrophages undergo phenotypic reprogramming highlighted by decreased surface human leukocyte antigen DR (a critical receptor in antigen presentation), which also may contribute to host immunocompromise during sepsis.[47]

Neutrophils

Neutrophils are among the first responders to sites of infection and injury and as such are potent mediators of acute inflammation. Chemotactic mediators from a site of injury induce neutrophil adherence to the vascular endothelium and promote eventual cell migration into the injured tissue. Neutrophils are circulating immunocytes with short half-lives (4 to 10 hours). On activation by inflammatory stimuli, including TNF, IL-1, and microbial pathogens, neutrophils are able to phagocytose, release lytic enzymes, and generate large amounts of toxic reactive oxygen species.[48]

ENDOTHELIUM-MEDIATED INJURY

Vascular Endothelium

Under physiologic conditions, vascular endothelium has overall anticoagulant properties mediated via the production and cell surface expression of heparin sulfate, dermatan sulfate, tissue factor pathway inhibitor, protein S, thrombomodulin, plasminogen, and tissue plasminogen activator. Endothelial cells also perform a critical function as barriers that regulate tissue migration of circulating cells. During sepsis, endothelial cells are differentially modulated, which results in an overall procoagulant shift via decreased production of anticoagulant factors, which may lead to microthrombosis and organ injury.

Neutrophil-Endothelium Interaction

The regulated inflammatory response to infection facilitates neutrophil and other immunocyte migration to compromised regions through the actions of increased vascular permeability, chemoattractants, and increased endothelial adhesion factors referred to as *selectins* that are elaborated on cell surfaces (Table 2-5). Prolonged and unremitting neutrophil activation and mediator release can lead to tissue injury through the production of toxic oxygen metabolites and lysosomal enzymes that degrade tissue basal membranes, cause microvascular thrombosis, and activate myeloperoxidases. In response to inflammatory stimuli, including chemokines, thrombin, IL-1, histamine, and TNF, vascular endothelium increases surface expression of the adhesion molecule P-selectin, which is observable in 10 to 20 minutes and mediates neutrophil rolling (Fig. 2-16). After 2 hours, however, cell surface expression favors E-selectin expression. L-selectin and P-selectin glycoprotein ligand-1 (PSGL-1) are responsible for over 85% of monocyte-to-monocyte and monocyte-to-endothelium adhesion activity. Endothelial selectins interact with leukocyte selectins (PSGL-1, L-selectin) to mediate leukocyte rolling, which allows targeted immunocyte migration. Also important are secondary leukocyte-leukocyte interactions in which PGSL-1 and L-selectin binding facilitates further leukocyte tethering. Although there are distinguishable properties among individual selectins in leukocyte rolling, effective rolling most likely involves a significant degree of functional overlap.[49]

Table 2-5 Molecules that Mediate Leukocyte-Endothelial Adhesion, Categorized by Family

Selectins
L-selectin
Fast rolling
Leukocytes
Native
Endothelium, platelets, eosinophils
P-selectin
Slow rolling
Platelets and endothelium
Thrombin, histamine
Neutrophils, monocytes
E-selectin
Very slow rolling
Endothelium
Cytokines
Neutrophils, monocytes, lymphocytes
Immunoglobulins
ICAM-1
Firm adhesion/transmigration
Endothelium, leukocytes, fibroblasts, epithelium
Cytokines
Leukocytes
ICAM-2
Firm adhesion
Endothelium, platelets
Native
Leukocytes
VCAM-1

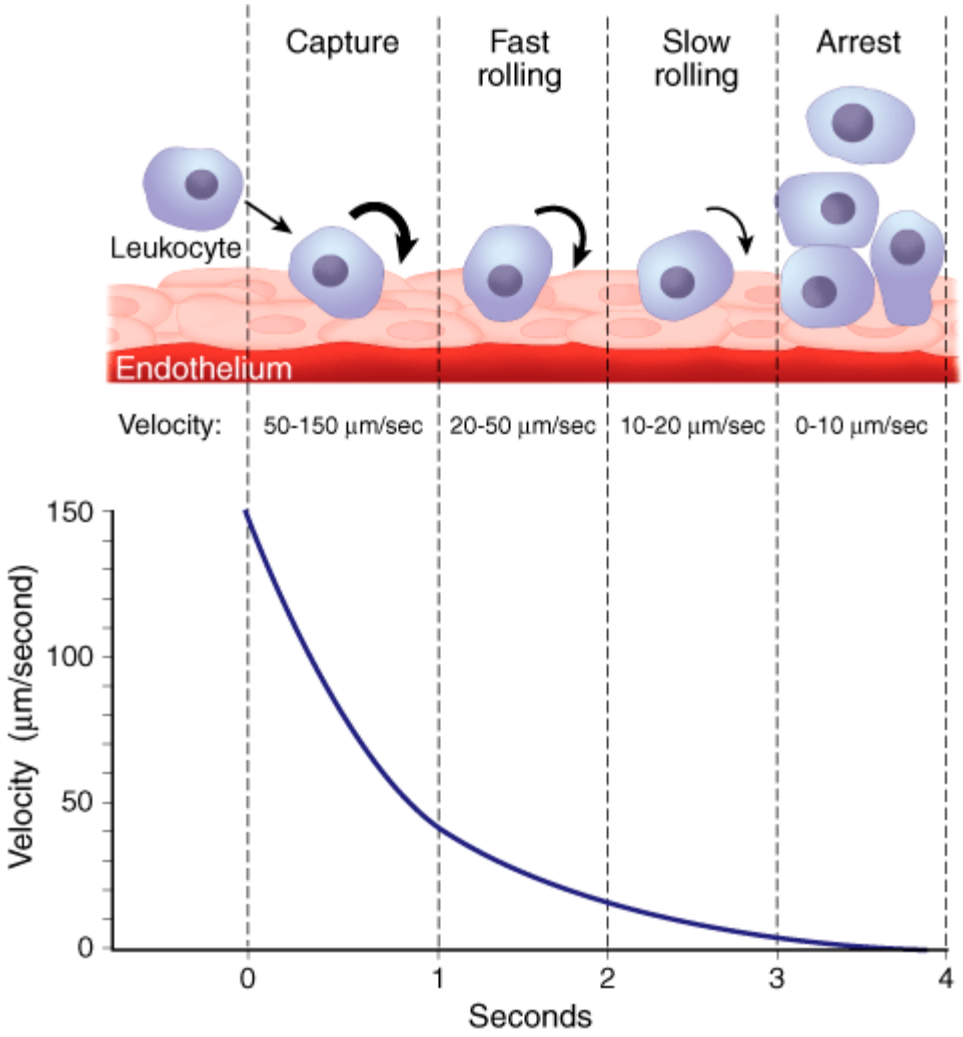
Firm adhesion/transmigration
Endothelium
Cytokines
Monocytes, lymphocytes
PECAM-1
Adhesion/transmigration
Endothelium, platelets, leukocytes
Native
Endothelium, platelets, leukocytes
β_2 *-(CD18) Integrins*
CD18/11a
Firm adhesion/transmigration
Leukocytes
Leukocyte activation
Endothelium
CD18/11b (Mac-1)
Firm adhesion/transmigration
Neutrophils, monocytes, natural killer cells
Leukocyte activation
Endothelium
CD18/11c
Adhesion
Neutrophils, monocytes, natural killer cells
Leukocyte activation
Endothelium
β_1 *-(CD29) Integrins*

VLA-4
Firm adhesion/transmigration
Lymphocytes, monocytes
Leukocyte activation
Monocytes, endothelium, epithelium

Adhesion Molecule	Action	Origin	Inducers of Expression	Target Cells

ICAM-1 = intercellular adhesion molecule-1; ICAM-2 = intercellular adhesion molecule-2; Mac-1 = macrophage antigen 1; PECAM-1 = platelet-endothelial cell adhesion molecule-1; VCAM-1 = vascular cell adhesion molecule-1; VLA-4 = very late antigen-4.

Fig. 2-16.



Simplified sequence of selectin-mediated neutrophil-endothelium interaction after an inflammatory stimulus. *CAPTURE* (tethering), predominantly mediated by cell L-selectin with contribution from endothelial P-selectin, describes the initial recognition between leukocyte and endothelium, in which circulating leukocytes marginate toward the endothelial surface. *FAST ROLLING* (20 to 50 µm/s) is a consequence of rapid L-selectin shedding from cell surfaces and formation of new downstream L-selectin to endothelium bonds, which occur in tandem. *SLOW ROLLING* (10 to 20 µm/s) is predominantly mediated by P-selectins. The slowest rolling (3 to 10 µm/s) before arrest is predominantly mediated by E-selectins, with contribution from P-selectins. *ARREST* (firm adhesion) leading to transmigration is mediated by β-integrins and the immunoglobulin family of adhesion molecules. In addition to interacting with the endothelium, activated leukocytes also recruit other leukocytes to the inflammatory site by direct interactions, which are mediated in part by selectins.

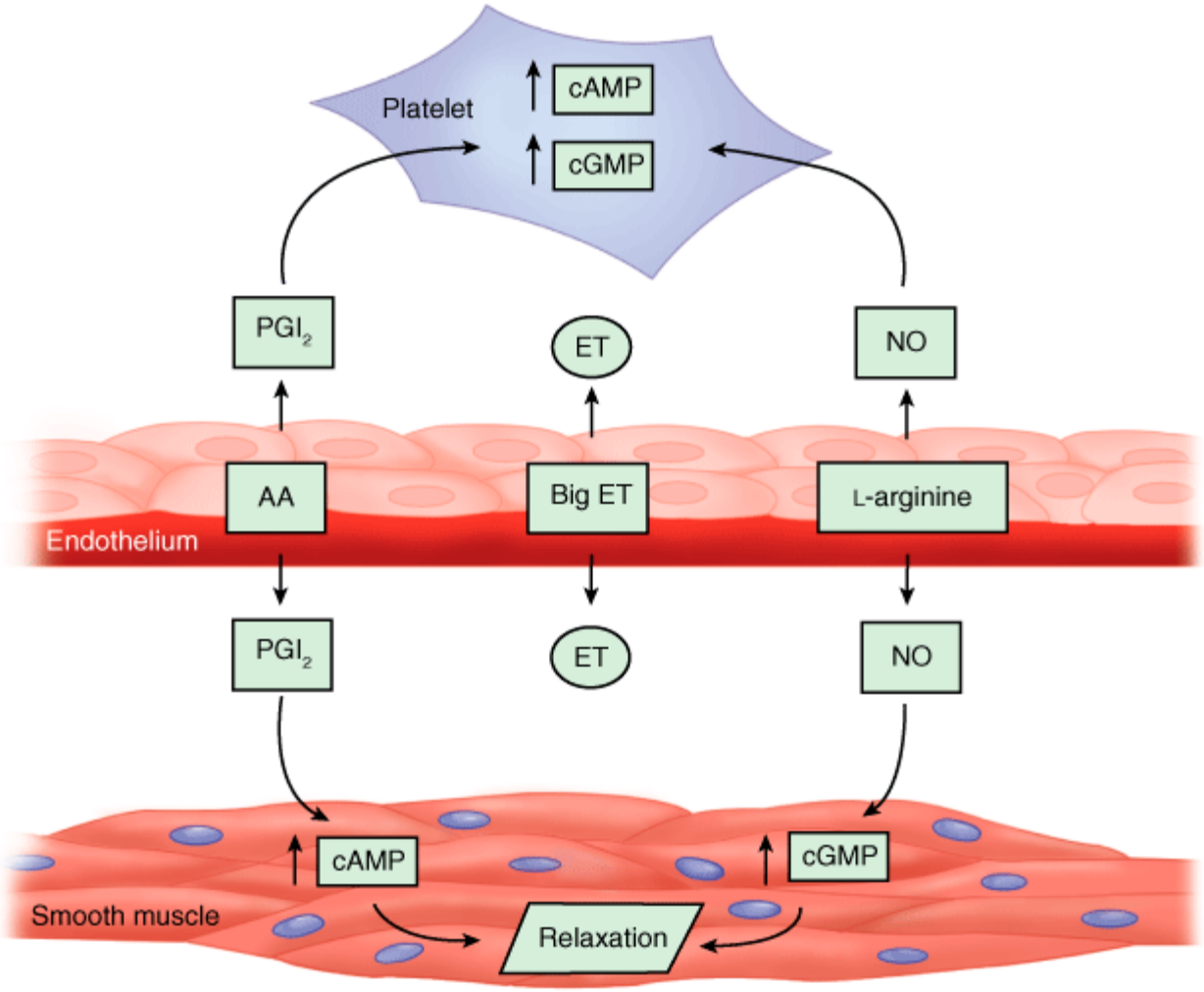
(Adapted with permission from Lin E, Calvano SE, Lowry SF: Selectin neutralization: Does it make biological sense? *Crit Care Med* 27:2050, 1999.)

Nitric Oxide

Nitric oxide (NO) was initially known as *endothelium-derived relaxing factor* due to its effect on vascular smooth

muscle and has important functions in both physiologic and pathologic control of vascular tone. Normal vascular smooth muscle relaxation is maintained by a constant output of NO and subsequent activation of soluble quanylyl cyclase. NO also can reduce microthrombosis by reducing platelet adhesion and aggregation (Fig. 2-17). NO easily traverses cell membranes and has a short half-life of a few seconds and is oxidized into nitrate and nitrite. NO is constitutively expressed by endothelial cells; however, inducible NO synthase, which is normally not expressed, is upregulated in response to inflammatory stimuli, which increases NO production. Increased NO is detectable in septic shock and in response to TNF, IL-1, IL-2, and hemorrhage. NO mediates hypotension observed during septic shock; however, a clinical trial of a nonselective NOS inhibitor showed increased organ dysfunction and mortality.[50]

Fig. 2-17.



Source: Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB, Pollock RE: *Schwartz's Principles of Surgery, 9th Edition:* http://www.accessmedicine.com

Endothelial interaction with smooth muscle cells and with intraluminal platelets. Prostacyclin (prostaglandin I_2 , or PGI2) is derived from arachidonic acid (AA), and nitric oxide (NO) is derived from L -arginine. The increase in cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) results in smooth muscle relaxation and inhibition of platelet thrombus formation. Endothelins (ETs) are derived from "big ET," and they counter the effects of prostacyclin and

NO.

Prostacyclin

Prostacyclin is a member of the eicosanoid family and is primarily produced by endothelial cells. Prostacyclin is an effective vasodilator and also inhibits platelet aggregation. During systemic inflammation, endothelial prostacyclin expression is impaired, and thus the endothelium favors a more procoagulant profile. Prostacyclin therapy during sepsis has been shown to reduce the levels of cytokines, growth factors, and adhesion molecules through a cAMP-dependent pathway. In clinical trials, prostacyclin infusion is associated with increased cardiac output, splanchnic blood flow, and oxygen delivery and consumption with no significant decrease in mean arterial pressure. However, further study is required before the widespread use of prostacyclin is recommended.[51]

Endothelins

Endothelins (ETs) are potent mediators of vasoconstriction and are composed of three members: ET-1, ET-2, and ET-3. ETs are 21-amino-acid peptides derived from a 38-amino-acid precursor molecule. ET-1, synthesized primarily by endothelial cells, is the most potent endogenous vasoconstrictor and is estimated to be 10 times more potent than angiotensin II. ET release is upregulated in response to hypotension, LPS, injury, thrombin, TGF-β, IL-1, angiotensin II, vasopressin, catecholamines, and anoxia. ETs are primarily released to the abluminal side of endothelial cells, and very little is stored in cells; thus a plasma increase is associated with a marked increase in production. The half-life of plasma ET is between 4 and 7 minutes, which suggests that ET release is primarily regulated at the transcriptional level. Three endothelin receptors, referred to as ET_A, ET_B, and ET_C, have been identified and function via the G-protein–coupled receptor mechanism. ET_B receptors are associated with increased NO and prostacyclin production, which may serve as a feedback mechanism. Atrial ET_A receptor activation has been associated with increased inotropy and chronotropy. ET-1 infusion is associated with increased pulmonary vascular resistance and pulmonary edema and may contribute to pulmonary abnormalities during sepsis. At low levels, in conjunction with NO, ETs regulate vascular tone. However, at increased concentrations, ETs can disrupt the normal blood flow and distribution and may compromise oxygen delivery to the tissue. In addition, increased plasma ET concentration correlates with the severity of injury after major trauma or major surgical procedures, and in patients with cardiogenic or septic shock.[52]

Platelet-Activating Factor

Another endothelium-derived product is platelet-activating factor (PAF), a natural phospholipid constituent of cell membranes that is minimally expressed under normal physiologic conditions. During acute inflammation, PAF is released by neutrophils, platelets, mast cells, and monocytes, and is expressed at the outer leaflet of endothelial cells. PAF can further activate neutrophils and platelets, and increase vascular permeability. Antagonists to PAF receptors have been experimentally shown to mitigate the effects of ischemia and reperfusion injury. Human sepsis is associated with a reduction in levels of PAF-acetylhydrolase, which is the endogenous inhibitor of PAF. Indeed, PAF-acetylhydrolase administration in patients with severe sepsis has yielded some reduction in multiple organ dysfunction and mortality.[53]

Atrial Natriuretic Peptides

Atrial natriuretic peptides (ANPs) are a family of peptides that are released primarily by atrial tissue but are also synthesized by the gut, kidney, brain, adrenal glands, and endothelium. They induce vasodilation as well as fluid and electrolyte excretion. ANPs are potent inhibitors of aldosterone secretion and prevent reabsorption of sodium.

There is some experimental evidence to suggest that ANP can reverse acute renal failure or early acute tubular necrosis.

SURGICAL METABOLISM

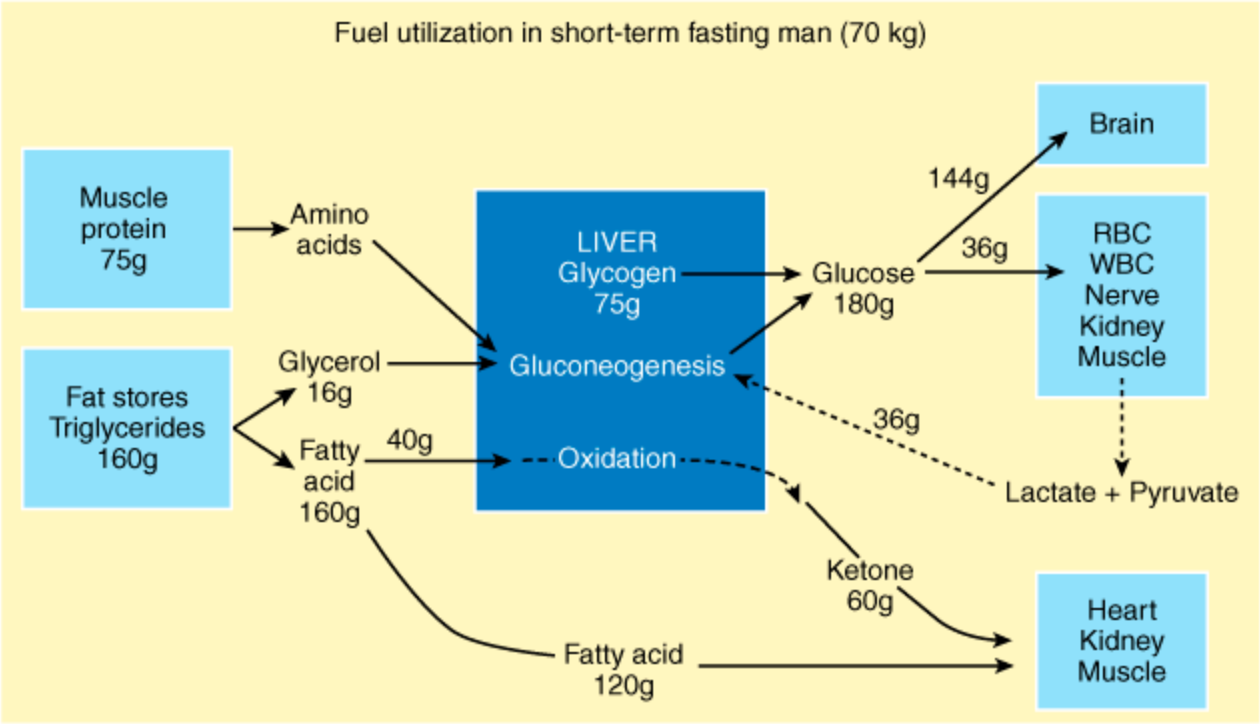
The initial hours after surgical or traumatic injury are metabolically associated with a reduced total body energy expenditure and urinary nitrogen wasting. On adequate resuscitation and stabilization of the injured patient, a reprioritization of substrate use ensues to preserve vital organ function and to support repair of injured tissue. This phase of recovery also is characterized by functions that participate in the restoration of homeostasis, such as augmented metabolic rates and oxygen consumption, enzymatic preference for readily oxidizable substrates such as glucose, and stimulation of the immune system.

Understanding of the collective alterations in amino acid (protein), carbohydrate, and lipid metabolism characteristic of the surgical patient lays the foundation upon which metabolic and nutritional support can be implemented.

Metabolism during Fasting

Fuel metabolism during unstressed fasting states has historically served as the standard to which metabolic alterations after acute injury and critical illness are compared (Fig. 2-18). To maintain basal metabolic needs (i.e., at rest and fasting), a normal healthy adult requires approximately 22 to 25 kcal/kg per day drawn from carbohydrate, lipid, and protein sources. This requirement can be as high as 40 kcal/kg per day in severe stress states, such as those seen in patients with burn injuries.

Fig. 2-18.



Source: Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB, Pollock RE: *Schwartz's Principles of Surgery, 9th Edition:* http://www.accessmedicine.com

Fuel utilization in a 70-kg man during short-term fasting with an approximate basal energy expenditure of 1800 kcal. During starvation, muscle proteins and fat stores provide fuel for the host, with the latter being most abundant. RBC = red blood cell; WBC = white blood cell.

(Adapted with permission from Cahill GF: Starvation in man. *N Engl J Med* 282:668, 1970. Copyright Massachusetts Medical Society. All rights reserved.)

In the healthy adult, principal sources of fuel during short-term fasting (<5 days) are derived from muscle protein and body fat, with fat being the most abundant source of energy (Table 2-6). The normal adult body contains 300 to 400 g of carbohydrates in the form of glycogen, of which 75 to 100 g are stored in the liver. Approximately 200 to 250 g of glycogen are stored within skeletal, cardiac, and smooth muscle cells. The greater glycogen stores within the muscle are not readily available for systemic use due to a deficiency in glucose-6-phosphatase but are available for the energy needs of muscle cells. Therefore, in the fasting state, hepatic glycogen stores are rapidly and preferentially depleted, which results in a fall of serum glucose concentration within hours (<16 hours).

Table 2-6 A. Body Fuel Reserves in a 70-kg Man

Water and minerals
49
0
0
Protein
6.0

24,000
13.0
Glycogen
0.2
800
0.4
Fat
15.0
140,000
78.0
Total
70.2
164,800
91.4

A. Component	Mass (kg)	Energy (kcal)	Days Available

B. Energy Equivalent of Substrate Oxidation

Glucose
0.75
0.75
1.0
4.0
7.2 g/kg per day
Dextrose
—
—
—
3.4
—
Lipid
2.0
1.4
0.7
9.0
1.0 g/kg per day
Protein
1.0
0.8
0.8
4.0
0.8 g/kg per day

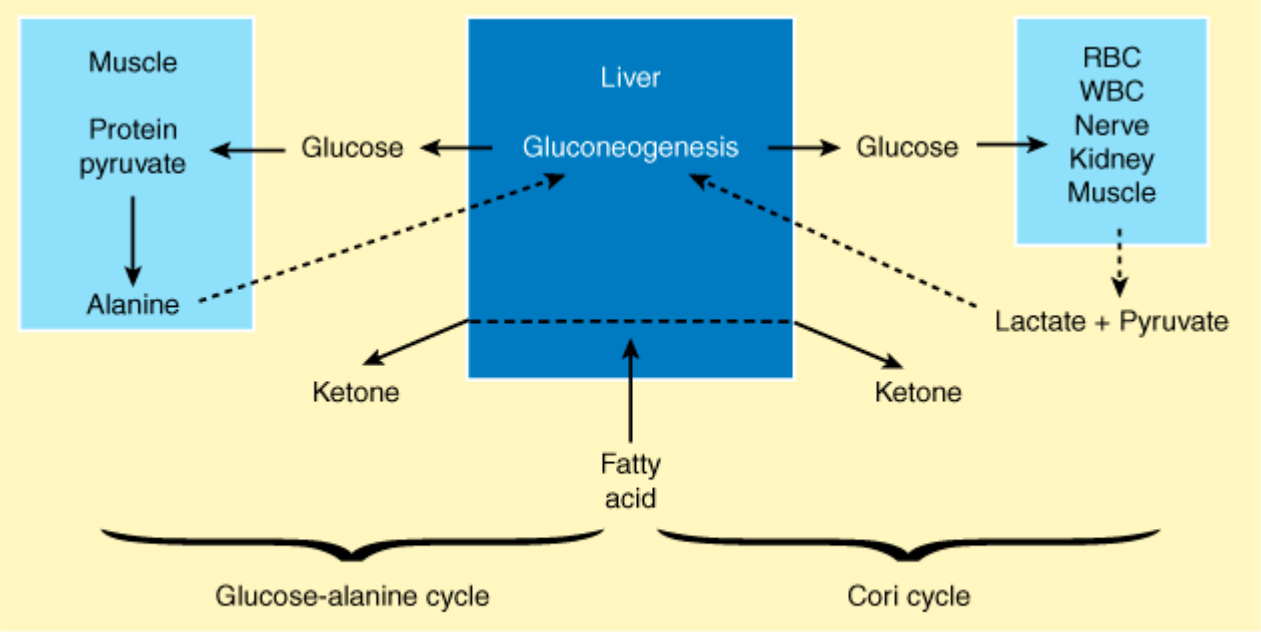
B. Substrate	O_2 Consumed (L/g)	CO_2 Produced (L/g)	Respiratory Quotient	kcal/g	Recommended Daily Requirement

During fasting, a healthy 70-kg adult will utilize 180 g of glucose per day to support the metabolism of obligate

glycolytic cells such as neurons, leukocytes, erythrocytes, and the renal medullae. Other tissues that use glucose for fuel are skeletal muscle, intestinal mucosa, fetal tissues, and solid tumors.

Glucagon, norepinephrine, vasopressin, and angiotensin II can promote the utilization of glycogen stores (glycogenolysis) during fasting. Although glucagon, epinephrine, and cortisol directly promote gluconeogenesis, epinephrine and cortisol also promote pyruvate shuttling to the liver for gluconeogenesis. Precursors for hepatic gluconeogenesis include lactate, glycerol, and amino acids such as alanine and glutamine. Lactate is released by glycolysis within skeletal muscles, as well as by erythrocytes and leukocytes. The recycling of lactate and pyruvate for gluconeogenesis is commonly referred to as the *Cori cycle,* which can provide up to 40% of plasma glucose during starvation (Fig. 2-19).

Fig. 2-19.



Source: Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB, Pollock RE: *Schwartz's Principles of Surgery, 9th Edition:* http://www.accessmedicine.com

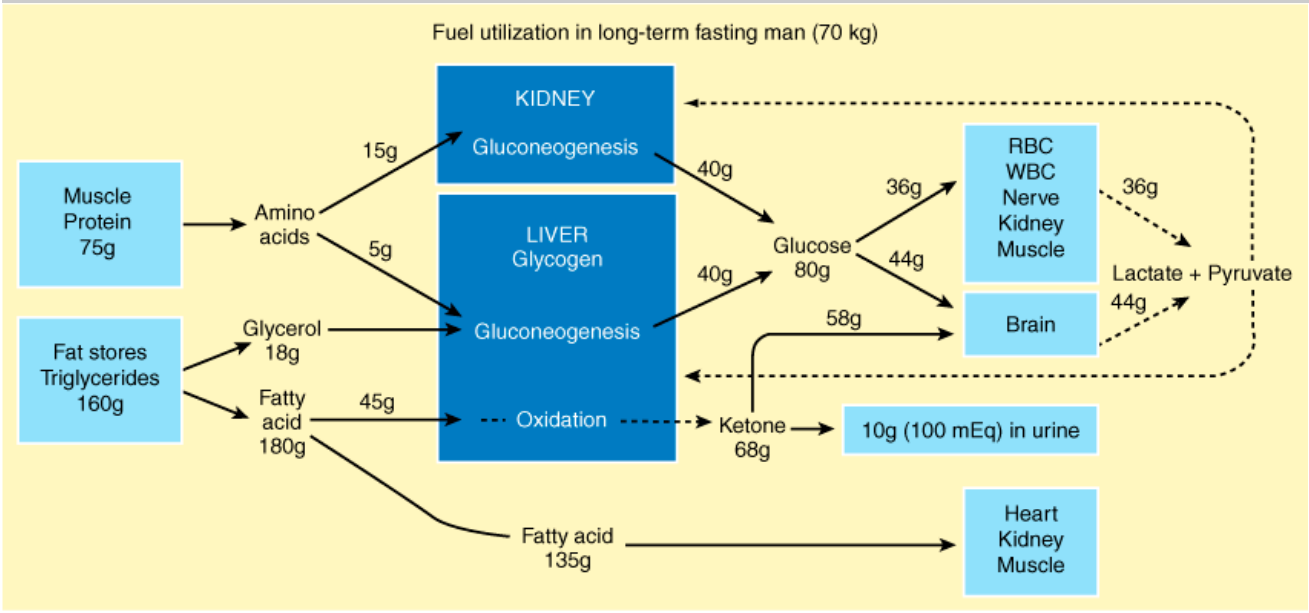
The recycling of peripheral lactate and pyruvate for hepatic gluconeogenesis is accomplished by the Cori cycle. Alanine within skeletal muscles can also be used as a precursor for hepatic gluconeogenesis. During starvation, such fatty acid provides fuel sources for basal hepatic enzymatic function. RBC = red blood cell; WBC = white blood cell.

Lactate production from skeletal muscle is insufficient to maintain systemic glucose needs during short-term fasting (simple starvation). Therefore, significant amounts of protein must be degraded daily (75 g/d for a 70-kg adult) to provide the amino acid substrate for hepatic gluconeogenesis. Proteolysis during starvation, which results primarily from decreased insulin and increased cortisol release, is associated with elevated urinary nitrogen excretion from the normal 7 to 10 g per day up to 30 g or more per day.[54] Although proteolysis during starvation occurs mainly within skeletal muscles, protein degradation in solid organs also occurs.

In prolonged starvation, systemic proteolysis is reduced to approximately 20 g/d and urinary nitrogen excretion

stabilizes at 2 to 5 g/d (Fig. 2-20). This reduction in proteolysis reflects the adaptation by vital organs (e.g., myocardium, brain, renal cortex, and skeletal muscle) to using ketone bodies as their principal fuel source. In extended fasting, ketone bodies become an important fuel source for the brain after 2 days and gradually become the principal fuel source by 24 days.

Fig. 2-20.



Fuel utilization in extended starvation. Liver glycogen stores are depleted, and there is adaptive reduction in proteolysis as a source of fuel. The brain uses ketones for fuel. The kidneys become important participants in gluconeogenesis. RBC = red blood cell; WBC = white blood cell.

(Adapted with permission from Cahill GF: Starvation in man. *N Engl J Med* 282:668, 1970. Copyright Massachusetts Medical Society. All rights reserved.)

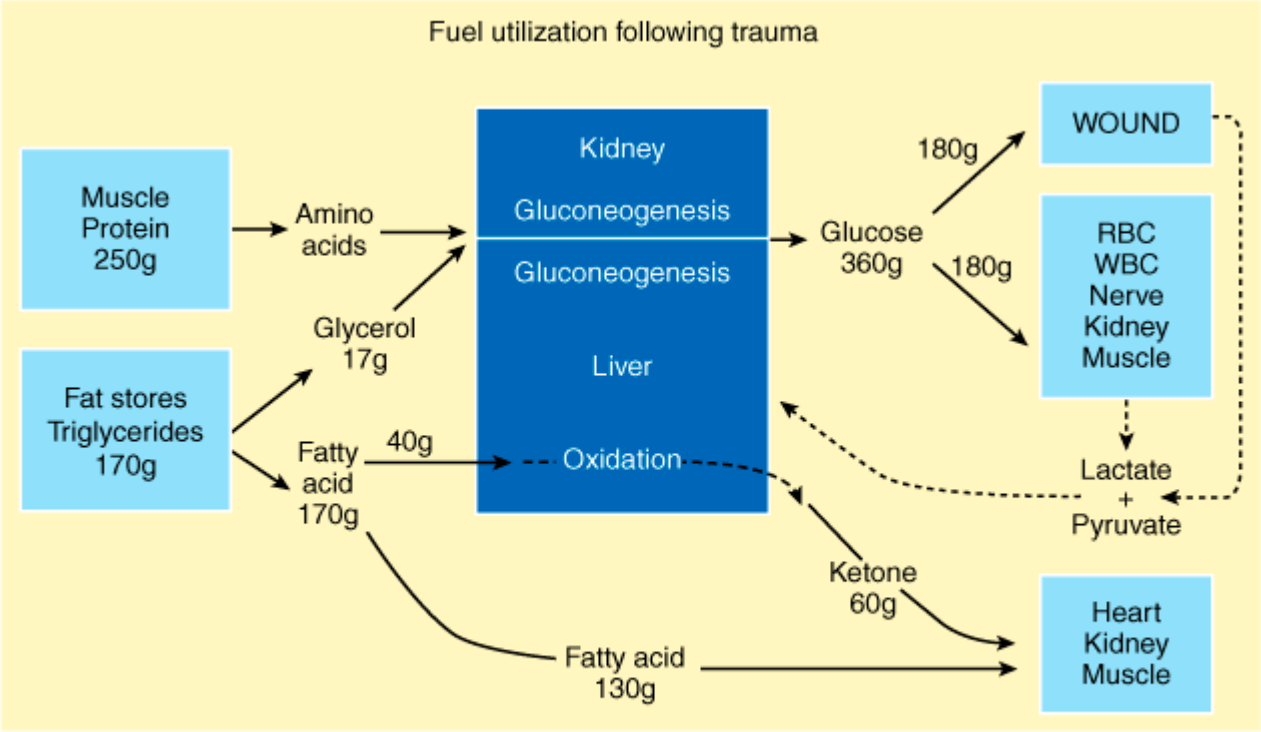
Enhanced deamination of amino acids for gluconeogenesis during starvation consequently increases renal excretion of ammonium ions. The kidneys also participate in gluconeogenesis by the use of glutamine and glutamate, and can become the primary source of gluconeogenesis during prolonged starvation, accounting for up to one half of systemic glucose production.

Lipid stores within adipose tissue provide 40% or more of caloric expenditure during starvation. Energy requirements for basal enzymatic and muscular functions (e.g., gluconeogenesis, neural transmission, and cardiac contraction) are met by the mobilization of triglycerides from adipose tissue. In a resting, fasting, 70-kg person, approximately 160 g of free fatty acids and glycerol can be mobilized from adipose tissue per day. Free fatty acid release is stimulated in part by a reduction in serum insulin levels and in part by the increase in circulating glucagon and catecholamine. Such free fatty acids, like ketone bodies, are used as fuel by tissues such as the heart, kidney (renal cortex), muscle, and liver. The mobilization of lipid stores for energy importantly decreases the rate of glycolysis, gluconeogenesis, and proteolysis, as well as the overall glucose requirement to sustain the host. Furthermore, ketone bodies spare glucose utilization by inhibiting the enzyme pyruvate dehydrogenase.

Metabolism after Injury

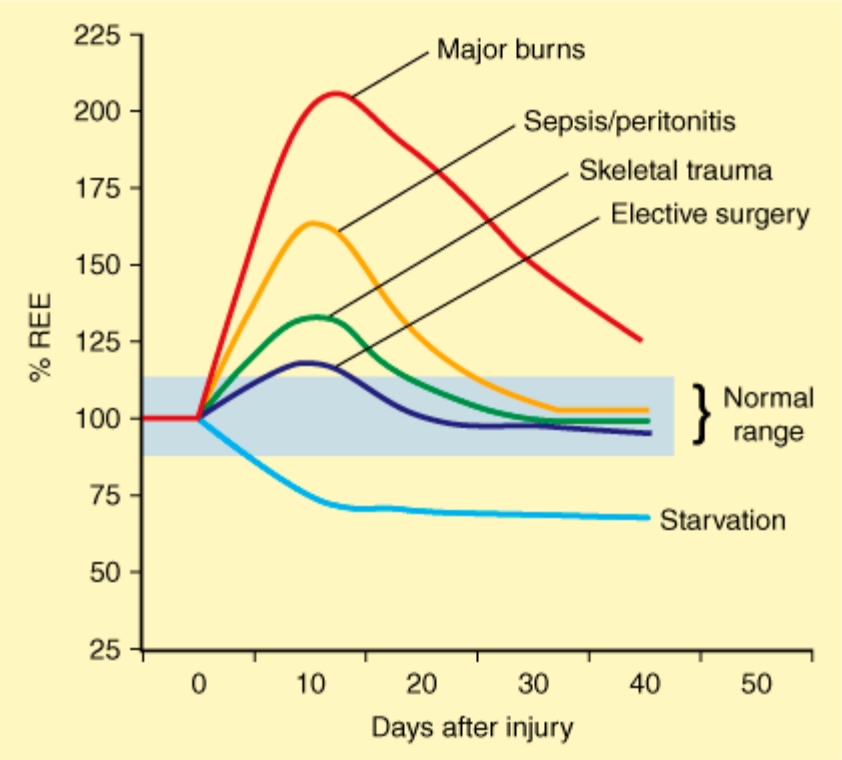
Injuries or infections induce unique neuroendocrine and immunologic responses that differentiate injury metabolism from that of unstressed fasting (Fig. 2-21). The magnitude of metabolic expenditure appears to be directly proportional to the severity of insult, with thermal injuries and severe infections having the highest energy demands (Fig. 2-22). The increase in energy expenditure is mediated in part by sympathetic activation and catecholamine release, which has been replicated by the administration of catecholamines to healthy human subjects. Lipid metabolism after injury is intentionally discussed first, because this macronutrient becomes the primary source of energy during stressed states.[55]

Fig. 2-21.



Acute injury is associated with significant alterations in substrate utilization. There is enhanced nitrogen loss, indicative of catabolism. Fat remains the primary fuel source under these circumstances. RBC = red blood cell; WBC = white blood cell.

Fig. 2-22.



Influence of injury severity on resting metabolism (resting energy expenditure, or REE). The shaded area indicates normal REE.

(Adapted with permission from Long CL et al: Metabolic response to injury and illness: Estimation of energy and protein needs from indirect calorimetry and nitrogen balance. *JPEN J Parenter Enteral Nutr* 3:452, 1979.)

LIPID METABOLISM AFTER INJURY

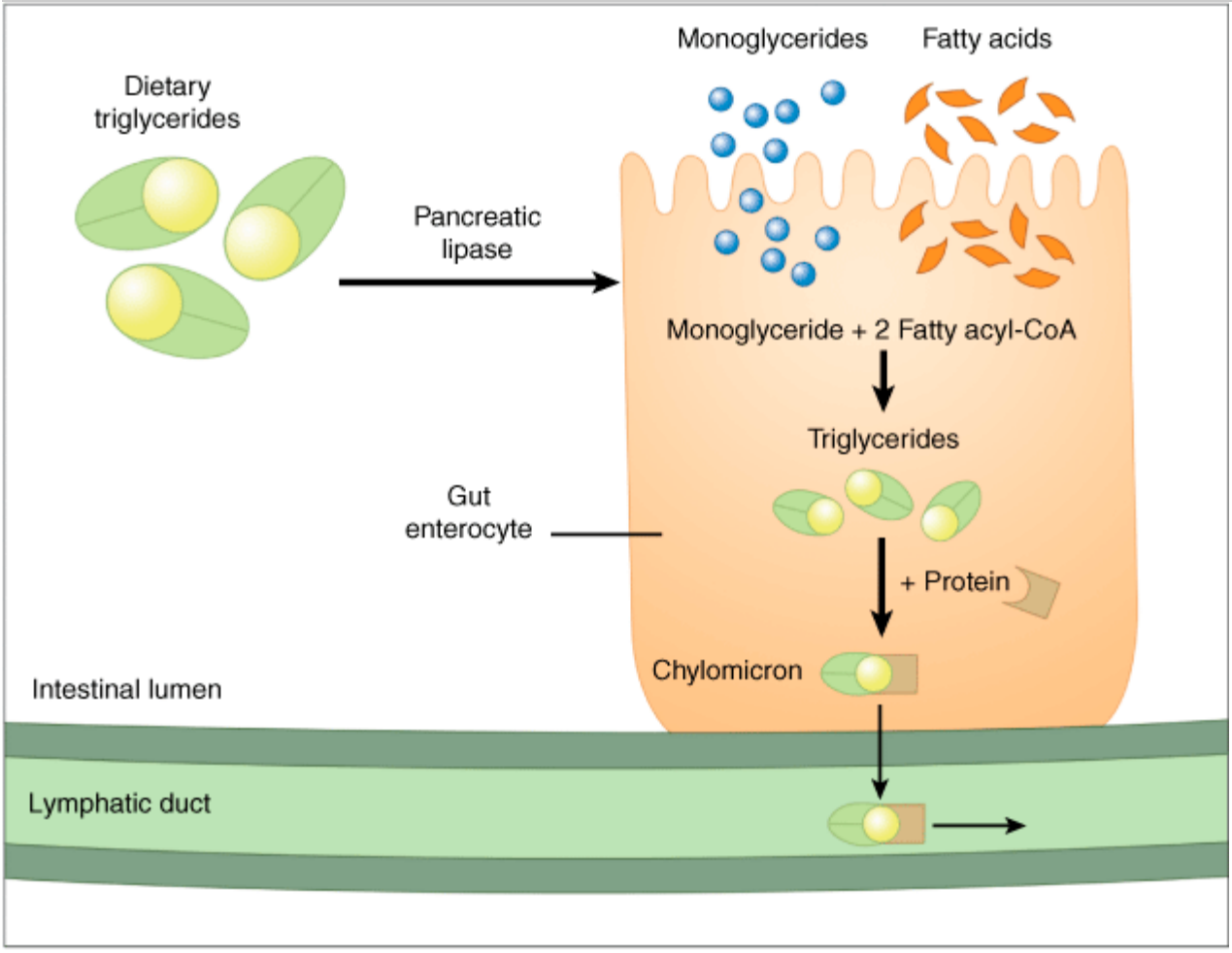
Lipids are not merely nonprotein, noncarbohydrate fuel sources that minimize protein catabolism in the injured patient. Lipid metabolism potentially influences the structural integrity of cell membranes as well as the immune response during systemic inflammation. Adipose stores within the body (triglycerides) are the predominant energy source (50 to 80%) during critical illness and after injury. Fat mobilization (lipolysis) occurs mainly in response to catecholamine stimulus of the hormone-sensitive triglyceride lipase. Other hormonal influences which potentiate lipolysis include adrenocorticotropic hormone (ACTH), catecholamines, thyroid hormone, cortisol, glucagon, growth hormone release, reduction in insulin levels, and increased sympathetic stimulus.[56]

Lipid Absorption

Although the process is poorly understood, adipose tissue provides fuel for the host in the form of free fatty acids and glycerol during critical illness and injury. Oxidation of 1 g of fat yields approximately 9 kcal of energy. Although the liver is capable of synthesizing triglycerides from carbohydrates and amino acids, dietary and exogenous sources provide the major source of triglycerides. Dietary lipids are not readily absorbable in the gut but require pancreatic lipase and phospholipase within the duodenum to hydrolyze the triglycerides into free fatty acids and

monoglycerides. The free fatty acids and monoglycerides are then readily absorbed by gut enterocytes, which resynthesize triglycerides by esterification of the monoglycerides with fatty acyl coenzyme A (acyl-CoA) (Fig. 2-23). Long-chain triglycerides (LCTs), defined as those with 12 carbons or more, generally undergo this process of esterification and enter the circulation through the lymphatic system as chylomicrons. Shorter fatty acid chains directly enter the portal circulation and are transported to the liver by albumin carriers. Hepatocytes use free fatty acids as a fuel source during stress states but also can synthesize phospholipids or triglycerides (i.e., very-low-density lipoproteins) during fed states. Systemic tissue (e.g., muscle and the heart) can use chylomicrons and triglycerides as fuel by hydrolysis with lipoprotein lipase at the luminal surface of capillary endothelium.[57] Trauma or sepsis suppresses lipoprotein lipase activity in both adipose tissue and muscle, presumably mediated by TNF.

Fig. 2-23.



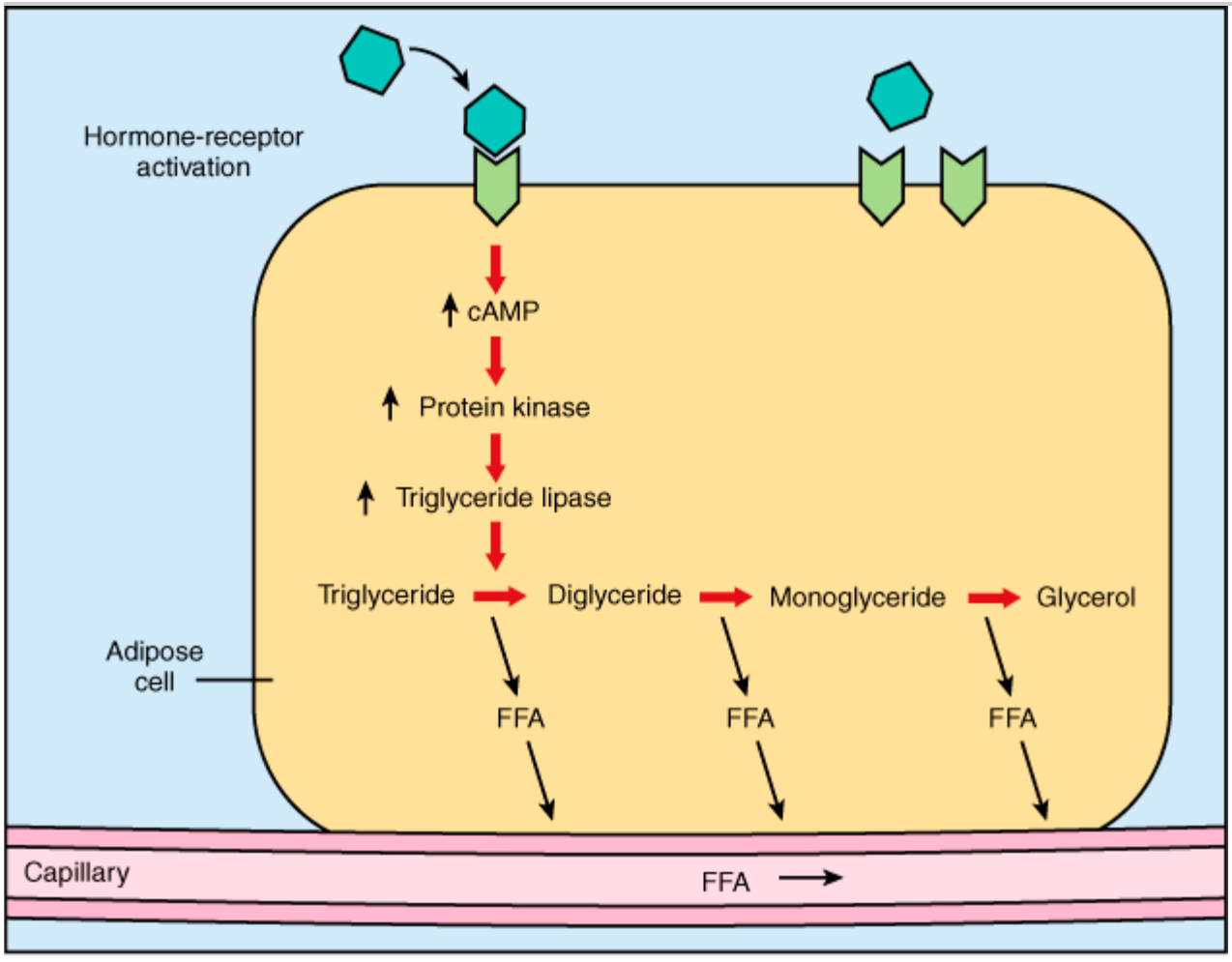
Pancreatic lipase within the small intestinal brush borders hydrolyzes triglycerides into monoglycerides and fatty acids. These components readily diffuse into the gut enterocytes, where they are re-esterified into triglycerides. The resynthesized triglycerides bind carrier proteins to form chylomicrons, which are transported by the lymphatic system. Shorter triglycerides (those with <10 carbon atoms) can bypass this process and directly enter the portal circulation for transport to the liver. CoA

= coenzyme A.

Lipolysis and Fatty Acid Oxidation

Periods of energy demand are accompanied by free fatty acid mobilization from adipose stores. This is mediated by hormonal influences (e.g., catecholamines, ACTH, thyroid hormones, growth hormone, and glucagon) on triglyceride lipase through a cAMP pathway (Fig. 2-24). In adipose tissues, triglyceride lipase hydrolyzes triglycerides into free fatty acids and glycerol. Free fatty acids enter the capillary circulation and are transported by albumin to tissues requiring this fuel source (e.g., heart and skeletal muscle). Insulin inhibits lipolysis and favors triglyceride synthesis by augmenting lipoprotein lipase activity as well as intracellular levels of glycerol-3-phosphate. The use of glycerol for fuel depends on the availability of tissue glycerokinase, which is abundant in the liver and kidneys.

Fig. 2-24.

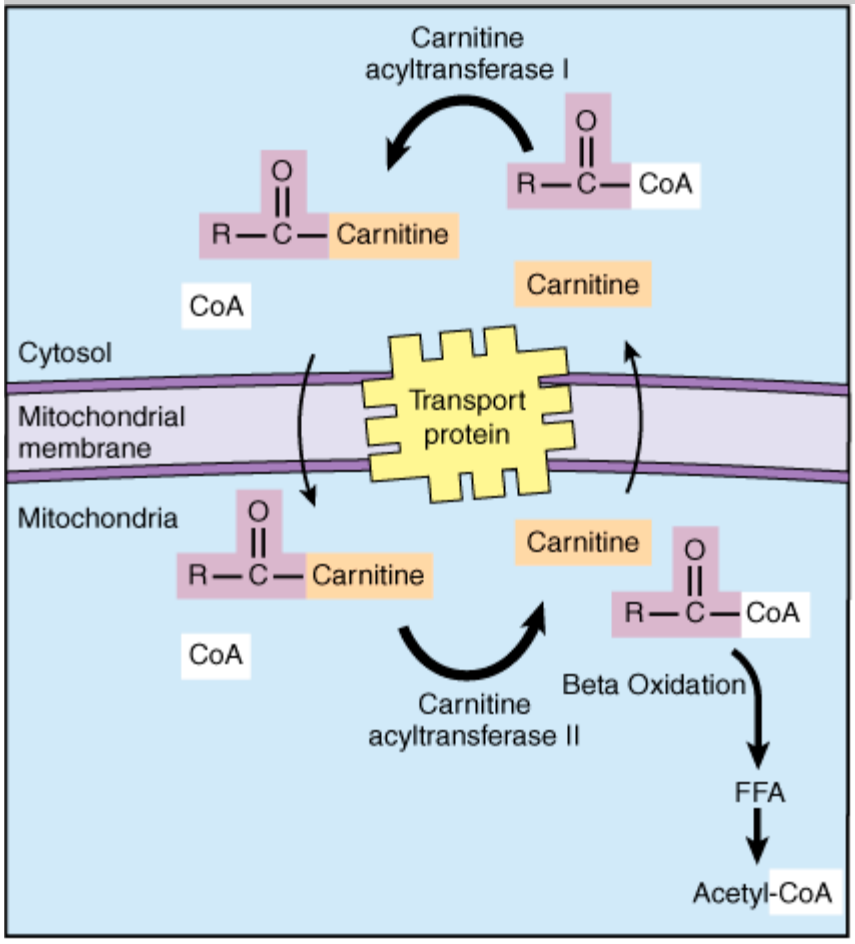


Fat mobilization in adipose tissue. Triglyceride lipase activation by hormonal stimulation of adipose cells occurs through the

cyclic adenosine monophosphate (cAMP) pathway. Triglycerides are serially hydrolyzed with resultant free fatty acid (FFA) release at every step. The FFAs diffuse readily into the capillary bed for transport. Tissues with glycerokinase can use glycerol for fuel by forming glycerol-3-phosphate. Glycerol-3-phosphate can esterify with FFAs to form triglycerides or can be used as a precursor for renal and hepatic gluconeogenesis. Skeletal muscle and adipose cells have little glycerokinase and thus do not use glycerol for fuel.

Free fatty acids absorbed by cells conjugate with acyl-CoA within the cytoplasm. The transport of fatty acyl-CoA from the outer mitochondrial membrane across the inner mitochondrial membrane occurs via the carnitine shuttle (Fig. 2-25). Medium-chain triglycerides (MCTs), defined as those 6 to 12 carbons in length, bypass the carnitine shuttle and readily cross the mitochondrial membranes. This accounts in part for the fact that MCTs are more efficiently oxidized than LCTs. Ideally, the rapid oxidation of MCTs makes them less prone to fat deposition, particularly within immune cells and the reticuloendothelial system—a common finding with lipid infusion in parenteral nutrition.[58] However, exclusive use of MCTs as fuel in animal studies has been associated with higher metabolic demands and toxicity, as well as essential fatty acid deficiency.

Fig. 2-25.



Free fatty acids (FFAs) in the cells form fatty acyl coenzyme A (CoA) with CoA. Fatty acyl-CoA cannot enter the inner mitochondrial membrane and requires carnitine as a carrier protein (carnitine shuttle). Once inside the mitochondria, carnitine dissociates and fatty acyl-CoA is re-formed. The carnitine molecule is transported back into the cytosol for reuse. The fatty acyl-CoA undergoes beta oxidation to form acetyl-CoA for entry into the tricarboxylic acid cycle. "R" represents a part of the acyl group of acyl-CoA.

Within the mitochondria, fatty acyl-CoA undergoes beta oxidation, which produces acetyl-CoA with each pass through the cycle. Each acetyl-CoA molecule subsequently enters the tricarboxylic acid (TCA) cycle for further oxidation to yield 12 adenosine triphosphate (ATP) molecules, carbon dioxide, and water. Excess acetyl-CoA molecules serve as precursors for ketogenesis. Unlike glucose metabolism, oxidation of fatty acids requires proportionally less oxygen and produces less carbon dioxide. This is frequently quantified as the ratio of carbon dioxide produced to oxygen consumed for the reaction and is known as the *respiratory quotient (RQ).* An RQ of 0.7 would imply greater fatty acid oxidation for fuel, whereas an RQ of 1 indicates greater carbohydrate oxidation (overfeeding). An RQ of 0.85 suggests the oxidation of equal amounts of fatty acids and glucose.

KETOGENESIS

Carbohydrate depletion slows the entry of acetyl-CoA into the TCA cycle secondary to depleted TCA intermediates and enzyme activity. Increased lipolysis and reduced systemic carbohydrate availability during starvation diverts excess acetyl-CoA toward hepatic ketogenesis. A number of extrahepatic tissues, but not the liver itself, are capable of using ketones for fuel. Ketosis represents a state in which hepatic ketone production exceeds extrahepatic ketone utilization.

The rate of ketogenesis appears to be inversely related to the severity of injury. Major trauma, severe shock, and sepsis attenuate ketogenesis by increasing insulin levels and by causing rapid tissue oxidation of free fatty acids. Minor injuries and infections are associated with modest elevations in plasma free fatty acid concentrations and ketogenesis. However, in minor stress states ketogenesis does not exceed that in nonstressed starvation.

CARBOHYDRATE METABOLISM

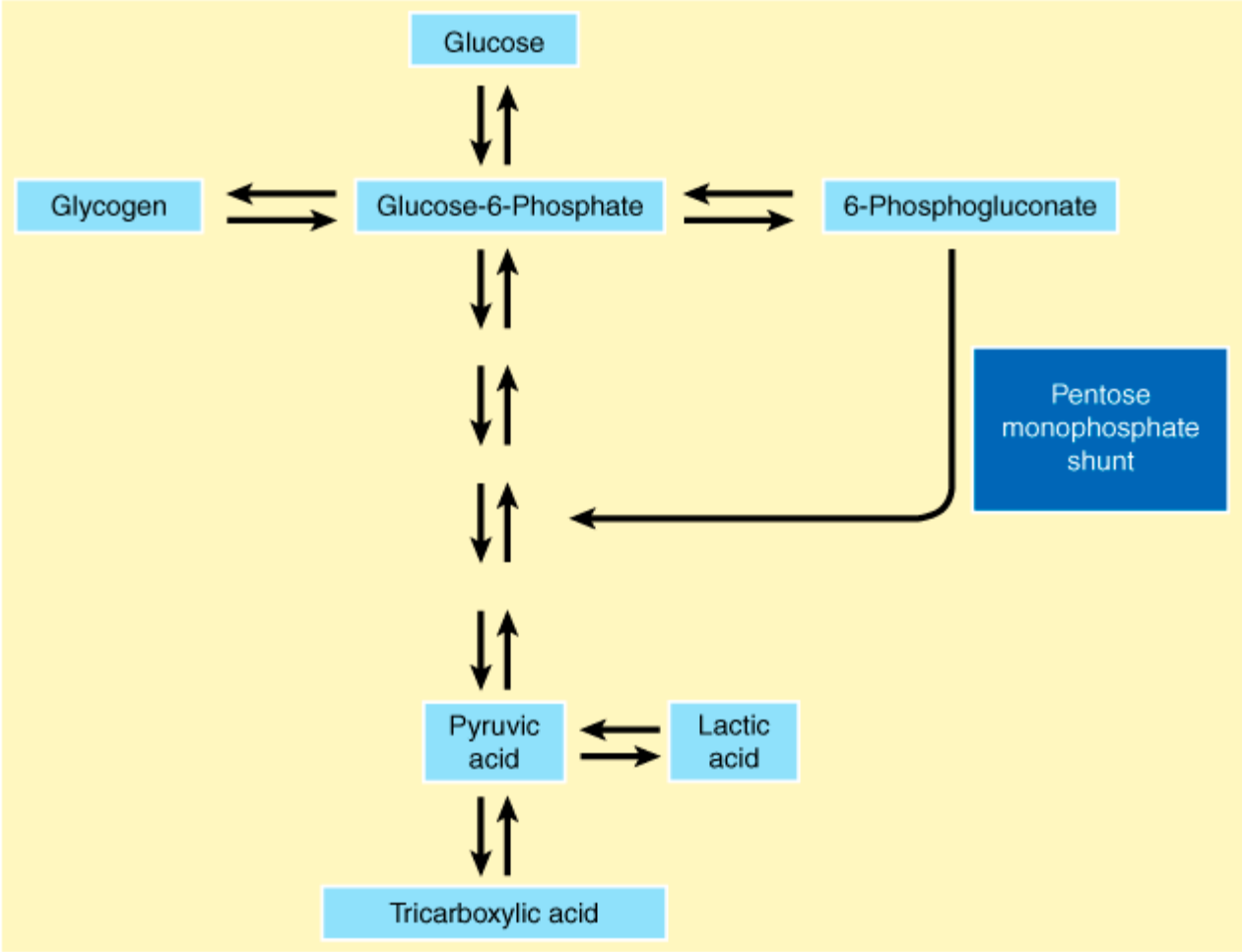
Ingested and enteral carbohydrates are primarily digested in the small intestine, where pancreatic and intestinal enzymes reduce the complex carbohydrates to dimeric units. Disaccharidases (e.g., sucrase, lactase, and maltase) within intestinal brush borders dismantle the complex carbohydrates into simple hexose units, which are transported into the intestinal mucosa. Glucose and galactose are primarily absorbed by energy-dependent active transport coupled to the sodium pump. Fructose absorption, however, occurs by concentration-dependent facilitated diffusion. Neither fructose and galactose within the circulation nor exogenous mannitol (for neurologic injury) evokes an insulin response. Intravenous administration of low-dose fructose in fasting humans has been associated with nitrogen conservation, but the clinical utility of fructose administration in human injury remains to be demonstrated.

Discussion of carbohydrate metabolism primarily refers to the utilization of glucose. The oxidation of 1 g of carbohydrate yields 4 kcal, but sugar solutions such as those found in intravenous fluids or parenteral nutrition provide only 3.4 kcal/g of dextrose. In starvation, glucose production occurs at the expense of protein stores (i.e., skeletal muscle). Hence, the primary goal for maintenance glucose administration in surgical patients is to minimize muscle wasting. The exogenous administration of small amounts of glucose (approximately 50 g/d) facilitates fat entry into the TCA cycle and reduces ketosis. Unlike in starvation in healthy subjects, in septic and trauma patients provision of exogenous glucose never has been shown to fully suppress amino acid degradation for gluconeogenesis. This suggests that during periods of stress, other hormonal and proinflammatory mediators have

a profound influence on the rate of protein degradation and that some degree of muscle wasting is inevitable. The administration of insulin, however, has been shown to reverse protein catabolism during severe stress by stimulating protein synthesis in skeletal muscles and by inhibiting hepatocyte protein degradation. Insulin also stimulates the incorporation of elemental precursors into nucleic acids in association with RNA synthesis in muscle cells.

In cells, glucose is phosphorylated to form glucose-6-phosphate. Glucose-6-phosphate can be polymerized during glycogenesis or catabolized in glycogenolysis. Glucose catabolism occurs by cleavage to pyruvate or lactate (pyruvic acid pathway) or by decarboxylation to pentoses (pentose shunt) (Fig. 2-26).

Fig. 2-26.



Simplified schema of glucose catabolism through the pentose monophosphate pathway or by breakdown into pyruvate. Glucose-6-phosphate becomes an important "crossroad" for glucose metabolism.

Excess glucose from overfeeding, as reflected by RQs >1.0, can result in conditions such as glucosuria,