eighth edition

Schwartz's PRINCIPLES OF SURGERY

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Timothy R. Billiar
David L. Dunn
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Schwartz's Principles of Surgery

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To my wife, Melissa, my children, Isaac and Jackson, my mother, Rose, and my late father, Edward Brunicardi, for their love and support.
F.C.B.

To my wife, Cindy, and my children, Ashley, Lauren, Kathryn, Thomas, and Olivia.
D.K.A.

To my father, Robert R. Billiar, D.V.M., my first role model for professional excellence.
T.R.B.

To the outstanding students and teachers of the discipline of surgery at the University of Minnesota—past, present, and future.
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To my wife Laura, my children, Sarah, Sam, and Jillian, and the residents, fellows, and surgical faculty at OHSU who have created a community of health, collegiality, and open minded intellectual rigor.
J.G.H.

To my children, Samuel and Jessica Pollock, and my late father.
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Foreword

It began during the summer of 1967 when John DeCarville of McGraw-Hill convened David Hume, Richard Lillehei, G. Tom Shires, Frank Spencer, Edward Storer, and myself and proposed that we edit a new surgical textbook to serve as a companion to Harrison's *Principles of Internal Medicine*. We agreed, with the proviso that we could create a textbook that would differ from the previous and existing works in the field of surgery. We envisioned a truly modern textbook of surgery that would be panoramic in its scope by including all surgical specialties, and offer material directed at a sophisticated audience, consisting of medical students, who were regarded as graduate students, and that the text would also incorporate the knowledge sought after by surgeons in training, and as part of the continuing education of practicing surgeons. The narrative's attraction would be the presentation of the physiologic basis of the practices in addition to the pathology, diagnosis, and therapy, made readable as a consequence of consistency of style.

The first edition was published in 1969, and I have had the privilege of shepherding six subsequent editions. In each instance, as part of the credo of modernity, the material was brought up to date by effecting changes of between 30 and 40 percent in the subsequent edition. Now, the time has come to pass the mantle of responsibility to Dr. Brunicardi and his five associate editors, all of whom are actively engaged in clinical practice, research, and education.

As Sir William Osler wrote: "Everywhere the old order changes and happy they who can change with it." The editorship of the past seven editions of *Principles of Surgery* has generated much personal happiness and satisfaction. I am particularly appreciative of the reception that has been received from the readership. It is my hope that, over our tenure of 35 years, the needs of the audience have been fulfilled, and the current and future editors provide a continuum of the past.

Seymour I. Schwartz, M.D., F.A.C.S.

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Preface

For the past 35 years, the *Principles of Surgery* has been edited by Dr. Seymour Schwartz and a group of outstanding co-editors. It has been considered the leading large textbook for general surgery worldwide. I was surprised and deeply honored to have been asked to assume the role of editor-in-chief and was determined to ensure that the reputation of this legendary book would carry on its tradition of excellence. In this effort, the first assigned task was to select a new group of co-editors. After careful deliberation, five departmental chairmen who are leading scholars in a variety of specialties were selected from universities around the country. Our first meeting to discuss the development of the eighth edition of *Schwartz's Principles of Surgery* defined our first goal: to preserve the style and structure of the classic *Principles of Surgery* with its basic and clinical sections and to preserve the titles of 95% of the chapters. However, it soon became apparent after a thorough review of each chapter that new authors, those who were leaders in their respective fields, would be selected to compose this extensively updated and modernized text. Upon completion, 76% of the chapters are from new authors. These chapters contain the latest in surgical science, surgical techniques, and therapy for students, residents, and surgeons. Six new chapters have been added to round out this eighth edition: Cell, Genomics, and Molecular Surgery, Soft Tissue Sarcomas, Anesthesia of the Surgical Patient, the Surgical Management of Obesity, Patient Safety, Errors, and Complications in Surgery, and Surgical Considerations in the Elderly. Another important component of this work identified by the editorial team was the artwork. A new artist (Philip Ashley & Associates) was selected to direct the art program, which provides clear and consistent learning aids throughout the text and visually reflects the comprehensive and updated nature of this book.

The editorial team is deeply honored to carry forward the tradition of this great textbook into the 21st century. As a team we have worked diligently to create a state-of-the-art textbook to help students, residents and surgeons study the craft of surgery and it is to students of surgery of all ages that we dedicate this book. It is your own devotion to learning the language of surgery that will translate into the best care of patients around the world. We hope the textbook will serve as the cornerstone of your own learning program as it has for the study of surgery for the past 35 years.

We wish to thank Katie Elsbury and Susie Lee for their exceptional skills in helping edit and coordinate all communication. We wish to thank Marc Strauss, Michelle Watt, and their team at McGraw-Hill for their willingness to work with us. We would also like to thank our families, whose love and support made this book possible.

F. Charles Brunicardi, M.D., F.A.C.S.
October 2004

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Preface to the First Edition

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

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

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

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

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

Seymour I. Schwartz, M.D., F.A.C.S.

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Schwartz's Principles of Surgery

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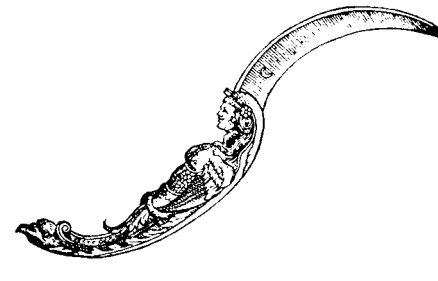
PART I

BASIC CONSIDERATIONS



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CHAPTER 1

Systemic Response to Injury and Metabolic Support

Edward Lin, Steven E. Calvano, and Stephen F. Lowry

INTRODUCTION

The inflammatory response to injury and activation of cellular processes are inherently designed to restore tissue function and eradicate invading microorganisms. Local injuries of limited duration are usually followed by functional restoration with minimal intervention. By contrast, major insults to the host are associated with an overwhelming inflammatory response that, without appropriate and timely intervention, can lead to multiple organ failure and adversely impact patient survival. Therefore understanding how the inflammatory response is mobilized and ultimately controlled provides a functional framework upon which interventions and therapeutics are formulated for the surgical patient. The maturation of minimally invasive techniques for major surgery during the last decade has brought complementary perspectives to the injury response paradigm, and the immunologic benefits for these surgical approaches are undergoing validation. Furthermore, the sequencing of the human genome and available technology such as deoxyribonucleic acid (DNA) microarray analysis potentially affords surgeons additional tools to profile the genetic mechanisms governing the host response to injury.

This chapter addresses the hormonal, immunologic, and cellular responses to injury. The resultant metabolic and nutritional alterations of injury are discussed in continuum because the utilization of fuel substrates during injury also is subject to the influences of hormonal and inflammatory mediators.

THE SYSTEMIC INFLAMMATORY RESPONSE SYNDROME (SIRS)

Conceptually, the systemic response to injury can be broadly compartmentalized into two phases: (1) a proinflammatory phase characterized by activation of cellular processes designed to restore tissue function and eradicate invading microorganisms, and (2) an anti-inflammatory or *counterregulatory* phase that is important for preventing excessive proinflammatory activities as well as restoring homeostasis in the individual (Fig. 1-1). While the terminologies that describe the various facets of systemic inflammation are often used interchangeably, there are distinct criteria for each term (Table 1-1).

CENTRAL NERVOUS SYSTEM REGULATION OF INFLAMMATION

Reflex Inhibition of Inflammation

The central nervous system, operating through autonomic signaling, has an integral role in regulating the inflammatory response that is primarily involuntary. Classically, the autonomic system regulates heart rate, blood pressure, respiratory rate, gastrointestinal motility, and body temperature. An additional role of the autonomic nervous system is to regulate inflammation in a reflex manner, much like the patellar tendon reflex. Inflammation originating from a specific location sends afferent signals to the hypothalamus, which in turn rapidly relays opposing anti-inflammatory messages to the site of inflammation to reduce inflammatory mediator release by immunocytes (Fig. 1-2).

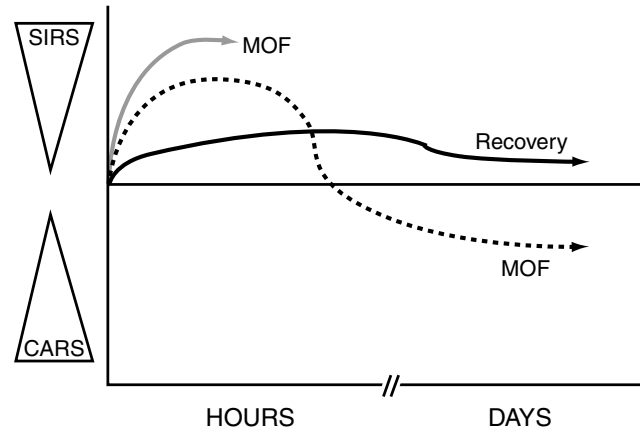

FIG. 1-1. Schematic representation of the systemic inflammatory response syndrome (SIRS) to injury, followed by a period of convalescence mediated by the counterregulatory anti-inflammatory response syndrome (CARS). Severe inflammation may lead to acute multiple organ failure (MOF) and early death following injury (*gray solid arrow*). A lesser inflammatory response followed by excessive CARS may induce a prolonged immunosuppressed state that can also be deleterious to the host (*broken arrow*). Normal recovery after injury requires a period of systemic inflammation followed by a return to homeostasis (*black solid arrow*). (*Concept adapted with permission from Guirao X, Lowry SF: Biologic control of injury and inflammation: Much more than too little or too late. World J Surg 20:437, 1996.*)

Afferent Signals to the Brain

The central nervous system (CNS) receives immunologic input from both the circulation and neural pathways. Indeed, areas of the CNS devoid of blood-brain barrier admit the passage of inflammatory mediators such as tumor necrosis factor (TNF-α). Fevers, anorexia, and depression in illness are attributed to the humoral (circulatory) route of inflammatory signaling. While the mechanism for vagal

Table 1-1
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 Temperature $\geq$38°C or $\leq$36°C Heart rate $\geq$90 beats/min Respiratory rate $\geq$20 breaths/min or $Paco_2$ $\leq$32 mm Hg or mechanical ventilation White blood cell count $\geq$12,000/μL or $\leq$4000/μL or $\geq$10% band forms
Sepsis	Identifiable source of infection + SIRS
Severe sepsis	Sepsis + organ dysfunction
Septic shock	Sepsis + cardiovascular collapse (requiring vasopressor support)

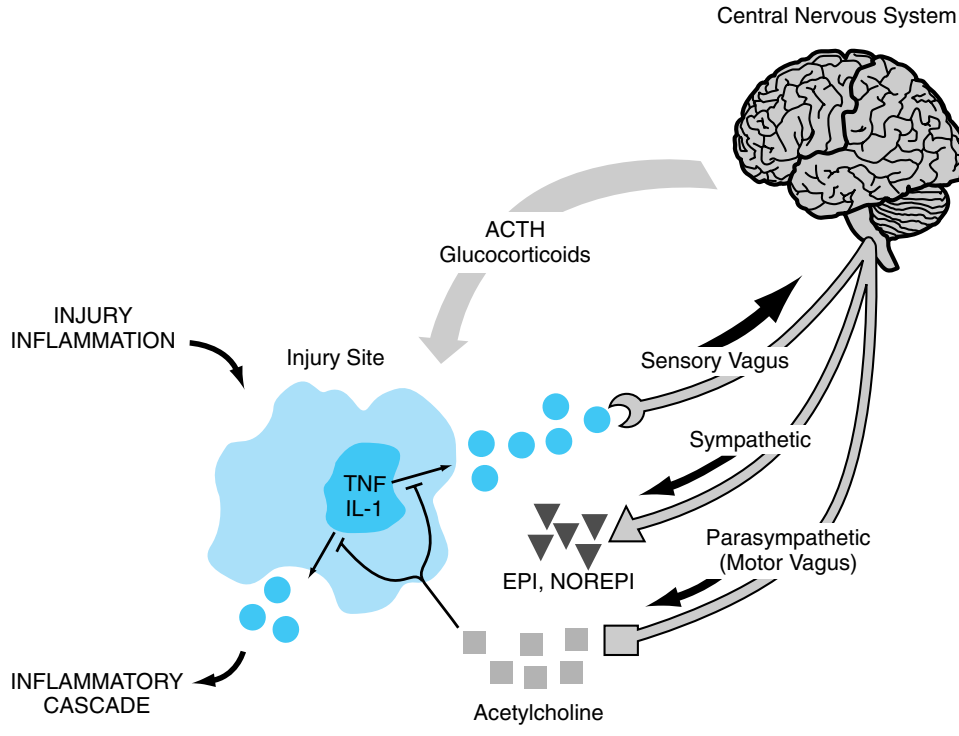

FIG. 1-2. Neural circuit relaying messages of localized injury to the brain (nucleus tractus solitarius). The brain follows with a hormonal response (ACTH, glucocorticoids) into the systemic circulation and by sympathetic release. The vagal response rapidly induces acetylcholine release directed at the site of injury to curtail the inflammatory response elicited by the activated immunocytes. This vagal response occurs in real time and is site specific. (*Concept adapted and recreated with permission from Tracey KJ: The inflammatory reflex. Nature 420:853, 2002.*)

sensory input is not fully understood, it has been demonstrated that afferent stimuli to the vagus nerve include cytokines (e.g., TNF-α and interleukin [IL]-1), baroreceptors, chemoreceptors, and thermoreceptors originating from the site of injury. This phenomenon is further demonstrated by blunting of fever response in animals after regional vagotomy at the site of injury.

Cholinergic Anti-Inflammatory Pathways

Tracey and colleagues have further linked reflex inhibition of inflammation to the parasympathetic signaling pathway whereby *acetylcholine,* the primary neurotransmitter of the parasympathetic system, reduces tissue macrophage activation. Furthermore, cholinergic stimulation directly reduces tissue macrophage release of the proinflammatory mediators TNF-α, IL-1, IL-18, and high mobility group protein (HMG-1), but not the anti-inflammatory cytokine IL-10. The attenuated inflammatory response induced by cholinergic stimuli was further validated by the identification of acetylcholine (nicotinic) receptors on tissue macrophages. In experimental models, direct electrical stimulation of the vagus nerve inhibits the tissue synthesis of inflammatory cytokines in the liver, spleen, and heart and reduces circulating levels as well. Complete vagotomy in mice significantly increases proinflammatory mediator release in response to injury.

In summary, vagal stimulation reduces heart rate, increases gut motility, dilates arterioles, and causes pupil constriction, as well as regulates inflammation. Unlike the humoral anti-inflammatory mediators that are released into the circulation and allowed to travel to a site of injury, signals discharged from the vagus nerve are precisely targeted at the site of injury or infection. Moreover, this cholinergic signaling occurs rapidly in real time. From the available preclinical studies, it can be proposed that impaired cholinergic activity from the vagus nerve portends a greater proinflammatory response in patients who are critically ill.

HORMONAL RESPONSE TO INJURY

Hormone Signaling Pathways

Hormones are chemically classified as *polypeptides* (e.g., cytokines, glucagon, and insulin), *amino acids* (e.g., epinephrine, serotonin, and histamine), or *fatty acids* (e.g., glucocorticoids, prostaglandins, and leukotrienes). Most hormone receptors generate signals by one of three major pathways, which overlap. Specifically, these receptor pathways are (1) *receptor kinases* such as insulin and insulin-like growth factor receptors, (2) *guanine nucleotide-binding* or *G-protein receptors* such as neurotransmitter and prostaglandin receptors, and (3) *ligand-gated ion channels* which permit ion transport when activated. Upon activation of membrane receptors, secondary signaling pathways are often utilized to amplify the initial stimuli. Hormone signals are further mediated by intracellular receptors with binding affinities for both the hormone itself, as well as for the targeted gene sequence on the DNA. These intracellular receptors may be located within the cytosol or may already be localized in the nucleus, bound to the DNA. The classic example of a cytosolic hormonal receptor is the glucocorticoid (GC) receptor (Fig. 1-3). Intracellular GC receptors are maintained in the cytosol by linking to the stress-induced protein, heat shock protein (HSP). When the glucocorticoid ligand binds to the GC receptor, the dissociation of HSP from the receptor activates the receptor-ligand complex and is transported to the nucleus.

Virtually every hormone of the hypothalamic-pituitary-adrenal (HPA) axis influences the physiologic response to injury and stress (Table 1-2), but some with direct influence on the inflammatory response or immediate clinical impact will be highlighted.

Adrenocorticotropic Hormone

Adrenocorticotropic hormone (ACTH) is synthesized and released by the anterior pituitary. In healthy humans, ACTH release

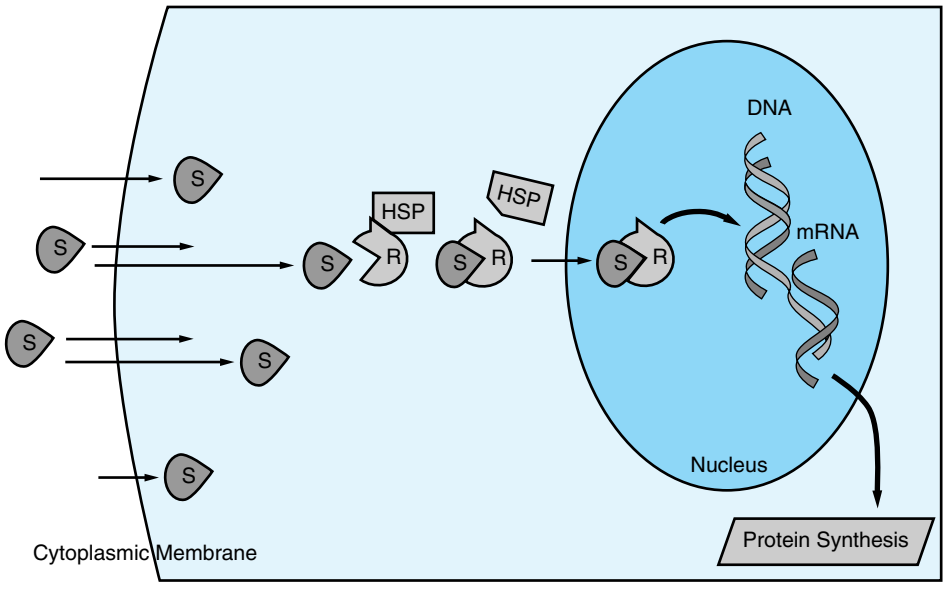

FIG. 1-3. Simplified schematic of steroid transport into the nucleus. Steroid molecules (S) diffuse readily across cytoplasmic membranes. Intracellularly the receptors (R) are rendered inactive by being coupled to heat shock protein (HSP). When S and R bind, HSP dissociates, and the S-R complex enters the nucleus where the S-R complex induces DNA transcription, resulting in protein synthesis.

is regulated by circadian signals such that the greatest elevation of ACTH occurs late at night until the hours immediately before sunrise. This pattern is dramatically altered or obliterated in the injured subject. Most injury is characterized by elevations in corticotropin-releasing hormone and ACTH that are proportional to the severity of injury. Pain, anxiety, vasopressin, angiotensin II, cholecystokinin, vasoactive intestinal polypeptide (VIP), catecholamines, and proinflammatory cytokines are all prominent mediators of ACTH release in the injured patient.

Table 1-2
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

Within the zona fasciculata of the adrenal gland, ACTH signaling activates intracellular pathways that lead to glucocorticoid production (Fig. 1-4). Conditions of excess ACTH stimulation will result in adrenal cortical hypertrophy.

Cortisol and Glucocorticoids

Cortisol is the major glucocorticoid in humans and is essential for survival during significant physiologic stress. Following injury, cortisol is elevated depending on the type of systemic stress. Burn patients have elevated circulating cortisol levels for up to 4 weeks, while soft tissue injury and hemorrhage may exhibit shorter periods of cortisol elevation.

Metabolically, cortisol potentiates the actions of glucagon and epinephrine that manifest as hyperglycemia. In the liver, cortisol stimulates the enzymatic activities favoring gluconeogenesis, but induces insulin resistance in muscles and adipose tissue. In skeletal muscle, cortisol induces protein degradation as well as the release of lactate that serve as substrates for hepatic gluconeogenesis. During injury, cortisol potentiates the release of free fatty acids, triglycerides, and glycerol from adipose tissue as a means of providing additional energy sources.

Acute adrenal insufficiency (AAI) can be a life-threatening complication most commonly seen in acutely ill patients with adrenal suppression from exogenously administered glucocorticoids with consequent atrophy of the adrenal glands. Clinically, these patients present with weakness, nausea, vomiting, fever, and hypotension. Objective findings include hypoglycemia from decreased gluconeogenesis, hyponatremia from impaired renal tubular sodium resorption, and hyperkalemia from diminished kaliuresis. In addition to cortisol deficiency, insufficient mineralocorticoid (aldosterone) activity also contributes to hyponatremia and hyperkalemia.

Glucocorticoids have long been employed as effective immunosuppressive agents. Immunologic changes associated with glucocorticoid administration include thymic involution, depressed cell-mediated immune responses reflected by decreases in T-killer and natural killer cell functions, T-lymphocyte blastogenesis, mixed lymphocyte responsiveness, graft-versus-host reactions, and delayed hypersensitivity responses. With glucocorticoid administration, monocytes lose the capacity for intracellular killing but appear

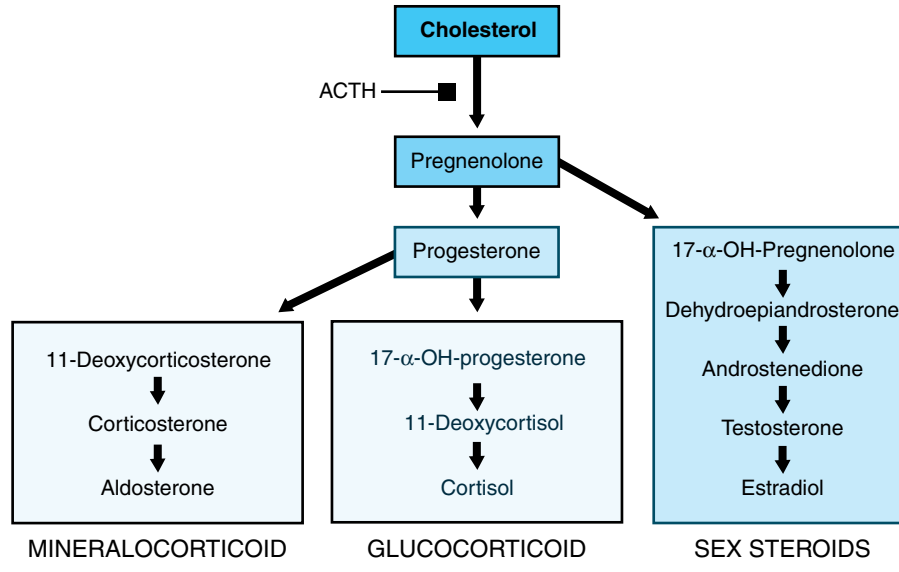

FIG. 1-4. *Steroid synthesis from cholesterol. Adrenocorticotropic hormone (ACTH) is a principal regulator of steroid synthesis. The end products are mineralocorticoids, glucocorticoids, and sex steroids.*

to maintain normal chemotactic and phagocytic properties. For neutrophils, glucocorticoids inhibit intracellular superoxide reactivity, suppress chemotaxis, and normalize apoptosis signaling mechanisms. However, neutrophil phagocytosis function remains unchanged. Finally, glucocorticoid infusion in human endotoxemia downregulates proinflammatory cytokine production (TNF-α, IL-1, and IL-6) and increases the production of the anti-inflammatory mediator IL-10. This glucocorticoid-induced downregulation of cytokine stimulation serves an important negative regulatory function in the inflammatory response. Clinically, the administration of pharmacologic doses of glucocorticoids has been associated with modest reductions in proinflammatory response in septic shock, surgical trauma, and coronary artery bypass surgery. However, the appropriate dosing, timing, and duration of glucocorticoid administration have not been validated.

Macrophage Inhibitory Factor

Macrophage inhibitory factor (MIF) is a glucocorticoid antagonist produced by the anterior pituitary that potentially reverses the immunosuppressive effects of glucocorticoids. MIF can be secreted systemically from the anterior pituitary and by T lymphocytes situated at the sites of inflammation. MIF is a proinflammatory mediator that potentiates gram-negative and gram-positive septic shock. In mice endotoxemia experiments, the administration of anti-MIF significantly improves survival.

Growth Hormones and Insulin-Like Growth Factors

During periods of stress, growth hormone (GH) promotes protein synthesis and also enhances the mobilization of fat stores. The protein synthesis properties of growth hormone in the recovering patient are mediated in part by the secondary release of insulin-like growth factor-1 (IGF-1). IGF, formerly called somatomedin C, circulates predominantly in bound form with several binding proteins and promotes amino acid incorporation and cellular proliferation and attenuates proteolysis. In the liver, IGFs are mediators of protein synthesis and glycogenesis. In adipose tissue, IGF increases glucose uptake and fat utilization. In skeletal muscles, IGF increases glucose uptake and protein synthesis. IGF also has a role in skeletal growth by promoting the incorporation of sulfate and proteoglycans into cartilage. The effects of IGF-1 can be inhibited by interleukin (IL)-1α, TNF-α, and IL-6. The decrease in protein synthesis and observed negative nitrogen balance following injury is attributed in large part to a reduction in IGF-1 levels. GH administration has been shown to improve the clinical course of pediatric burn patients. Its use in injured adult patients remains unproven. The liver is the predominant source of IGF-1, and pre-existing hepatic dysfunction (e.g., end-stage liver disease and protein-energy malnutrition) may further contribute to the negative nitrogen balance following injury. IGF binding proteins also are produced within the liver and are necessary for effective transport of IGF to the cell. IGF has the potential for attenuating the catabolic effects following surgical insults. Growth hormones also stimulate leukocyte function and cell proliferation, but the clinical benefits of such a response are unclear.

Catecholamines

The hypermetabolic state observed following severe injury is attributed to activation of the adrenergic system. Both norepinephrine (NE) and epinephrine (EPI) are increased three- to fourfold in plasma immediately following injury, with elevations lasting 24 to 48 hours before returning toward baseline levels.

In the liver, EPI promotes glycogenolysis, gluconeogenesis, lipolysis, and ketogenesis. It also causes decreased insulin release, but increases glucagon secretion. Peripherally, EPI increases lipolysis in adipose tissues and induces insulin resistance in skeletal muscle. These collectively manifest as stress-induced hyperglycemia, not unlike the effects of cortisol on blood sugar. Catecholamines also increase the secretion of thyroid and parathyroid hormones, T_4, T_3, and renin, but inhibit the release of aldosterone.

Like cortisol, EPI enhances leukocyte demargination with resultant neutrophilia and lymphocytosis. However, EPI occupation of β receptors present on leukocytes increases intracellular cyclic adenosine monophosphate (cAMP) and ultimately decreases lymphocyte responsiveness to mitogens.

There is strong evidence that blockade of β receptors in children with thermal injury reduces cardiac oxygen consumption and retention of lean muscle mass. In noncardiac surgical patients with heart disease, perioperative β-receptor blockade also reduced sympathetic activation and cardiac oxygen demand with significant reductions in cardiac-related deaths.

Table 1-3
Cytokines and Their Sources

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

(*Continued*)

Table 1-3
Cytokines and Their Sources (*continued*)

Cytokine	*Source*	*Comment*
IL-10	*T lymphocytes* B lymphocytes Macrophages Basophils Mast cells Keratinocytes	Prominent anti-inflammatory cytokine; reduces mortality in animal sepsis and ARDS models
IL-12	*Macrophages/monocytes* Neutrophils Keratinocytes Dendritic cells B lymphocytes	Promotes T_H1 differentiation; synergistic activity with IL-2
IL-13	*T lymphocytes*	Promotes B-lymphocyte function; structurally similar to IL-4; inhibits nitric oxide and endothelial activation
IL-15	*Macrophages/monocytes* Epithelial cells	Anti-inflammatory effect; promotes lymphocyte activation; promotes neutrophil phagocytosis in fungal infections
IL-18	*Macrophages* Kupffer cells Keratinocytes Adrenal cortical cells Osteoblasts	Similar to IL-12 in function; elevated in sepsis, particularly gram-positive infections; high levels found in cardiac deaths
IFN-γ	*T lymphocytes* NK cells Macrophages	Mediates IL-12 and IL-18 function; half-life, days; found in wounds 5–7 days after injury; promotes ARDS
GM-CSF	*T lymphocytes* Fibroblasts Endothelial cells Stromal cells	Promotes wound healing and inflammation through activation of leukocytes
IL-21	*T lymphocytes*	Preferentially secreted by T_H2 cells; structurally similar to IL-2 and IL-15; activates NK cells, B and T lymphocytes; influences adaptive immunity
HMGB-I	*Monocytes/lymphocytes*	High mobility group box chromosomal protein; DNA transcription factor; late (downstream) mediator of inflammation (ARDS, gut barrier disruption); induces "sickness behavior"

ARDS = acute respiratory distress syndrome; GM-CSF = granulocyte-macrophage colony-stimulating factor; IFN = interferon; IgE = immunoglobulin E; IgG = immunoglobulin G; IL = interleukin; NK = natural killer; T_H1 = T helper subset cell 1; T_H2 = T helper subset cell 2; TNF = tumor necrosis factor.

Aldosterone

The mineralocorticoid aldosterone is synthesized, stored, and released in the adrenal zona glomerulosa. ACTH is the most potent stimulant of aldosterone release. The major function of aldosterone is to maintain intravascular volume by conserving sodium and eliminating potassium and hydrogen ions in the early distal convoluted tubules of the nephrons.

Patients with aldosterone deficiency develop hypotension and hyperkalemia, whereas patients with aldosterone excess develop edema, hypertension, hypokalemia, and metabolic alkalosis.

Insulin

Hormones and inflammatory mediators associated with stress response inhibit insulin release. Therefore, in conjunction with peripheral insulin resistance following injury, this results in stress-induced hyperglycemia and is in keeping with the general catabolic state immediately following major injury.

In the healthy individual, insulin exerts a global anabolic effect by promoting hepatic glycogenesis and glycolysis, glucose transport into cells, adipose tissue lipogenesis, and protein synthesis. In the injured patient, there are two phases to the pattern of insulin release. The first phase suppresses overall insulin release and occurs within a few hours after injury. The later phase is characterized by a return to normal or excessive insulin production, but with persistent hyperglycemia, consistent with peripheral resistance to insulin.

Activated lymphocytes express insulin receptors, and activation enhances T-cell proliferation and cytotoxicity. Institution of insulin therapy to newly diagnosed diabetics is associated with increased functional B- and T-lymphocyte populations. Recent evidence strongly suggests that tight control of glucose levels in the intensive care unit, particularly in diabetics, was associated with significant reductions in mortality.

Acute Phase Proteins

The acute phase proteins are nonspecific biochemical markers produced by hepatocytes in response to tissue injury, infection, or inflammation. Interleukin (IL)-6 is a potent inducer of acute phase proteins that can include proteinase inhibitors, coagulation and complement proteins, and transport proteins. Clinically, only C-reactive protein (CRP) has been consistently used as a marker of injury response due to its dynamic reflection of inflammation. Importantly, CRP levels do not show diurnal variations and are not affected by feeding. Only pre-existing liver failure will impair CRP production. Therefore it has become a useful biomarker of inflammation as well as response to treatment. Its accuracy surpasses that of the erythrocyte sedimentation rate.

MEDIATORS OF INFLAMMATION

Cytokines

Cytokines appear to be the most potent mediators of the inflammatory response. When functioning locally at the site of injury or infection, cytokines eradicate invading microorganisms and promote wound healing. However, overwhelming production of proinflammatory cytokines in response to injury can cause hemodynamic instability (i.e., septic shock) or metabolic derangements (i.e., muscle wasting). If uncontrolled, the outcome of these exaggerated responses is end-organ failure and death. The production of anti-inflammatory cytokines as part of the inflammation cascade serves to oppose the excessive actions of proinflammatory cytokines. However, inappropriate anti-inflammatory mediator release may render the patient immunocompromised and susceptible to overwhelming infections. To view cytokines merely as proinflammatory or anti-inflammatory oversimplifies their functions, and overlapping bioactivity is the rule (Table 1-3).

Heat Shock Proteins

Stimuli such as hypoxia, trauma, heavy metals, local trauma, and hemorrhage all induce the production of intracellular heat shock proteins (HSPs). HSPs are intracellular protein modifiers and transporters that are presumed to protect cells from the deleterious effects of traumatic stress. The classic example of HSP activity relates to the intracellular transport of steroid molecules. The formation of HSPs requires gene induction by the heat shock transcription factor. HSP expression is also ACTH-sensitive, and the production seems to decline with age.

Reactive Oxygen Metabolites

Reactive oxygen metabolites are short-lived, highly reactive molecular oxygen species with an unpaired outer orbit. They cause tissue injury by oxidation of unsaturated fatty acids within cell membranes.

Oxygen radicals are produced by complex processes that involve anaerobic glucose oxidation coupled with the reduction of oxygen to superoxide anion. Superoxide anion is an oxygen metabolite that is further metabolized to other reactive species such as hydrogen peroxide and hydroxyl radicals. Activated leukocytes are potent generators of reactive oxygen metabolites. Cells are not immune to damage by their own reactive oxygen metabolites, but are generally protected by oxygen scavengers that include glutathione and catalases. In ischemic tissues, the intracellular mechanisms for production of oxygen metabolites are fully activated, but remain nonfunctional due to a lack of oxygen supply. Upon restoration of blood flow and oxygen supply, large quantities of reactive oxygen metabolites are produced that lead to reperfusion injury.

Eicosanoids

The eicosanoid class of mediators, which encompasses prostaglandins (PG), thromboxanes (TX), leukotrienes (LT), hydroxyeicosatetraenoic acids (HETE), and lipoxins (LX), are oxidation derivatives of the membrane phospholipid arachidonic acid (eicosatetraenoic acid). Eicosanoids are secreted by virtually all nucleated cells except lymphocytes. The synthesis of arachidonic acid from phospholipids requires enzymatic activation of phospholipase A_2 (Fig. 1-5). Eicosanoids are generated either by the cyclooxygenase or the lipoxygenase pathways. Products of the cyclooxygenase pathway include all of the prostaglandins and thromboxanes. The lipoxygenase pathway generates the leukotrienes and HETE.

Eicosanoids are not stored within cells, but instead are synthesized rapidly upon stimulation by hypoxic injury, direct tissue injury, endotoxin, norepinephrine, vasopressin, angiotensin II, bradykinin, serotonin, acetylcholine, cytokines, and histamine. Many of these stimuli also induce the production of the second cyclooxygenase enzyme (COX-2), which converts arachidonate to prostaglandin E_2 (PGE_2). PGE_2 increases fluid leakage from blood vessels, but a rising PGE_2 level over several hours eventually feeds back to COX-2 and induces the formation of the anti-inflammatory lipoxin from neutrophils. Nonsteroidal anti-inflammatory drugs acetylate COX-2, which consequently reduces the PGE_2 levels and increases lipoxin production. COX-2 activity also can be inhibited by glucocorticoids.

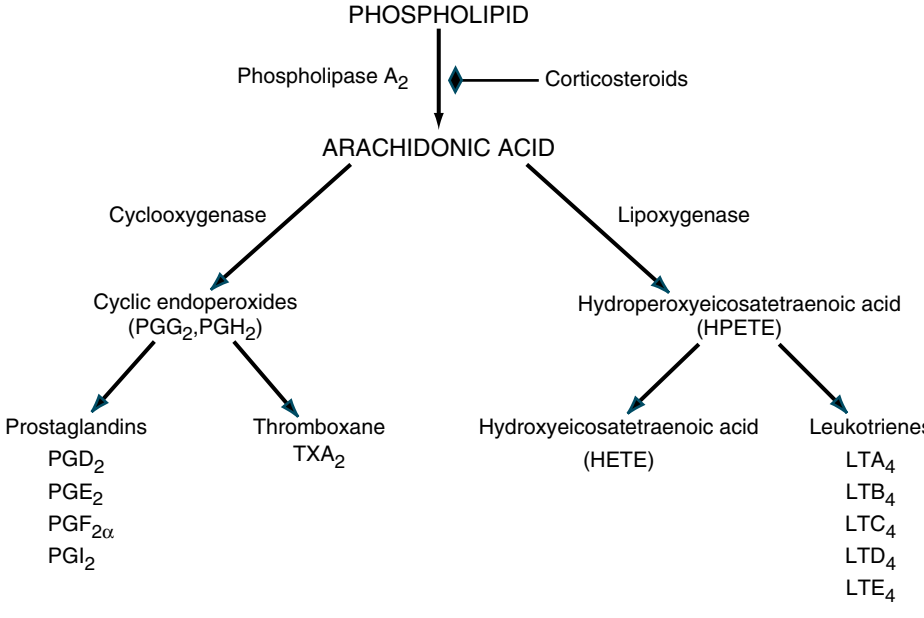

FIG. 1-5. *Schematic diagram of arachidonic acid metabolism.*

Table 1-4
Systemic Stimulatory and Inhibitory Actions of Eicosanoids

Organ/Function	*Stimulator*	*Inhibitor*
Pancreas		
Glucose-stimulated insulin secretion	12-HPETE	PGE_2
Glucagon secretion	PGD_2, PGE_2	
Liver		
Glucagon-stimulated glucose production	PGE_2	
Fat		
Hormone-stimulated lipolysis	PGE_2	
Bone		
Resorption	PGE_2, PGE-m, 6-K-PGE_1, $PGF_{1\alpha}$, PGI_2	
Pituitary		
Prolactin	PGE_1	
LH	PGE_1, PGE_2, 5-HETE	
TSH	PGA_1, PGB_1, PGE_1, $PGE_{1\alpha}$	
GH	PGE_1	
Parathyroid		
PTH	PGE_2	$PGF_{2\alpha}$
Pulmonary		
Bronchoconstriction	$PGF_{2\alpha}$, TXA_2, LTC_4, LTD_4, LTE_4	PGE_2
Renal		
Stimulate renin secretion	PGE_2, PGI_2	
Gastrointestinal		
Cytoprotective effect	PGE_2	
Immune Response		
Suppress lymphocyte activity	PGE_2	
Hematologic		
Platelet aggregation	TXA_2	PGI_2

GH = growth hormone; 5-HETE = 5-hydroxyeicosatetraenoic acid; 12-HETE = 12-hydroxyperoxy-eicosatetraenoic acid; 6-K-PGE_1 = 6-keto-prostaglandin E_1; LH = luteinizing hormone; LTC_4 = leukotriene C_4; LTD_4 = leukotriene D_4; LTE_4 = leukotriene E_4; PGA_1 = prostaglandin A_1; PGB_1 = prostaglandin B_1; PGD_2 = prostaglandin D_2; PGE_1 = prostaglandin E_1; $PGE_{1\alpha}$ = prostaglandin $E_{1\alpha}$; PGE_2 = prostaglandin E_2; PGE-m = 13,14-dihydro-15-keto-PGE_2 (major urine metabolite of PGE_2); PGF = prostaglandin F; $PGF_{1\alpha}$ = prostaglandin $F_{1\alpha}$; $PGF_{2\alpha}$ = prostaglandin $F_{2\alpha}$; PGI = prostaglandin I; PGI_2 = prostaglandin I_2; PTH = parathyroid hormone; TSH = thyroid-stimulating hormone; TXA_2 = thromboxane A_2.

Eicosanoids have diverse effects systemically on endocrine and immune function, neurotransmission, and vasomotor regulation (Table 1-4). Collectively, their deleterious effects are implicated in acute lung injury, pancreatitis, and renal failure. Leukotrienes are 1000 times more potent than histamines in promoting capillary leakage. They also are effective promoters of leukocyte adherence, neutrophil activation, bronchoconstriction, and vasoconstriction.

The metabolic effects of eicosanoids are well recognized. In the regulation of glucose, products of the cyclooxygenase pathway inhibit pancreatic β-cell release of insulin, while products of the lipoxygenase pathway promote β-cell activity. Hepatocytes also express specific receptors for PGE_2 that, when activated, inhibit gluconeogenesis. PGE_2 also can inhibit hormone-stimulated lipolysis.

Fatty Acid Metabolites

The role of fatty acid metabolism potentially has a role in the inflammatory response. Most commercially prepared enteral nutrition formulas contain omega-6 fatty acids as the primary source of lipids. Omega-6 fatty acids also serve as precursors of inflammatory mediators associated with injury and the stress response. Such mediators include leukotrienes, prostaglandins, and platelet-activating factor. By contrast, 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. Although the mechanisms are still unclear, animal studies substituting omega-3 for omega-6 fatty acids have demonstrated attenuated inflammatory response in hepatic Kupffer cells as measured by TNF and IL-1 release and PGE_2 production. In animal injury studies, omega-3 reduces metabolic rate, normalizes glucose metabolism, attenuates weight loss, and improves nitrogen balance. Omega-3 fatty acid–supplemented feeding in animals minimizes ischemia/reperfusion injury in the myocardium, small intestine, and skeletal muscles. In rats, dietary omega-3 fatty acids, when compared to omega-6 fatty acids, ameliorates endotoxin-induced acute lung injury by suppressing the levels of proinflammatory eicosanoids in bronchoalveolar lavage fluid and reducing pulmonary neutrophil accumulation.

Kallikrein-Kinin System

Bradykinins are potent vasodilators that are produced through kininogen degradation by the serine protease kallikrein. Kallikrein exists in blood and tissues as inactive prekallikrein that is activated by various factors such as Hageman factor, trypsin, plasmin, factor XI, glass surfaces, kaolin, and collagen.

Kinins increase capillary permeability and tissue edema, evoke pain, inhibit gluconeogenesis, and increase bronchoconstriction. They also increase renal vasodilation and consequently reduce renal perfusion pressure. The resulting increase in renin formation activates sodium and water retention via the renin-angiotensin system.

Bradykinin release is stimulated by hypoxic and ischemic injury. Increased kallikrein activity and bradykinin levels are observed following hemorrhage, sepsis, endotoxemia, and tissue injury. Furthermore, these elevations are proportional to the magnitude of injury

and mortality. Clinical trials utilizing bradykinin antagonists in attempts to reduce the deleterious sequelae of septic shock have only demonstrated modest reversal in gram-negative sepsis, but no overall improvement in survival.

Serotonin

The neurotransmitter serotonin (5-hydroxytryptamine, 5-HT) is a tryptophan derivative that is found in chromaffin cells of the intestine and in platelets. Patients with midgut carcinoid tumors often secrete 5-HT in excess. This neurotransmitter stimulates vasoconstriction, bronchoconstriction, and platelet aggregation. Serotonin is also a myocardial chronotrope and inotrope. Although serotonin is clearly released at sites of injury, its role in the inflammatory response is unclear.

Histamine

Histamine is derived from histidine and stored in neurons, skin, gastric mucosa, mast cells, basophils, and platelets. Histamine release is activated by increased calcium levels. There are two receptor types for histamine binding. H_1 binding stimulates bronchoconstriction, intestinal motility, and myocardial contractility. H_2 binding inhibits histamine release. Both H_1 and H_2 receptor activation induce hypotension, peripheral pooling of blood, increased capillary permeability, decreased venous return, and myocardial failure. The rise in histamine levels has been documented in hemorrhagic shock, trauma, thermal injury, endotoxemia, and sepsis.

CYTOKINE RESPONSE TO INJURY

Tumor Necrosis Factor

Following acute injury or during infections, TNF-α is among the earliest and most potent mediators of subsequent host responses. The primary sources of TNF-α synthesis include monocytes/macrophages and T cells, which are abundant in the peritoneum and splanchnic tissues. Furthermore, Kupffer cells represent the single largest concentrated population of macrophages in the human body. Therefore, surgical or traumatic injuries to the abdominal viscera undoubtedly have profound influence on the generation of inflammatory mediators and homeostatic responses such as acute phase protein production. Although the half-life of TNF-α is less than 20 minutes, this brief appearance is sufficient to evoke marked metabolic and hemodynamic changes and activate mediators distally in the cytokine cascade. TNF-α is also a major inducer of muscle catabolism and cachexia during stress by shunting available amino acids to the hepatic circulation as fuel substrates. Other functions of TNF-α include coagulation activation, promoting the expression or release of adhesion molecules, prostaglandin E_2, platelet-activating factor (PAF), glucocorticoids, and eicosanoids.

Soluble (i.e., circulating) TNF receptors (sTNFRs) are proteolytically cleaved extracellular domains of membrane-associated TNFRs that are elevated and readily detectable in acute inflammation. sTNFRs retain their affinity for the binding of TNF-α and therefore compete with the cellular receptors for the binding of free TNF-α. This potentially represents an endogenous counterregulatory response to excessive systemic TNF-α activity. However, it should be noted that the functional biology of sTNFRs may not be limited to TNF-α antagonism, but may also serve as a carrier (e.g., transporter) or as a storage pool of bioactive TNF-α in the circulation.

Interleukin-1

IL-1 is primarily released by activated macrophages and endothelial cells. There are two known species of IL-1: IL-1α and IL-1β. IL-1α is predominantly cell membrane associated and exerts its influence via cellular contacts. IL-1β is more readily detectable in the circulation and capable of eliciting similar physiologic and metabolic alterations as TNF-α. With high doses of either IL-1 or TNF-α, these cytokines independently initiate a state of hemodynamic decompensation. At low doses, they can produce the same response only if administered simultaneously. These observations emphasize the synergistic roles of TNF-α and IL-1 in the inflammatory response. IL-1 is predominantly a local mediator with a half-life of approximately 6 minutes, making its ability to be detected in acute injury or illness even less likely than that of TNF-α. IL-1 induces the classic inflammatory febrile response to injury by stimulating local prostaglandin activity in the anterior hypothalamus. Attenuated pain perception after surgery can be mediated by IL-1 by promoting the release of β-endorphins from the pituitary gland and increasing the number of central opioid-like receptors.

Endogenous IL-1 receptor antagonists (IL-1ra) also are released during injury and serve as an endogenous autoregulator of IL-1 activity. This molecule effectively competes for binding to IL-1 receptors, yet exacts no overt signal transduction.

Interleukin-2

IL-2 is a primary promoter of T-lymphocyte proliferation, immunoglobulin production, and gut barrier integrity. Partly due to its circulation half-life of less than 10 minutes, IL-2 has not been readily detectable following acute injury. Attenuated IL-2 expression associated with major injuries or perioperative blood transfusions potentially contribute to the transient immunocompromised state of the surgical patient. There is evidence to suggest that accelerated lymphocyte apoptosis (i.e., lymphocyte depletion) exacerbates the injury-induced immunocompromise as a result of diminished IL-2 stimulation.

Interleukin-4

IL-4 is produced by activated type 2 T-helper (T_H2) lymphocytes and possesses diverse influence on hematopoietic cell proliferation. It is particularly important in antibody-mediated immunity and in antigen presentation. IL-4 also induces class switching in differentiating B lymphocytes to produce predominantly IgG4 and IgE, which are important immunoglobulins in allergic and anthelmintic responses. IL-4 has potent anti-inflammatory properties against activated macrophages by downregulating the effects of IL-1, TNF-α, IL-6, and IL-8, as well as oxygen radical production. IL-4 also appears to increase macrophage susceptibility to the anti-inflammatory effects of glucocorticoids.

Interleukin-6

TNF-α and IL-1 are potent inducers of IL-6 production from virtually all cells and tissues, including the gut. 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. Circulating IL-6 levels appear to be proportional to the extent of tissue injury during an operation, more so than the duration of the surgical procedure itself. Recent evidence has demonstrated both a proinflammatory role and an anti-inflammatory role for IL-6. IL-6 is an important mediator of the hepatic acute phase response during injury and convalescence.

IL-6 not only induces neutrophil activation during injury and inflammation but also may delay the disposal of such neutrophils, thereby prolonging the injurious effects mediated by these cells. IL-6 also possesses anti-inflammatory properties during injury by attenuating TNF-α and IL-1 activity while promoting the release of soluble tumor necrosis factor receptors (sTNFRs) and IL-1 receptor antagonists.

Interleukin-8

IL-8 expression and activity is similar to that of IL-6 after injury and has been proposed as an additional biomarker for the risk of multiple organ failure. IL-8 does not produce the hemodynamic instability characteristic of TNF-α and IL-1, but is a chemoattractant and a potent activator of neutrophils.

Interleukin-10

IL-10 has emerged as a modulator of TNF-α activity. Experimental evidence has demonstrated that neutralization of IL-10 during endotoxemia increases monocyte TNF-α production and mortality, but restitution of IL-10 reduces TNF-α levels and the associated deleterious effects. IL-10 is also capable of attenuating IL-18 messenger ribonucleic acid (mRNA) expression in monocytes. In animal experiments, induction of IL-10 transcription has been shown to attenuate the systemic inflammatory response and reduce mortality during septic peritonitis. However, excessive rIL-10 administration in similar animal models has been associated with increased bacterial load and mortality.

Interleukin-12

IL-12 has a primary role in cell-mediated immunity and promotes the differentiation of T_H1 cells. In mice with fecal peritonitis as well as those with burn injury, survival increases with IL-12 administration, while IL-12 neutralization results in high mortality. IL-12 administration in nonhuman primates is capable of inducing an inflammatory response for up to 48 hours, independently of TNF-α and IL-1. IL-12 promotes neutrophil and coagulation activation, as well as the expression of both proinflammatory and anti-inflammatory mediators. Furthermore, IL-12 toxicity appears to be synergistic with IL-2. Although IL-12 detection following injury or severe infections is variable, most evidence would suggest that this cytokine contributes to the overall proinflammatory response.

Interleukin-13

IL-13 shares many structural and functional properties of IL-4. IL-4 and IL-13 modulate macrophage function, but unlike IL-4, IL-13 has no identifiable effect on T lymphocytes and only has influence on selected B-lymphocyte populations. IL-13 can inhibit nitric oxide production and the expression of proinflammatory cytokines and can enhance the production of IL-1ra. Furthermore, IL-13 attenuates leukocyte interaction with activated endothelial surfaces. The net effect of IL-13, along with IL-4 and IL-10, is anti-inflammatory.

Interleukin-15

IL-15 is a macrophage-derived cytokine with potent autocrine regulatory properties. As a result of shared receptor signaling components, both IL-15 and IL-2 possess similar bioactivity in promoting lymphocyte activation and proliferation. In neutrophils, IL-15 induces IL-8 production and nuclear factor-κB (NF-κB) activation and enhances phagocytic function against fungal infections.

Interleukin-18

IL-18, formerly interferon (IFN)-γ-inducing factor, is a proinflammatory cytokine product of activated macrophages. Structurally similar to IL-1β and functionally similar to IL-12, IL-18 promotes early resolution of bacterial infections in mice. Bacterial products IL-4 and IFN-γ can stimulate IL-18 production from monocytes. IL-18 signaling is associated with NF-κB and c-Jun N-terminal kinase (JNK) pathway activation, as well as the expression of functionally active intercellular adhesion molecule-1 (ICAM-1). Furthermore, murine endotoxemia models indicate that IL-18 is a downstream mediator of both TNF-α and Fas ligand–induced hepatotoxicity. Preliminary data have demonstrated significant elevations of circulating IL-18 during sepsis for as long as 21 days. This elevation in IL-18 is particularly pronounced in gram-positive sepsis.

Interferon-γ

Much of interleukin (IL)-12 and IL-18 biology is mediated via interferon (IFN)-γ. Human T helper lymphocytes activated by bacterial antigens, IL-2, IL-12, or IL-18 readily produce IFN-γ. Conversely, IFN-γ can induce the production of IL-2, IL-12, and IL-18. When released into the circulation, IFN-γ is detectable *in vivo* by 6 hours and may be persistently elevated for as long as 8 days. Injured tissues, such as operative wounds, also demonstrate the presence of IFN-γ production 5 to 7 days after injury. IFN-γ has important roles in activating circulating and tissue macrophages. Alveolar macrophage activation mediated by IFN-γ may induce acute lung inflammation after major surgery or trauma.

Granulocyte-Macrophage Colony-Stimulating Factor

In vitro studies have demonstrated a prominent role for granulocyte-macrophage colony-stimulating factor (GM-CSF) in delaying apoptosis (programmed cell death) of macrophages and neutrophils. This process may contribute to organ injury such as that found in acute respiratory distress syndrome (ARDS). This growth factor is effective in promoting the maturation and recruitment of functional leukocytes necessary for normal inflammatory cytokine response, and potentially in wound healing. Results of perioperative GM-CSF administration in patients undergoing major oncologic procedures and in patients with major burns have demonstrated enhanced neutrophil numbers and function.

High Mobility Group Box-1

High mobility group box-1 (HMGB-1) is a DNA transcription factor that is expressed 24 to 48 hours after the initial injurious event. Its peak has been associated with deleterious outcomes such as advanced ARDS and death. The appearance of this mediator is in contrast to the early appearances of TNF-α, IL-1, IL-6, and IL-8, which peak within minutes of injury and therefore are difficult to block. HMGB-1 is associated with weight loss, food aversion, shock, and the general "sickness behavior" seen in sepsis and the systemic inflammatory response syndrome. As a late mediator of the inflammatory response, anti-HMGB-1 strategies might be used in efforts to control the progression of the deleterious effects of inflammation and sepsis.

CELLULAR RESPONSE TO INJURY

Gene Expression and Regulation

A broad reiteration of terminology is used to characterize gene regulation. Identical DNA chains are found in every cell of the body; however, each of these cells expresses distinct structural and functional characteristics. By the activation and deactivation of certain genes in a stem cell, the highly organized process of *differentiation* leads to the ultimate function of the cell.

In humans, most genes are regulated at the stage of DNA transcription (i.e., intranuclear) (Fig. 1-6). Therefore, whether a gene is expressed or not in a disease is often determined by the production of corresponding messenger ribonucleic acid (mRNA). RNA from the original transcript can be further modified, termed *splicing,* to produce related but dissimilar mRNA and resultant proteins. In cytokine production in which RNA is required for rapid translation (i.e., protein synthesis) upon demand, protein caps at the 5′ and 3′ ends ensure RNA stability and prevent splicing. Once out of the nucleus, the mRNA can be inactivated or translated to form proteins. These proteins can further be modified for specific functions. In essence, these cytosolic modifications supplement the primary regulatory mechanisms within the nucleus.

How a particular gene is activated depends on the orderly assemblage of transcription factors (i.e., regulatory proteins) to specific DNA sequences immediately upstream to the target gene, known as the *promoter region*. The DNA binding sites are the *enhancer sequences,* and proteins that inhibit the initiation of transcription are *repressors*. Transcription factors become important during the inflammatory response because the ability to control the pathways leading to their activation means the ability to regulate the manner and magnitude by which a cell can respond to an injury stimulus.

Cell Signaling Pathways

Heat Shock Proteins

Heat shock proteins (HSPs), also known as stress proteins, are produced by cells in response to injury or tissue ischemia. HSPs are essential for the ability of cells to overcome stress. Cytosolic heat shock factors (HSFs) are the transcription factors that are activated by conformational changes upon injury, which translocate into the nucleus and bind to the HSP promoter regions. The overarching role of HSPs is to attenuate the inflammatory response. Major mechanisms include reduction of oxygen metabolites, promoting T_H2 cell proliferation, and inhibiting NF-κB activation.

G-Protein Receptors

GTP-binding proteins (G-proteins) are the largest family of signaling receptors for cells and include many of the pathways associated with the inflammatory response. G-protein receptor activation turns on an adjacent effector protein, leading to downstream signaling. The two major second messengers of the G-protein pathway are (1) formation of cyclic adenosine monophosphate (cAMP), and (2) calcium, released from the endoplasmic reticulum (Fig. 1-7). An increase in cellular cAMP can activate gene transcription. For example, binding of epinephrine and norepinephrine activates the adrenergic receptor, leading to signaling through the G-protein/cAMP signaling pathways.

G-protein/calcium activation requires activation of the effector phospholipase C and phosphoinositols. When calcium is not needed, it is pumped into the mitochondria and the endoplasmic reticulum for storage. Further downstream in G-protein signaling is the activation of protein kinase C (PKC), which can activate NF-κB as well as other transcription factors.

Ligand-Gated Ion Channels

These receptor channels, when activated by a ligand, permit rapid flux of ions across the cell membrane. Neurotransmitters function by this pathway, and an example of such a receptor is the nicotinic acetylcholine receptor (Fig. 1-8).

Receptor Tyrosine Kinases

Receptor tyrosine kinases also are known as tyrosine kinase receptors because of their significant intracellular tyrosine kinase domains (Fig. 1-9). Examples of these receptors include insulin and various hormone growth factors (e.g., platelet-derived growth factor [PDGF], insulin-like growth factor [IGF]-1, epidermal growth factor [EGF], and vascular endothelial growth factor [VEGF]). Some cytokine-receptor activation also utilizes the tyrosine kinase pathway. When activated, the receptors dimerize, undergo

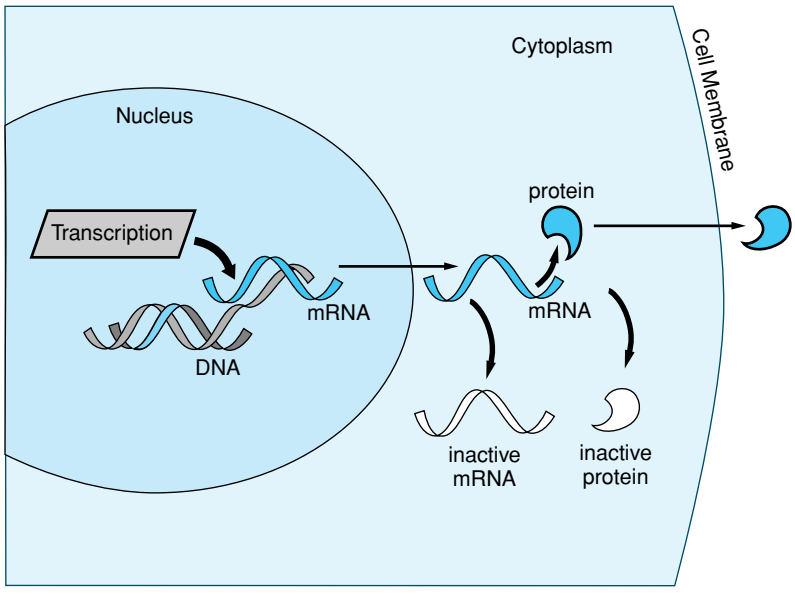

FIG. 1-6. Gene expression and protein synthesis can occur within a 24-hour period. The process can be regulated at various stages: transcription, mRNA processing, or protein packaging. At each stage, it is possible to inactivate the mRNA or protein, rendering these molecules nonfunctional.

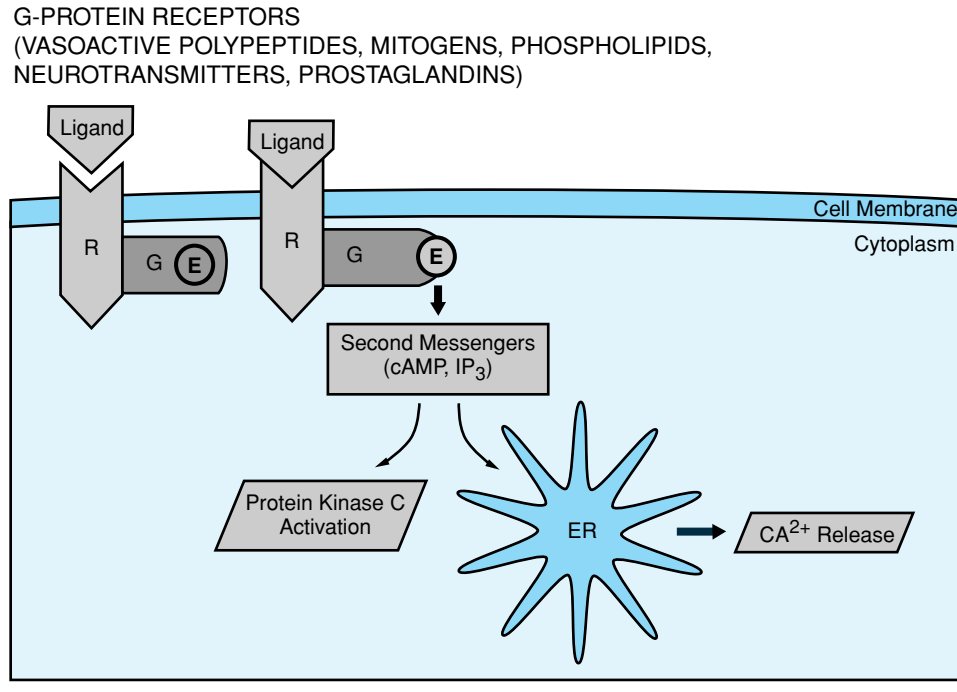

FIG. 1-7. *G-protein–coupled receptors are transmembrane proteins. The G-protein receptors respond to ligands such as adrenaline and serotonin. Upon ligand binding to the receptor (R), the G-protein undergoes a conformational change through GTP-GDP conversion, and in turn activates the effector (E) component. The E component subsequently activates second messengers. The role of IP_3 is to induce release of calcium from the endoplasmic reticulum (ER).*

phosphorylation, and recruit secondary signaling molecules. Activation of protein kinase receptors is important for gene transcription and cell proliferation.

Janus Kinase/Signal Transduction and Activator of Transcription (STAT) Signaling

Janus kinase (JAK) is the receptor for over 20 cytokines, including IFN-γ, IL-6, IL-10, IL-12, and IL-13. When ligands bind to the receptors, receptor dimerization occurs and enzymatic activation propagates through the JAK domains of the receptors (Fig. 1-10).

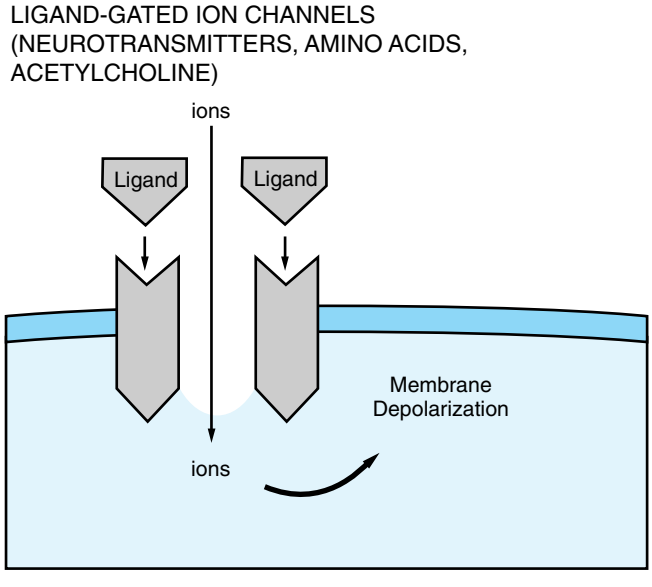

FIG. 1-8. *Ligand-gated ion channels convert chemical signals into electrical signals, inducing a change in cell membrane potential. Upon activation of the channel, millions of ions per second influx into the cell. These channels are composed of many subunits, and the nicotinic acetylcholine receptor is one such example.*

Activation occurs by phosphorylation, the common currency of most intracellular signal transduction, which then recruits STAT (*s*ignal *t*ransduction and *a*ctivator of *t*ranscription) proteins to the cytosolic portion of the receptors. Activated STAT proteins further dimerize and translocate into the nucleus as transcription factors. STAT-mediated transcription can activate different T-cell responses during injury and inflammation. For example, STAT4 activation promotes a T_H1 response, while STAT6 shifts towards a T_H2 response.

Suppressors of Cytokine Signaling

Suppressors of cytokine signaling (SOCS) specifically block JAK and STAT activation and ultimately regulate the signaling of

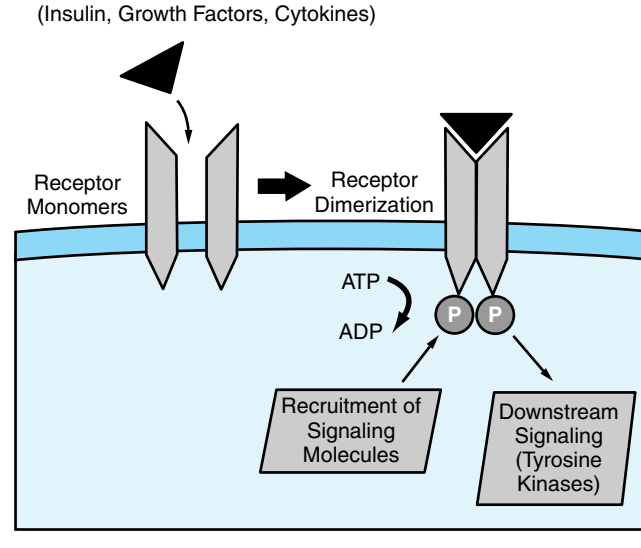

FIG. 1-9. *The receptor tyrosine kinase requires dimerization of monomeric units. These receptors possess intrinsic enzymatic activity that requires multiple autophosphorylation steps to recruit and activate intracellular signaling molecules.*

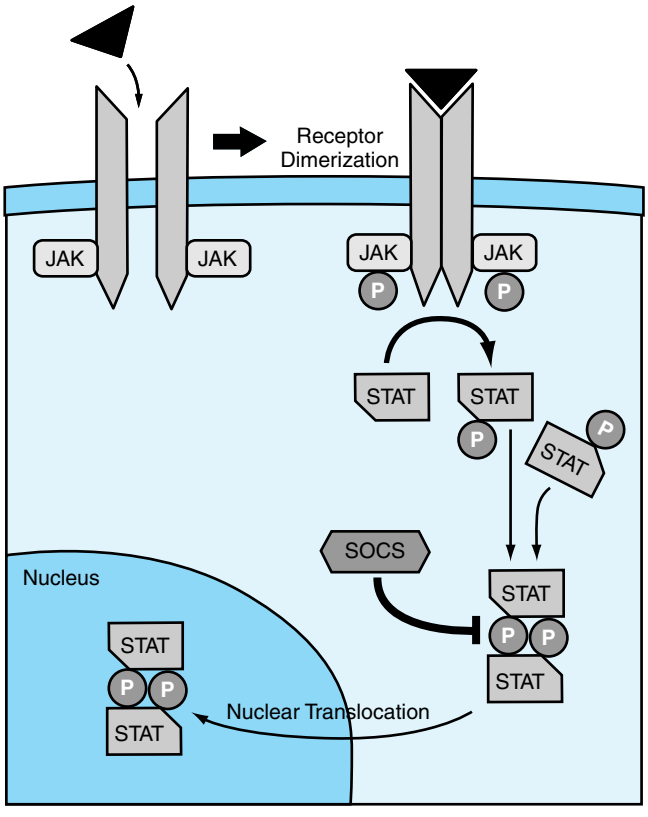

FIG. 1-10. *The JAK/STAT signaling pathway also requires dimerization of monomeric units. STAT (signal transducers and activators of transcription) molecules possess "docking" sites that allow for STAT dimerization. The STAT complexes translocate into the nucleus and serve as gene transcription factors. JAK/STAT activation occurs in response to cytokines (e.g., IL-6) and cell stressors, and has been found to induce cell proliferation and inflammatory function. Intracellular molecules that inhibit STAT function, known as SOCS (suppressors of cytokine signaling), have been identified.*

certain cytokines. A deficiency of SOCS activity may render a cell hypersensitive to certain stimuli such as inflammatory cytokines and growth hormones. One very clear association has been the specific attenuation of IL-6 signaling in macrophages by SOCS3 through the inhibition of STAT3.

Mitogen-Activated Protein Kinases

The mitogen-activated protein kinase (MAPK) pathway is a major cellular inflammatory signaling pathway with regulatory roles over cell proliferation and cell death (Fig. 1-11). There are over 20 MAPK isoforms, and the three major groups that alter gene expression are the JNK (c-Jun NH_2-terminal kinase), ERK (extracellular regulatory protein kinase), and p38 kinase. Broadly, these isoforms undergo several phosphorylations in order to reach final active forms. Conversely, removal of any phosphate groups significantly diminishes MAPK activity. The JNK pathway has clear links to the inflammatory response, with a regulatory role in apoptosis. TNF-α and IL-1 can activate the JNK pathway. Heat shock protein 72 is one example of a JNK inhibitor. The p38 kinase is activated in response to endotoxin, viruses, IL-1, IL-2, IL-7, IL-17, IL-18, TNF-α, and transforming growth factor (TGF)-β. The major role of p38-kinase activation is the recruitment and activation of leukocytes. These MAPK isoforms do not function independently, but exhibit appreciable "cross-talk," which can modulate the inflammatory response.

Nuclear Factor-κB

Nuclear factor (NF)-κB activates a wide spectrum of genes important for the activation of proinflammatory cytokines and acute phase proteins (Fig. 1-12). NF-κB is really a complex of smaller proteins, and the p50-p65 heterodimer complex is the most widely studied. In the cytosol, NF-κB is maintained by binding to the inhibitor protein I-κB. When a cell is exposed to an inflammatory stimulus (TNF-α or interleukin [IL]-β), a series of phosphorylation events leads to I-κB degradation. Interestingly, the rapid resynthesis of I-κB is one mechanism by which NF-κB activity is inhibited. Low intracellular I-κB concentration is a mechanism of prolonging the inflammatory response, because the enhanced activity of NF-κB appears to delay the apoptosis of activated immune cells.

Toll-Like Receptors and CD14

More than one half of the occurrences of sepsis syndrome is the result of gram-negative infections mediated by lipopolysaccharide (LPS), an endotoxin. Recognition of LPS and mounting the

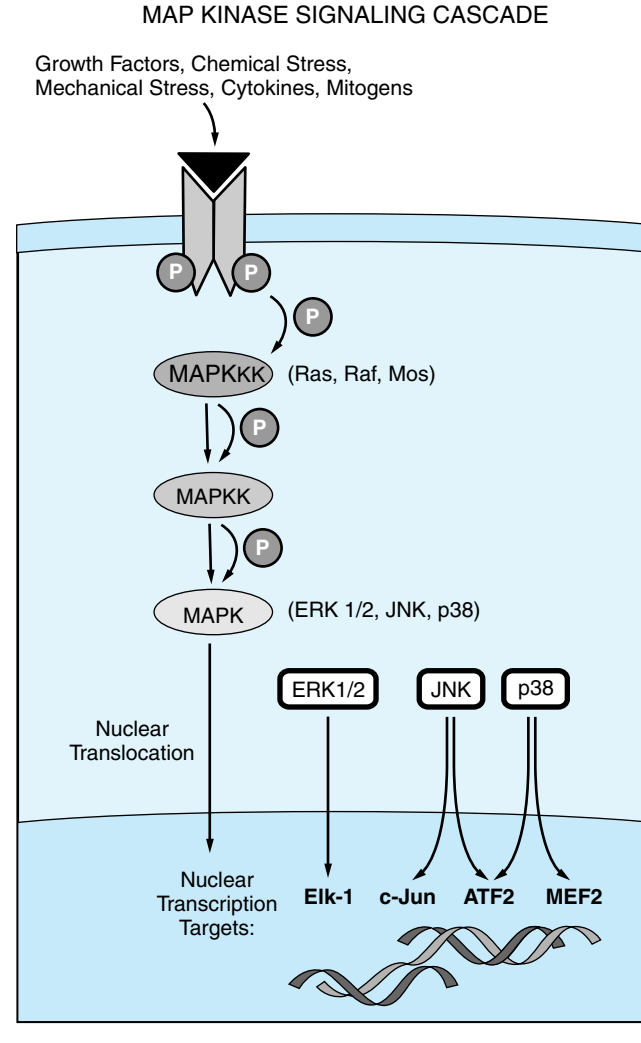

FIG. 1-11. *The MAPK (mitogen-activated protein kinase) signaling pathway requires multiple phosphorylation steps. Ras, Raf, and Mos are examples of the MAP kinase kinase kinase (MAPKKK), which are upstream molecules. Well-characterized downstream kinases are ERK 1/2, JNK or SAPK (c-Jun NH_2-terminal kinases or stress-activated protein kinases), and p38 MAP kinases that target specific gene transcription sites in the nucleus. ATF = activating transcription factor; ERK = extracellular signal regulated kinase; MEF = myocyte-enhancing factor.*

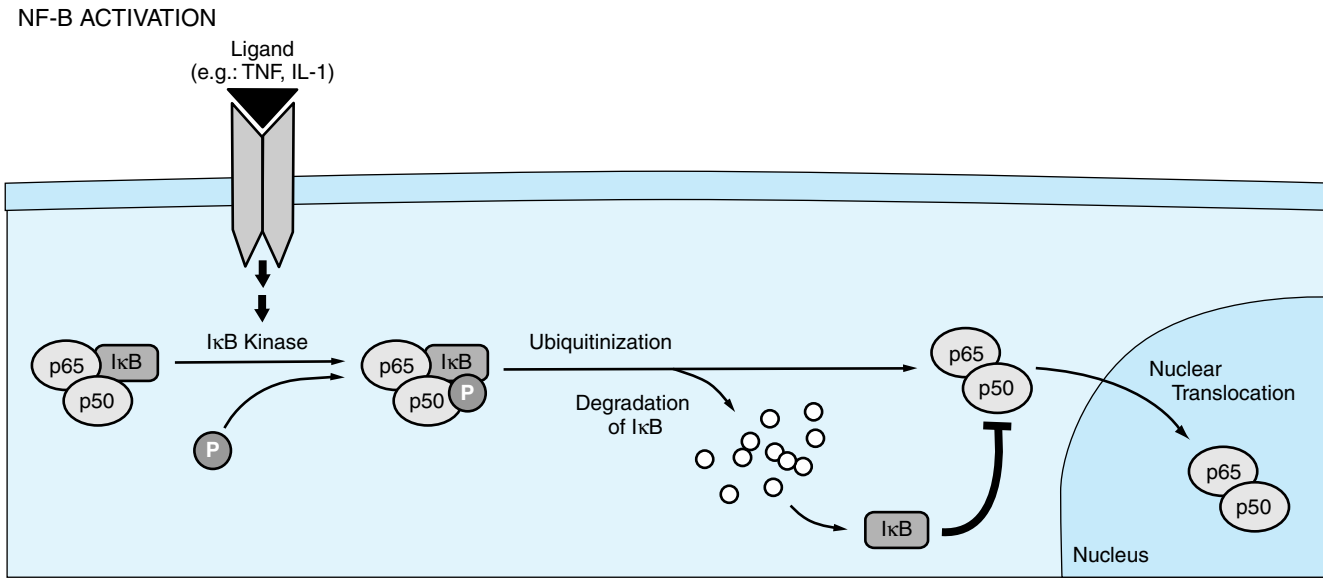

FIG. 1-12. I-κB binding to the p50-p65 subunits of NF-κB inactivates the molecule. Ligand binding to the receptor activates a series of downstream signaling molecules, of which I-κB kinase is one. The phosphorylated NF-κB complex further undergoes ubiquitinization and proteosome degradation of I-κB, activating NF-κB, which translocates into the nucleus. Rapid resynthesis of I-κB is one method of inactivating the p50-p65 complex.

appropriate inflammatory response by immune cells occurs primarily by the toll-like receptor-4 (TLR4) mechanism (Fig. 1-13). LPS-binding proteins (LBPs) carry LPS to the CD14/TLR4 complex, which sets into motion cellular mechanisms that activate MAPK, NF-κB, and cytokine gene promoters. TLR4 is primarily the receptor for gram-negative endotoxins and TLR2 is the counterpart for gram-positive sepsis. Receptors for IL-1 and IL-18 appear to share similar intracellular domains with toll-like receptors, and so there are significant similarities in signaling mechanisms. The fact that some patient populations are more susceptible to infectious complications than others recently has been associated with specific point mutations in the TLR gene.

Tumor Necrosis Factor and CD95-Induced Apoptosis

In the normal host, apoptosis is the principal mechanism by which senescent or dysfunctional cells, including macrophages and neutrophils, are systematically disposed of without activating other immunocytes or the release of proinflammatory contents. The cellular environment created by systemic inflammation disrupts the normal apoptotic machinery in activated immunocytes, consequently prolonging the inflammatory response.

Several proinflammatory cytokines (e.g., TNF-α, IL-1, IL-3, IL-6, GM-CSF, granulocyte colony-stimulating factor [G-CSF], and IFN-γ) and bacterial products (e.g., endotoxin) have been shown to delay macrophage and neutrophil apoptosis in vitro, while IL-4 and IL-10 accelerate apoptosis in activated monocytes.

In acute inflammation, the response of the immunocyte to TNF-α is perhaps the most widely investigated. This cytokine exerts its biologic effects by binding to specific cellular receptors, tumor necrosis factor receptor (TNFR)-1 (55 kDa) and TNFR-2 (75 kDa) (Fig. 1-14). Under physiologic conditions, TNFR-1 mediates most known biologic effects of soluble TNF-α, including inflammatory responses, NF-κB activation, and apoptosis. When TNFR-1 is exclusively activated, it precipitates circulatory shock reminiscent of

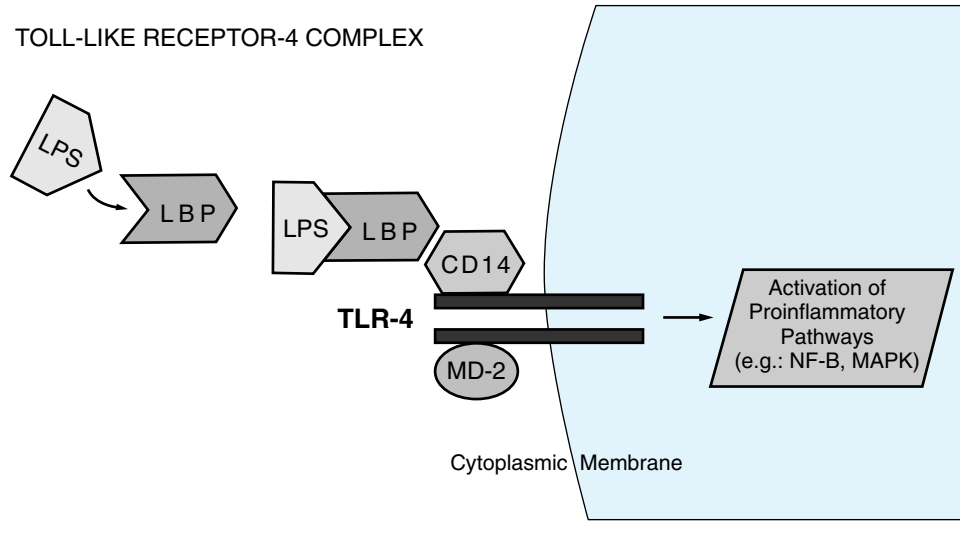

FIG. 1-13. LPS recognition by immune cells is primarily by the toll-like receptor-4/CD14/MD-2 complex. LPS is transported by LPS-binding protein (LBP) to the cell surface complex. Other cell surface LPS sensors include ion-gated channels, CD11b/CD18, and macrophage scavenger receptors.

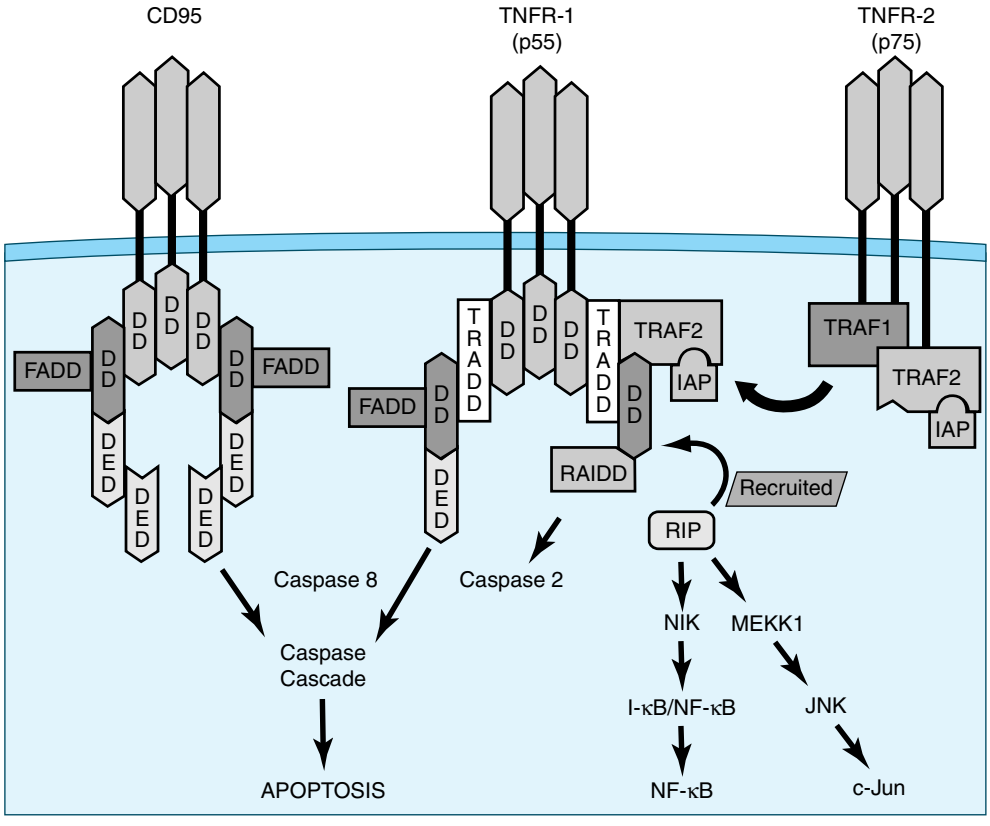

FIG. 1-14. *Signaling pathway for tumor necrosis factor receptor (TNFR)-1 (55 kDa) and TNFR-2 (75 kDa) occurs by the recruitment of several adapter proteins to the intracellular receptor complex. Optimal signaling activity requires receptor trimerization. TNFR-1 initially recruits TNFR-associated death 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 (DD), and both recruit the same adapter proteins known as Fas-associated death domains (FADD) prior to activating caspase-8. TNFR-1 also induces apoptosis by activating caspase-2 through the recruitment of RIP (receptor-interacting protein). RIP also has a functional component that can initiate 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 TRAF1 and TRAF2 (TNFR-associated factor) that interact with RIP to mediate NF-κB and c-Jun activation. TRAF2 also recruits additional proteins that are antiapoptotic, known as IAP (inhibitors of apoptosis protein). DED = death effector domain; RAIDD = RIP-associated ICH-1-like protein with death domain, which activates proapoptotic caspases; MEKK1 = mitogen-activated protein/ERK kinase kinase-1; JNK = c-Jun N-terminal kinase; NIK = NF-κB–inducing kinase; I-κB/NF-κB = inactive complex of NF-κB that becomes activated when the I-κB portion is cleaved. [Adapted with permission from Lin E, Calvano SE, Lowry SF: Tumor necrosis factor receptors in systemic inflammation, in Vincent JL (ed): Update in Intensive Care and Emergency Medicine: Immune Response in Critical Illness. Berlin: Springer-Verlag, 1999, p 365.]*

severe sepsis. However, exclusive activation of TNFR-2 fails to induce any inflammatory responses or shock.

Signal transduction experiments and studies employing receptor gene-knockout technology have consistently demonstrated intracellular signaling "cross-talk" between TNFR-1 and TNFR-2 upon receptor activation by TNF-α. TNFR-1 mediates most of the proinflammatory effects of TNF-α, and it has been demonstrated that the early activation of c-Jun NH_2-terminal kinase (JNK) and p38 kinase prevents TNFR-1–mediated apoptosis. The activation of NF-κB and JNK is believed to be the major antiapoptotic, and therefore proinflammatory, factor; it is signal induced by TNFR-1 and TNFR-2. It is well-known that TNF-α–induced NF-κB activation delays cell death and is associated with the activation of diverse genes that include proinflammatory mediators. Inhibiting NF-κB activation in endothelial cells has been shown to reduce the expression of E-selectins, P-selectins, and IL-8. Exaggerated peripheral blood monocyte NF-κB activation has been associated with higher mortality rates in patients with septic shock.

Members (i.e., homologues) of the intracellular human oncogene product Bcl-2 also are involved in regulating immunocyte survival during systemic inflammation. The intracellular expression of one such member, Bfl-1, is directly dependent upon NF-κB activity and is capable of suppressing TNF-α–induced apoptosis. Bfl-1 mRNA is inducible in neutrophils stimulated with agonists such as G-CSF, GM-CSF, and LPS. Inflammatory cytokines also can enhance neutrophil Mcl-1 expression, another antiapoptotic Bcl-2 homologue, which prolongs neutrophil survival and perpetuates inflammation. Monocytes activated by inflammatory stimuli such as TNF-α also can have prolonged survival as a result of upregulated Bfl-1 gene expression.

The CD95 (Fas) receptor shares much of its intracellular structure with TNFR-1. Unlike TNFR-1, the only known function

of CD95 is to initiate programmed cell death. Neutrophils and macrophages express CD95, and this expression may have important implications in the cellular contribution to the inflammatory response. In fact, both clinical sepsis and experimental endotoxemia have demonstrated prolonged survival of neutrophils and diminished responsiveness to CD95 stimuli. Although the mechanisms are unclear, CD95 and TNFR activity may participate in organ injury during systemic inflammation.

Cell-Mediated Inflammatory Response

Platelets

Clot formation at the site of injury releases inflammatory mediators and serves 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 mediated by serotonin release, platelet-activating factor, and prostaglandin E_2. Platelets can enhance or reduce neutrophil-mediated tissue injury by modulating neutrophil adherence to the endothelium and subsequent respiratory burst. Platelets are an important source of eicosanoids and vasoactive mediators. Nonsteroidal anti-inflammatory drugs irreversibly inhibit thromboxane production.

Lymphocytes and T-Cell Immunity

Injury, surgical or traumatic, is associated with acute impairment of cell-mediated immunity and macrophage function (Fig. 1-15).

T-helper lymphocytes are functionally divided into two subgroups, referred to as T_H1 and T_H2. While both T_H1 and T_H2 cells produce IL-3, TNF-α, and GM-CSF, T_H1 cell response is further characterized by the production of IFN-γ, IL-2, IL-12, and TNF-β (lymphotoxin), and T_H2 cell response is primarily characterized by IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13 production. In severe infections and major injury, there appears to be a reduction in T_H1 (cell-mediated immunity) cytokine production, with a lymphocyte population shift toward the T_H2 response and its associated immunosuppressive effects. In patients with major burns, a shift to a T_H2 cytokine response has been a predictor of infectious complications. However, studies in patients undergoing major surgery have demonstrated a postoperative reduction in T_H1 cytokine production that is not necessarily associated with increased T_H2 response. Nevertheless, depressed T_H1 response and systemic immunosuppression following major insults to the host may be a useful paradigm in predicting the subset of patients who are prone to infectious complications and poor outcome. It should be noted that an excessive T_H1 response can conceivably lead to overwhelming inflammatory response and organ injury, but this phenomenon has not been well documented in surgical or trauma patients.

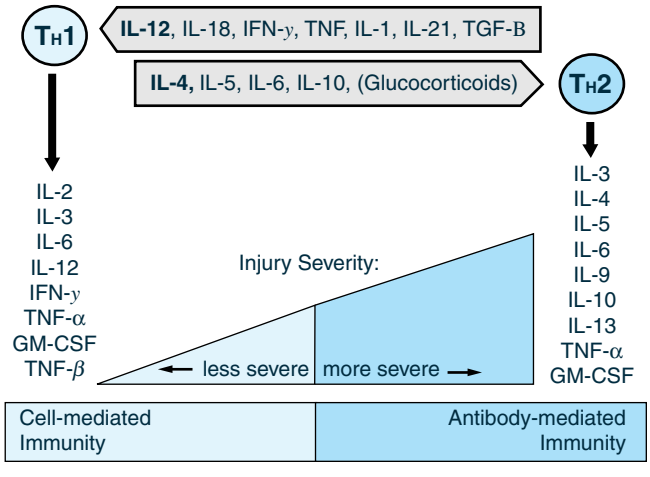

FIG. 1-15. *Specific immunity mediated by type I (T_H1) and type 2 (T_H2) T-helper lymphocytes following injury. A T_H1 response is favored in lesser injuries, with intact cell-mediated and opsonizing antibody immunity against microbial infections. This cell-mediated immunity includes activation of monocytes, B lymphocytes, and cytotoxic T lymphocytes. A shift toward the T_H2 response from naïve T-helper cells is associated with injuries of greater magnitude and is not as effective against microbial infections. A T_H2 response includes the activation of eosinophils, mast cells, and B-lymphocyte IgG4 and IgE production. (Primary stimulants and principal cytokine products of such responses are in* **bold** *characters.) IL-4 and IL-10 are known inhibitors of the T_H1 response. IFN-γ is a known inhibitor of the T_H2 response. Although not cytokines, glucocorticoids are potent stimulants of a T_H2 response, which may partly contribute to the immunosuppressive effects of cortisol. (Adapted with permission from Lin E, Calvano SE, Lowry SF: Inflammatory cytokines and cell response in surgery. Surgery 127:117, 2000.)*

Eosinophils

Eosinophils are characteristically similar to neutrophils in that they migrate to inflamed endothelium and release cytoplasmic granules that are cytotoxic. As a result of different chemokine receptor expressions, eosinophils preferentially migrate to sites of parasitic infection and allergen challenge. Mature eosinophils reside in gastrointestinal, lung, and genitourinary tissues, but also can re-enter the circulation when needed. Major activators of eosinophils include IL-3, GM-CSF, IL-5, platelet-activating factor, and complement anaphylatoxins C3a and C5a.

Mast Cells

Mast cells are important as first-responders at sites of injury because they are pre-existent in tissues. In response to trauma or infection, activated mast cells produce histamine, cytokines, eicosanoids, proteases, and chemokines. The immediate results are vasodilation, recruitment of other immunocytes, and capillary leakage. TNF-α is secreted rapidly by mast cells because of the abundant stores within granules. Mast cells also can synthesize IL-3, IL-4, IL-5, IL-6, IL-10, IL-13, and IL-14, as well as migration-inhibitory factor (MIF).

Monocytes

In humans, downregulation in monocyte and neutrophil TNFR expression has been demonstrated experimentally and clinically (Fig. 1-16). In clinical sepsis, nonsurviving patients with severe sepsis have an immediate reduction in monocyte surface TNFR expression with failure to recover, while surviving patients have normal or near-normal receptor levels from the onset of clinically-defined sepsis (Fig. 1-17). In patients with congestive heart failure, there is also a significant decrease in the amount of monocyte surface TNFR expression when compared with control patients (Fig. 1-18). Thus, TNFR expression potentially can be used as a prognostic indicator of outcome in patients with systemic inflammation. There is also decreased CD95 expression following experimental endotoxemia in humans, which correlates with diminished CD95-mediated apoptosis. Taken together, the reduced receptor expression and delayed apoptosis may be a mechanism for prolonging the inflammatory response during injury or infection.

Neutrophils

Neutrophils mediate important functions in every form of acute inflammation, including acute lung injury, ischemia/reperfusion

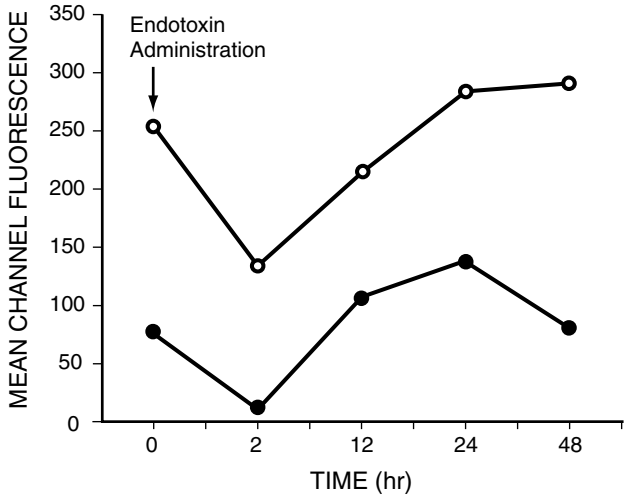

FIG. 1-16. Monocyte CD95 and TNFR expression in healthy adult subjects following intravenous endotoxin administration at time = 0 hours. A reduction in receptor expression is observed at time = 2 hours, corresponding to the time of maximal clinical response to the endotoxin. In the absence of further stimulus, receptor expression recovers to normal levels by 48 hours. (*Adapted with permission from Lin E, Katz JA, Calvano SE, et al: The influence of human endotoxemia on CD95-induced apoptosis. Arch Surg 133:1322, 1998.*)

injury, and inflammatory bowel disease. Within the bone marrow, G-CSF is the primary stimulus for neutrophil maturation. Inflammatory mediators from a site of injury induce neutrophil adherence to the vascular endothelium and promote eventual cell migration into the injured tissue. Neutrophil function is mediated by a vast array of intracellular granules that are chemotactic or cytotoxic to local tissue and invading microorganisms.

ENDOTHELIUM-MEDIATED INJURY

Neutrophil-Endothelium Interaction

Increased vascular permeability during inflammation is intended to facilitate oxygen delivery and immunocyte migration to the sites of injury. However, the accumulation and infiltration of inflammatory leukocytes, specifically neutrophils, at sites of injury contribute to the cytotoxicity of vital tissues and result in organ dysfunction. Ischemia/reperfusion (I/R) injury potentiates this response by unleashing oxygen metabolites, lysosomal enzymes that degrade tissue basal membranes, cause microvascular thrombosis, and activate myeloperoxidases. The recruitment of circulating neutrophils to endothelial surfaces is mediated by concerted actions of adhesion molecules referred to as selectins that are elaborated on cell surfaces (Table 1-5). Neutrophil rolling in the first 10 to 20 minutes following injury is mainly mediated by P-selectin expression (Fig. 1-19). This is consistent with the rapid expression of P-selectins from intracellular stores. Beyond 20 minutes, the influence of P-selectins diminishes secondary to internal degradation, and L-selectin becomes the principal mediator of leukocyte rolling. In conjunction with L-selectin, P-selectin glycoprotein ligand-1 (PSGL-1) is responsible for over 85% of monocyte-to-monocyte and monocyte-to-endothelium adhesion activity. Although there are distinguishable properties among individual selectins in leukocyte rolling, effective rolling most likely involves a significant degree of functional overlap. Similarly, L-selectin also initiates neutrophil-to-neutrophil interaction, in part by binding to leukocyte surface PSGL-1.

Nitric Oxide

Nitric oxide (NO) is derived from endothelial surfaces in response to acetylcholine stimulation, hypoxia, endotoxin, cellular injury, or mechanical shear stress from circulating blood. Normal vascular smooth muscle relaxation is maintained by a constant output of NO. NO also can reduce microthrombosis by reducing platelet adhesion

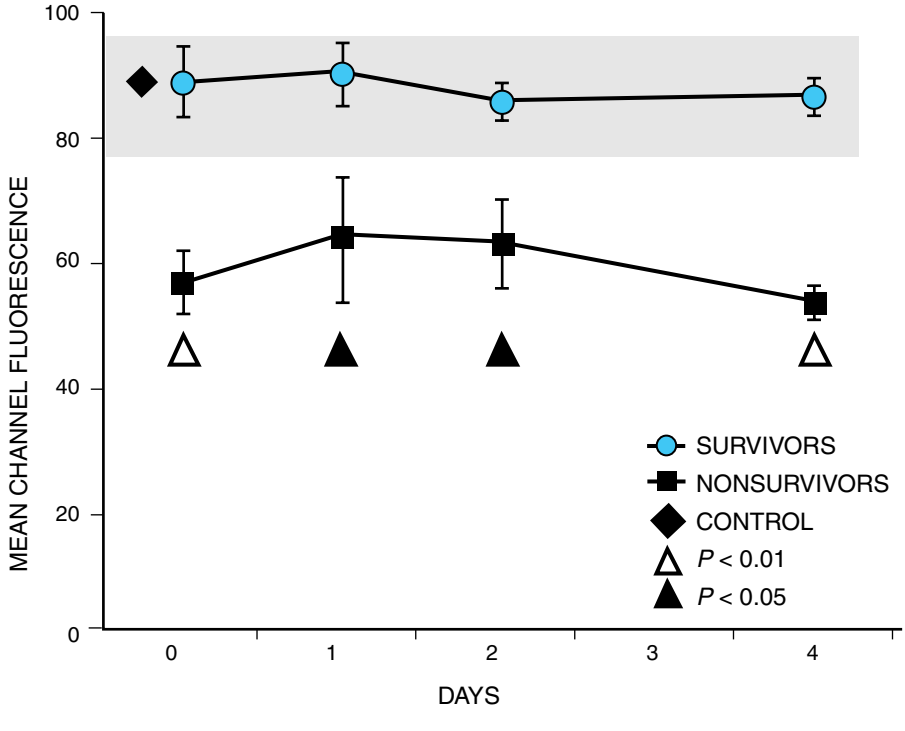

FIG. 1-17. Monocyte TNFR expression in healthy subjects, and in surviving and nonsurviving septic patients, on days 0 to 4. The gray box indicates the range of monocyte TNFR expression in surviving patients and healthy subjects. (*Adapted with permission from Calvano SE, van der Poll T, Coyle SM, et al: Monocyte tumor necrosis factor receptor levels as a predictor of risk in human sepsis. Arch Surg 131:434, 1996.*)

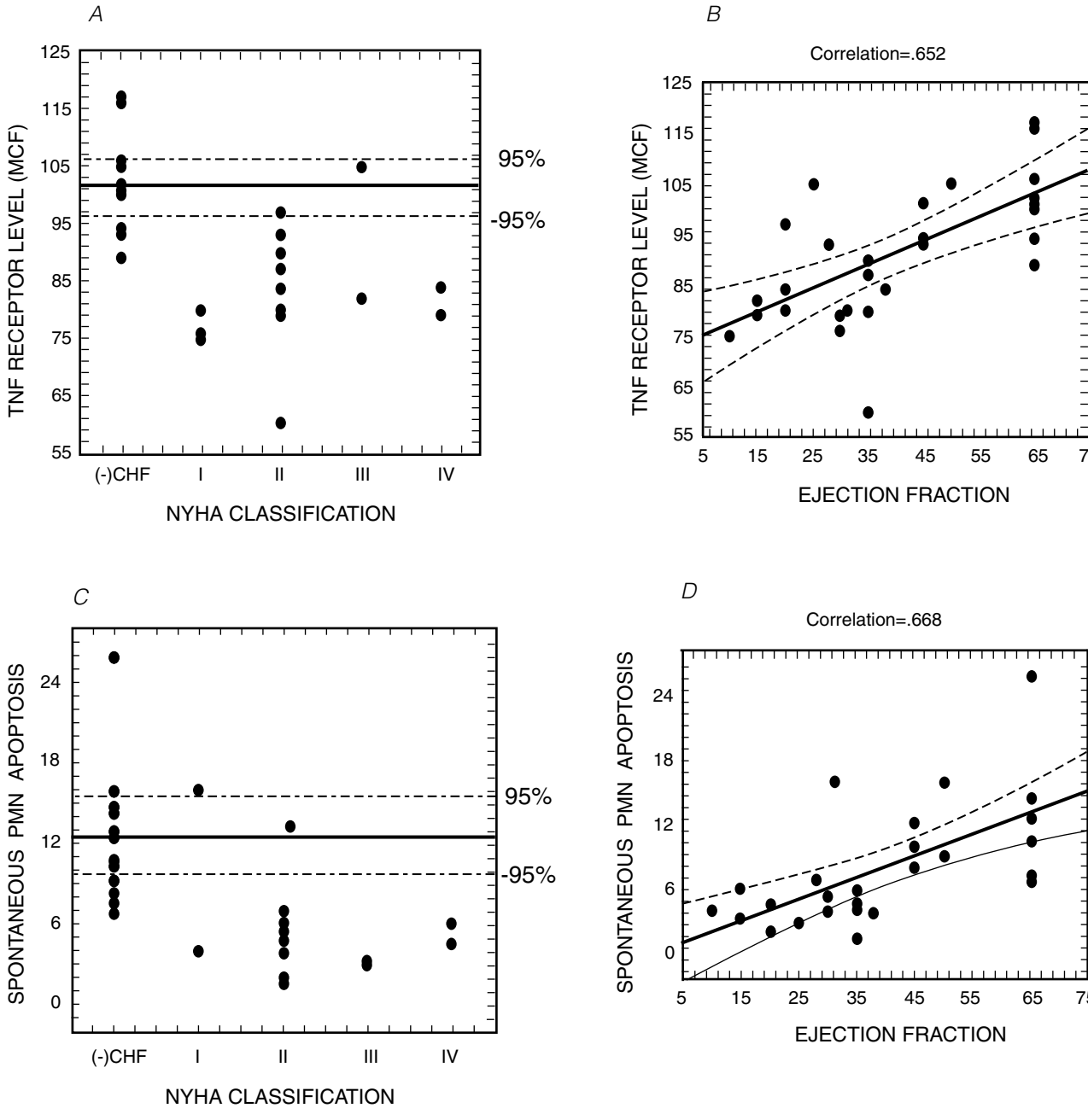

FIG. 1-18. *A*. Patients without congestive heart failure (CHF) expressed higher TNFR levels than patients with CHF stratified by New York Heart Association (NYHA) classification. Monocyte membrane-associated TNFR levels are expressed as mean channel fluorescence (MCF). *B*. Patients with higher monocyte TNFR expression also exhibited higher ejection fractions. *C*. Spontaneous apoptosis of polymorphonuclear cells (PMNs) was lower in patients with CHF, suggesting that the chronic inflammatory milieu of CHF patients contributes to the delay in PMN disposal. *D*. Patients with higher ejection fractions also exhibited higher spontaneous PMN apoptosis.

and aggregation (Fig. 1-20). NO also mediates protein synthesis in hepatocytes and electron transport in hepatocyte mitochondria. It is a readily diffusible substance with a half-life of a few seconds. NO spontaneously decomposes into nitrate and nitrite.

NO is formed from oxidation of L-arginine, a process catalyzed by nitric oxide synthase (NOS). Cofactors of NOS activity include calmodulin, ionized calcium, and reduced nicotinamide adenine dinucleotide phosphate (NADPH). In addition to the endothelium, NO formation also occurs in neutrophils, monocytes, renal cells, Kupffer cells, and cerebellar neurons.

Prostacyclin

Although it is an arachidonate product, prostacyclin (PGI_2) is another important endothelium-derived vasodilator synthesized in response to vascular shear stress and hypoxia. PGI_2 shares similar

Table 1-5
Molecules That Mediate Leukocyte-Endothelial Adhesion, Categorized by Family

Adhesion Molecule	*Action*	*Origin*	*Inducers of Expression*	*Target Cells*
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

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

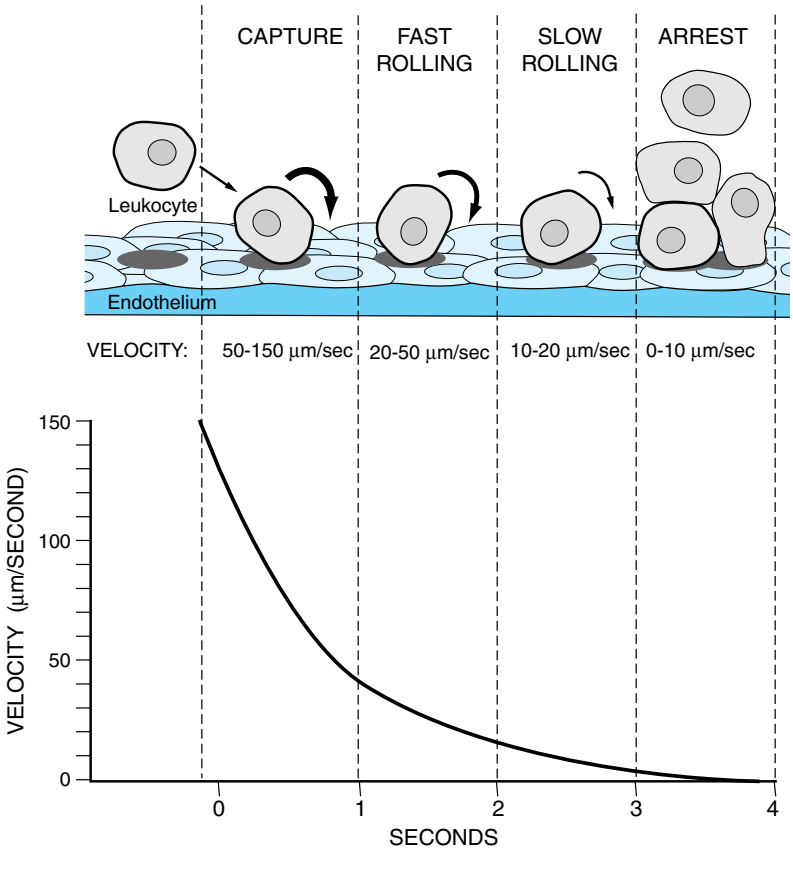

FIG. 1-19. Simplified sequence of selectin-mediated neutrophil-endothelium interaction following an inflammatory stimulus. *CAPTURE* (tethering), predominantly mediated by cell L-selectin with contribution from endothelial P-selectin, describes the initial recognition between leukocyte and endothelium, where circulating leukocytes marginate toward the endothelial surface. *FAST ROLLING* (50 to 150 μm/s) is a consequence of rapid L-selectin shedding from cell surfaces and formation of new downstream L-selectin to endothelium bonds, occurring in tandem. *SLOW ROLLING* (20 to 50 μm/s) is predominantly mediated by P-selectins. The slowest rolling (3 to 10 μm/s) prior to 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 interactions 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.*)

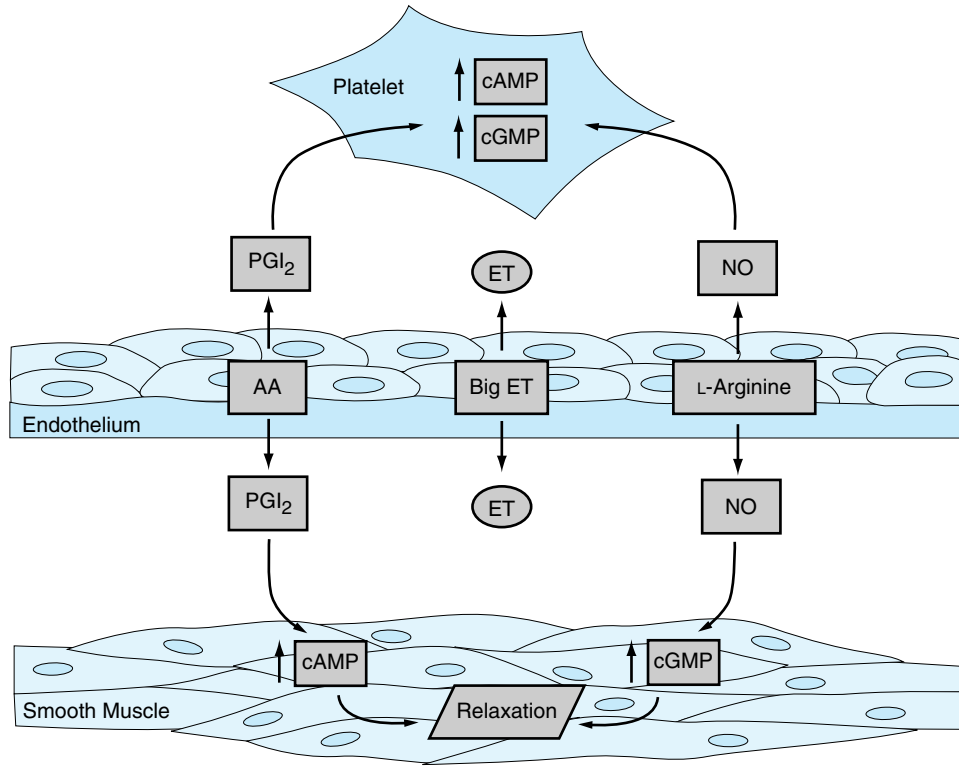

FIG. 1-20. *Endothelial interaction with smooth muscle cells and with intraluminal platelets. Prostacyclin (PGI_2) is derived from arachidonic acid, and nitric oxide (NO) is derived from L-arginine. The increase in cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) results 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 nitric oxide.*

functions with NO, inducing vasorelaxation and platelet deactivation by increasing cAMP. Clinically, it has been used to reduce pulmonary hypertension, particularly in the pediatric population.

Endothelins

Endothelins (ETs) are elaborated by vascular endothelial cells in response to injury, thrombin, transforming growth factor-β (TGF-β), IL-1, angiotensin II, vasopressin, catecholamines, and anoxia. Structurally formed from a 38-amino-acid precursor molecule, ET is a 21-amino-acid peptide with potent vasoconstricting properties. Of the peptides in this family (e.g., ET-1, ET-2, and ET-3), endothelial cells appear to exclusively produce ET-1. Moreover, ET-1 appears to be the most biologically active and the most potent known vasoconstrictor. It is estimated to be 10 times more potent than angiotensin II. Three endothelin receptors, referred to as ET_A, ET_B, and ET_C, have been identified and function by the G-protein-coupled receptor mechanism. ET_B receptors are linked to the formation of NO and prostacyclin (PGI_2), which serve as negative feedback mechanisms. The maintenance of physiologic tone in vascular smooth muscle depends on the balance between NO and ET production. The vasoconstrictor activity of ET can be reversed by the administration of acetylcholine, which stimulates NO production. Increased serum levels of ETs correlate with the severity of injury following major trauma, major surgical procedures, and in cardiogenic or septic shock.

Platelet-Activating Factor

Another endothelial-derived product is platelet-activating factor (PAF), a natural phospholipid constituent of cell membranes, which under normal physiologic conditions is minimally expressed. 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/reperfusion injury. Human sepsis is associated with a reduction in PAF-acetylhydrolase levels, which is the endogenous inactivator of PAF. Indeed, PAF-acetylhydrolase administration in patients with severe sepsis has shown some reduction in multiple organ dysfunction and mortality.

Atrial Natriuretic Peptides

Atrial natriuretic peptides (ANPs) are a family of peptides 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 following surgical or traumatic injury are metabolically associated with a reduced total body energy expenditure and urinary nitrogen wasting. Upon adequate resuscitation and stabilization of the injured patient, a reprioritization of substrate utilization ensues to preserve vital organ function and for the repair of injured tissue. This phase of recovery also is characterized by functions that all 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 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.

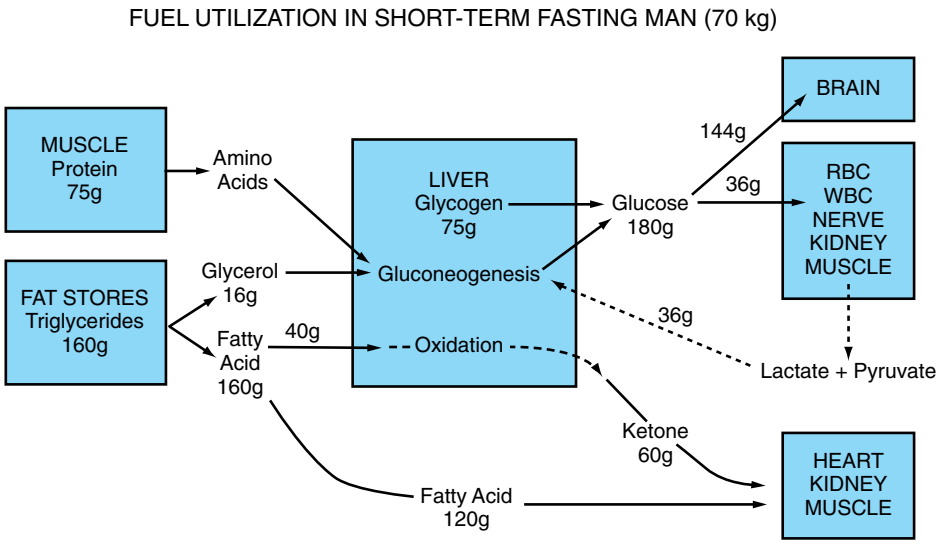

FIG. 1-21. Fuel utilization in a 70-kg man during short-term fasting with an approximate basal energy expenditure of 1800 calories. During starvation, muscle proteins and fat stores provide fuel for the host, with the latter being most abundant. (*Adapted with permission from Cahill GF: Starvation in man. N Engl J Med 282:668, 1970.*)

Metabolism During Fasting

Fuel metabolism during unstressed fasting states has historically served as the standard to which metabolic alterations following acute injury and critical illness are compared (Fig. 1-21). To maintain basal metabolic needs (i.e., at rest and fasting), a normal healthy adult requires approximately 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.

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 1-6). 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, resulting in a fall of serum glucose concentration within hours (<16 hours).

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 utilize 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. While 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. 1-22).

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. While proteolysis during starvation occurs mainly within skeletal muscles, protein degradation in solid organs also occurs.

Table 1-6
***A.* Body Fuel Reserves in a 70-kg Man and *B.* Energy Equivalent of Substrate Oxidation**

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

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

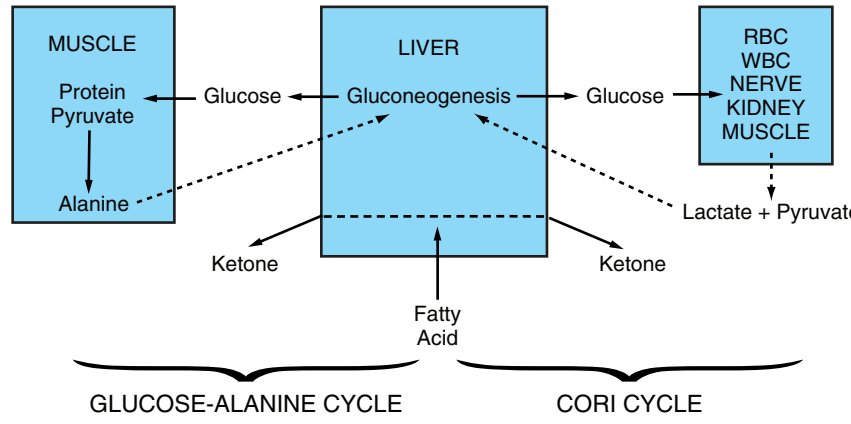

FIG. 1-22. The recycling of peripheral lactate and pyruvate for hepatic gluconeogenesis is accomplished by the Cori cycle. Alanine within skeletal muscles can also be utilized as a precursor for hepatic gluconeogenesis. During starvation, such fatty acid provides fuel sources for basal hepatic enzymatic function.

In *prolonged* starvation, systemic proteolysis is reduced to approximately 20 g per day and urinary nitrogen excretion stabilizes at 2 to 5 g per day (Fig. 1-23). 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.

Enhanced deamination of amino acids for gluconeogenesis during starvation consequently increases renal excretion of ammonium ions. The kidneys also participate in gluconeogenesis by the utilization 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 up to 40% 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. 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, as with 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 Following Injury

Injuries or infections induce unique neuroendocrine and immunologic responses that differentiate injury metabolism from that of unstressed fasting (Fig. 1-24). 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. 1-25). 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

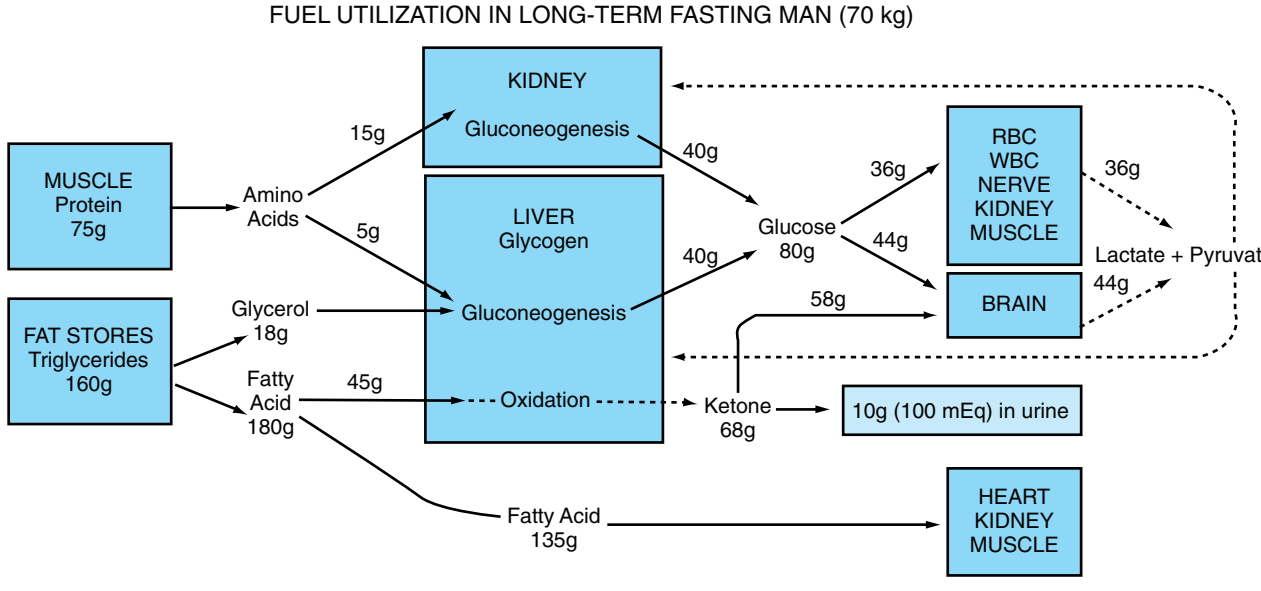

FIG. 1-23. Fuel utilization in extended starvation. Liver glycogen stores are depleted and there is adaptive reduction in proteolysis as a source of fuel. The brain utilizes ketones for fuel. The kidneys become important participants in gluconeogenesis. (*Adapted with permission from Cahill GF: Starvation in man. N Engl J Med 282:668, 1970.*)

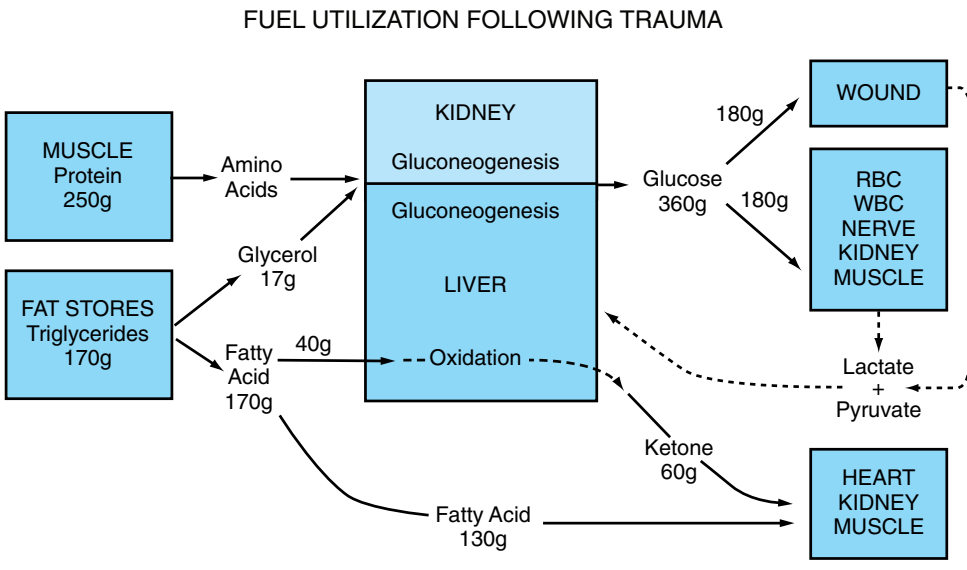

FIG. 1-24. *Acute injury is associated with significant alterations in substrate utilization. There is enhanced nitrogen loss, indicative of catabolism. Fat remains the primary fuel source under these circumstances.*

healthy human subjects. The discussion of lipid metabolism following injury is intentionally discussed first, because this macronutrient becomes the primary source of energy during stressed states.

Lipid Metabolism Following Injury

Lipids are not merely nonprotein, noncarbohydrate fuel sources that minimize protein catabolism in the injured patient, but 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 following injury. Fat mobilization (lipolysis) occurs mainly in response to catecholamine stimulus of the hormone-sensitive triglyceride lipase. Other hormonal influences on lipolysis include adrenocorticotropic hormone, catecholamines, thyroid hormone, cortisol, glucagon, growth hormone release, reduction in insulin levels, and increased sympathetic stimulus.

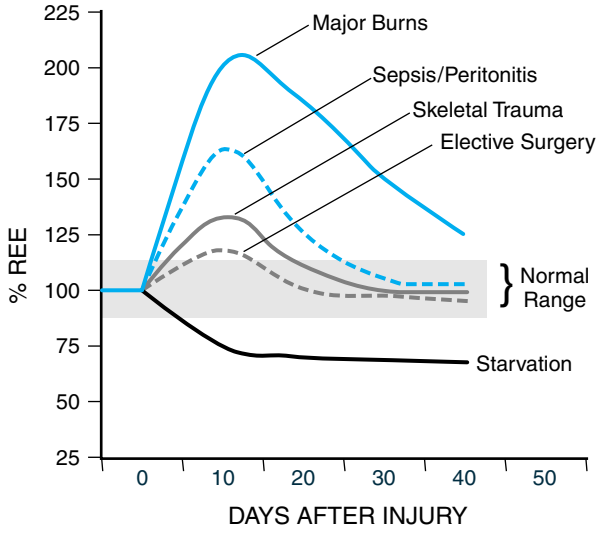

FIG. 1-25. *The influence of injury severity on resting metabolism (resting energy expenditure, REE). The shaded area indicates normal REE. (Adapted with permission from Long CL: Metabolic response to injury and illness: Estimation of energy and protein needs from indirect calorimetry and nitrogen balance. J Parenter Enteral Nutr 3:452, 1979.)*

Lipid Absorption. Although 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. 1-26). Long-chain triglycerides (LCT), 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 utilize free fatty acids as a fuel source during stress states, but can also synthesize phospholipids or triglycerides (i.e., very-low-density lipoproteins) during fed states. Systemic tissue (e.g., muscle and the heart) can utilize chylomicrons and triglycerides as fuel by hydrolysis with lipoprotein lipase at the luminal surface of capillary endothelium. Trauma or sepsis suppresses lipoprotein lipase activity in both adipose tissue and muscle, presumably mediated by TNF-α.

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, adrenocorticotropic hormone [ACTH], thyroid hormones, growth hormone, and glucagon) on triglyceride lipase through a cAMP pathway (Fig. 1-27). 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

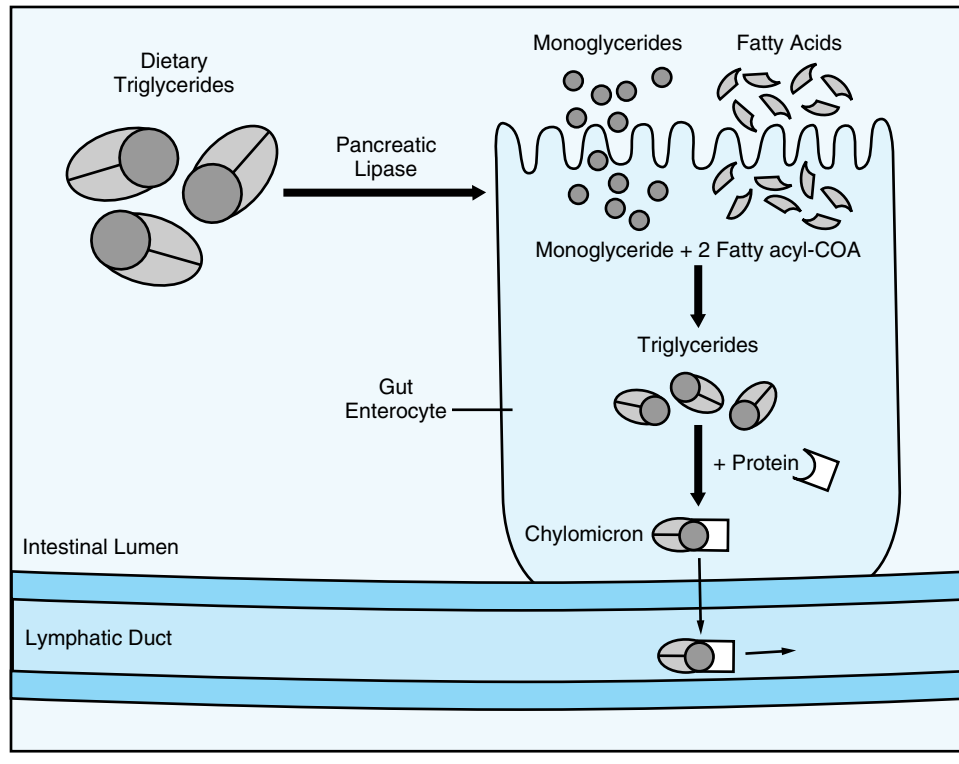

FIG. 1-26. Pancreatic lipase within the small intestinal brush borders hydrolyzes triglycerides into monoglycerides and fatty acids. These components readily diffuse into the gut enterocytes, where they are re-esterified into triglycerides. The resynthesized triglycerides bind carrier proteins to form chylomicrons, which are transported by the lymphatic system. Shorter triglycerides (those with less than 10 carbon atoms) can bypass this process and directly enter the portal circulation for transport to the liver.

fuel depends on the availability of tissue glycerokinase, which is abundant in the liver and kidneys.

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. 1-28). Medium-chain triglycerides (MCT), defined as those 6 to 12 carbons in length, bypass the carnitine shuttle and readily cross the mitochondrial membranes. This accounts in part for why 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

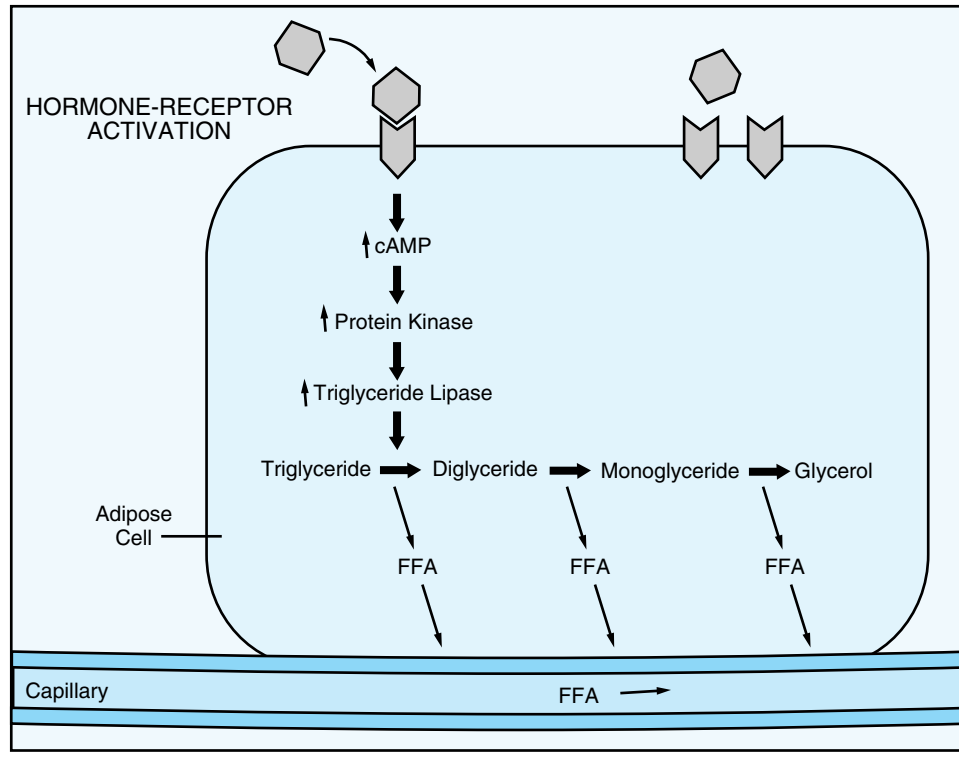

FIG. 1-27. Fat mobilization in adipose tissue. Triglyceride lipase activation by hormonal stimulation of adipose cells occurs through the cAMP pathway. Triglycerides are serially hydrolyzed with resultant free fatty acid (FFA) release at every step. The FFAs diffuse readily into the capillary bed for transport. Tissues with glycerokinase can utilize 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.

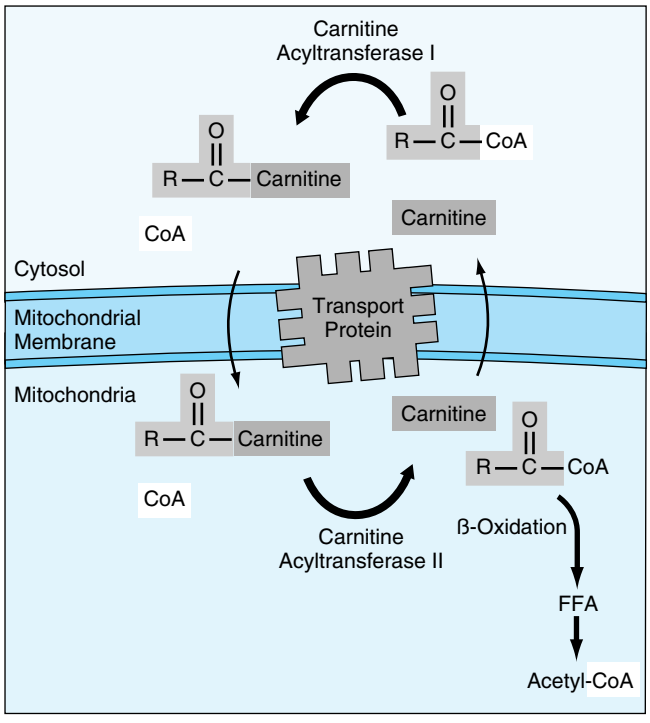

FIG. 1-28. Free fatty acids in the cells form fatty acyl-CoA with coenzyme A. Fatty acyl-CoA cannot enter the inner mitochondrial membrane and requires carnitine as a carrier protein (carnitine shuttle). Once inside the mitochondria, carnitine dissociates and fatty acyl-CoA is re-formed. The carnitine molecule is transported back into the cytosol for reuse. The fatty acyl-CoA undergoes β-oxidation to form acetyl-CoA for entry into the tricarboxylic acid cycle.

infusion in parenteral nutrition. 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.

Within the mitochondria, fatty acyl-CoA undergoes β-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, while 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 acetyl-CoA entry 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 utilizing 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 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, ketogenesis in minor stress states does not exceed that of 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. Both fructose and galactose within the circulation as well as exogenous mannitol (for neurologic injury) do not evoke 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 administered sugar solutions such as that found in intravenous fluids or parenteral nutrition provides 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 serves 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 starvation in healthy subjects, studies providing exogenous glucose to septic and trauma patients never have been shown to fully suppress amino acid degradation for gluconeogenesis. This suggests that during periods of stress, other hormonal and proinflammatory mediators have 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 associated with RNA synthesis in muscle cells.

In cells, glucose is phosphorylated to form glucose-6-phosphate (G6P). G6P 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. 1-29).

Excess glucose from overfeeding, as reflected by RQs greater than 1.0, can result in conditions such as glucosuria, thermogenesis, and conversion to fat (lipogenesis). Excessive glucose administration results in elevated carbon dioxide production, which may be deleterious in patients with suboptimal pulmonary function.

Injury and severe infections acutely induce a state of peripheral glucose intolerance, despite ample insulin production severalfold above baseline. This may occur in part due to reduced skeletal muscle pyruvate dehydrogenase activity following injury, which diminishes the conversion of pyruvate to acetyl-CoA and subsequent entry into the TCA cycle. The consequent accumulation of three-carbon structures (e.g., pyruvate and lactate) are shunted to the liver as substrate for gluconeogenesis. Furthermore, regional tissue catheterization and isotope dilution studies have shown an increase in net splanchnic glucose production in septic patients by

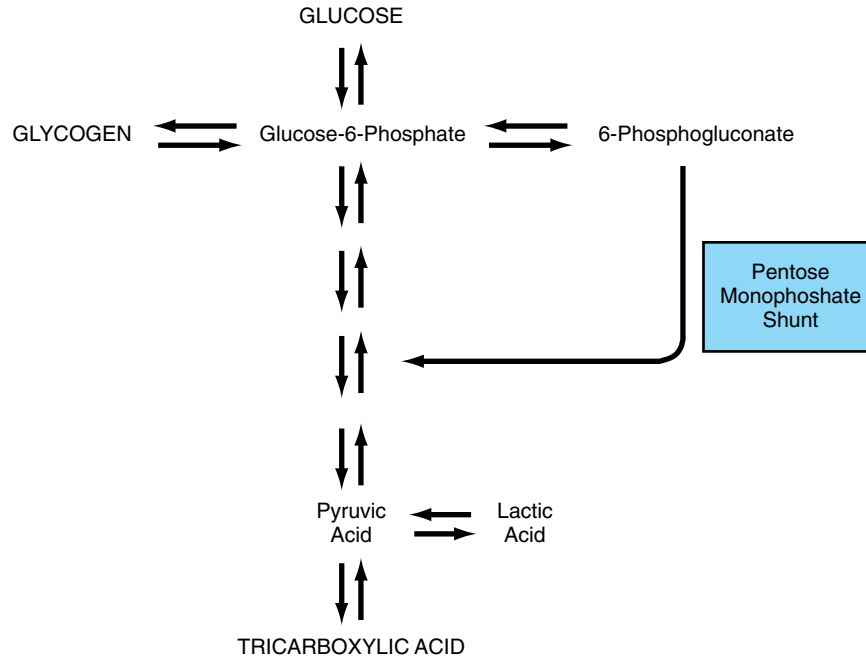

FIG. 1-29. Simplified schema of glucose catabolism through the pentose monophosphate pathway or by breakdown into pyruvate. Glucose-6-phosphate becomes an important "crossroad" for glucose metabolism.

50 to 60%, and a 50 to 100% increase in burn patients. The increase in plasma glucose levels is proportional to the severity of injury, and this net hepatic gluconeogenic response is believed to be under the influence of glucagon. Unlike the nonstressed subject, the hepatic gluconeogenic response to injury or sepsis cannot be suppressed by exogenous or excess glucose administration, but rather persists in the hypermetabolic, critically ill patient. Hepatic gluconeogenesis, arising primarily from alanine and glutamine catabolism, provides a ready fuel source for tissues such as those of the nervous system, wounds, and erythrocytes, which do not require insulin for glucose transport. The elevated glucose concentrations also provide a necessary energy source for leukocytes in inflamed tissues and in sites of microbial invasions.

The shunting of glucose away from nonessential organs such as skeletal muscle and adipose tissues is mediated by catecholamines. Experiments with infusing catecholamines and glucagon in animals have demonstrated elevated plasma glucose levels as a result of increased hepatic gluconeogenesis and peripheral insulin resistance. Interestingly, while glucocorticoid infusion alone does not increase glucose levels, it does prolong and augment the hyperglycemic effects of catecholamines and glucagon when infused concurrently.

Glycogen stores within skeletal muscles can be mobilized by epinephrine activation of β-adrenergic receptors, a GTP-binding protein (G-protein), which subsequently activates the second messenger, cAMP. cAMP activates phosphorylase kinase, which in turn leads to conversion of glycogen to glucose-1-phosphate. Phosphorylase kinase also can be activated by the second messenger, calcium, through the breakdown of phosphatidylinositol phosphate, which is the case in vasopressin-mediated hepatic glycogenolysis.

Glucose Transport and Signaling. Hydrophobic cell membranes are relatively impermeable to hydrophilic glucose molecules. There are two distinct classes of membrane glucose transporters in human systems. These are the facilitated diffusion glucose transporters (GLUT) that permit the transport of glucose down a concentration gradient (Table 1-7) and the Na^+/glucose transport system, which transports glucose molecules against concentration gradients by active transport. The energy-dependent Na^+/glucose transport system is relatively prevalent on brush borders of small intestine enterocytes and the epithelium of proximal renal tubules.

More than five human facilitated diffusion glucose transporters have been cloned since 1985. GLUT 1 is the transporter in human erythrocytes. It is expressed on several other tissues, but little is found in the liver and skeletal muscle. Importantly, it is a constitutive part of the endothelium in the blood-brain barrier. GLUT 2 is predominantly expressed in the sinusoidal membranes of liver, renal tubules, enterocytes, and insulin-secreting β cells of the pancreas. GLUT 2 is important for rapid export of glucose resulting from gluconeogenesis. GLUT 3 is highly expressed in neuronal tissue of the brain, the kidney, and placenta, but GLUT 3 mRNA has been detected in almost every human tissue. GLUT 4 is significant to human metabolism because it is the *primary* glucose transporter of insulin-sensitive tissues, adipose tissue, and skeletal and cardiac muscle. These transporters are usually packaged as intracellular vesicles, but insulin induces rapid translocation of these vesicles to the cell surface. GLUT 4 function has important implications in the physiology of patients with insulin-resistant diabetes. GLUT 5 has been identified in several tissues, but is primarily expressed in the jejunum. Although it possesses some capacity for glucose transport, it is predominantly a fructose transporter.

Na^+/glucose transport systems are distinct glucose transport systems found in the intestinal epithelium and in the proximal renal

Table 1-7
Human Facilitated Diffusion Glucose Transporter Family

Type	*Amino Acids*	*Major Expression Sites*
GLUT 1	492	Placenta, brain, kidney, colon
GLUT 2	524	Liver, pancreatic β cells, kidney, small intestine
GLUT 3	496	Brain, testis
GLUT 4	509	Skeletal muscle, heart muscle, brown and white fat
GLUT 5	501	Small intestine, sperm

tubules. This system transports both sodium and glucose intracellularly, and glucose affinity for this transporter increases when sodium ions are attached. In addition, the Na^+/glucose transport system within the intestinal lumen also enhances gut retention of water through osmotic absorption.

PROTEIN AND AMINO ACID METABOLISM

The average protein intake in healthy, young adults ranges from 80 to 120 g/d, and every 6 g of protein yields approximately 1 g of nitrogen. The degradation of 1 g of protein yields approximately 4 kcal of energy, almost the same as for carbohydrates.

Following injury the initial systemic proteolysis, mediated primarily by glucocorticoids, increases urinary nitrogen excretion to levels in excess of 30 g/d, which roughly corresponds to a loss in lean body mass of 1.5% per day. An injured individual who does not receive nutrition for 10 days can theoretically lose 15% lean body mass. Therefore amino acids cannot be considered a long-term fuel reserve, and indeed excessive protein depletion (i.e., 25 to 30% of lean body weight) is not compatible with sustaining life.

Protein catabolism following injury provides substrates for gluconeogenesis and for the synthesis of acute phase proteins. Radiolabeled amino acid incorporation studies and protein analyses confirm that skeletal muscles are preferentially depleted acutely following injury, while visceral tissues (e.g., the liver and kidney) remain relatively preserved. The accelerated urea excretion following injury is also associated with the excretion of intracellular elements such as sulfur, phosphorus, potassium, magnesium, and creatinine. Conversely, the rapid utilization of elements such as potassium and magnesium during recovery from major injury may indicate a period of tissue healing.

The net changes in protein catabolism and synthesis correspond to the severity and duration of injury (Fig. 1-30). Elective operations and minor injuries result in lower protein synthesis and moderate protein breakdown. Severe trauma, burns, and sepsis are associated with increased protein catabolism. The rise in urinary nitrogen and negative nitrogen balance can be detected early following injury and peak by 7 days. This state of protein catabolism may persist for as long as 3 to 7 weeks. The patient's prior physical status and age appear to influence the degree of proteolysis following injury or sepsis.

Activation of the ubiquitin-proteosome system in muscle cells is one of the major pathways for protein degradation during acute injury. This response is accentuated by tissue hypoxia, acidosis, insulin resistance, and elevated glucocorticoids.

NUTRITION IN THE SURGICAL PATIENT

The goal of nutritional support in the surgical patient is to prevent or reverse the catabolic effects of disease or injury. While several important biologic parameters have been used to measure the efficacy of nutrition regimens, the ultimate validation for nutritional support in surgical patients should be improvement in clinical outcome and restoration of function.

Estimating Energy Requirements

Overall nutritional assessment is undertaken to determine the severity of nutrient deficiencies or excess and to aid in predicting nutritional requirements. Pertinent information is obtained by determining the presence of weight loss, chronic illnesses, or dietary habits that influence the quantity and quality of food intake. Social habits predisposing to malnutrition and the use of medications that may influence food intake or urination should also be investigated. Physical examination seeks to assess loss of muscle and adipose tissues, organ dysfunction, and subtle changes in skin, hair, or neuromuscular function reflecting frank or impending nutritional deficiency. Anthropometric data (i.e., weight change, skinfold thickness, and arm circumference muscle area) and biochemical determinations (i.e., creatinine excretion, albumin, prealbumin, total lymphocyte count, and transferrin) may be used to substantiate the patient's history and physical findings. It is imprecise to rely on any single or fixed combination of the above findings to accurately assess nutritional status or morbidity. Appreciation for the stresses and natural history of the disease process, in combination with nutritional assessment, remains the basis for identifying patients in acute or anticipated need of nutritional support.

A fundamental goal of nutritional support is to meet the energy requirements for metabolic processes, core temperature

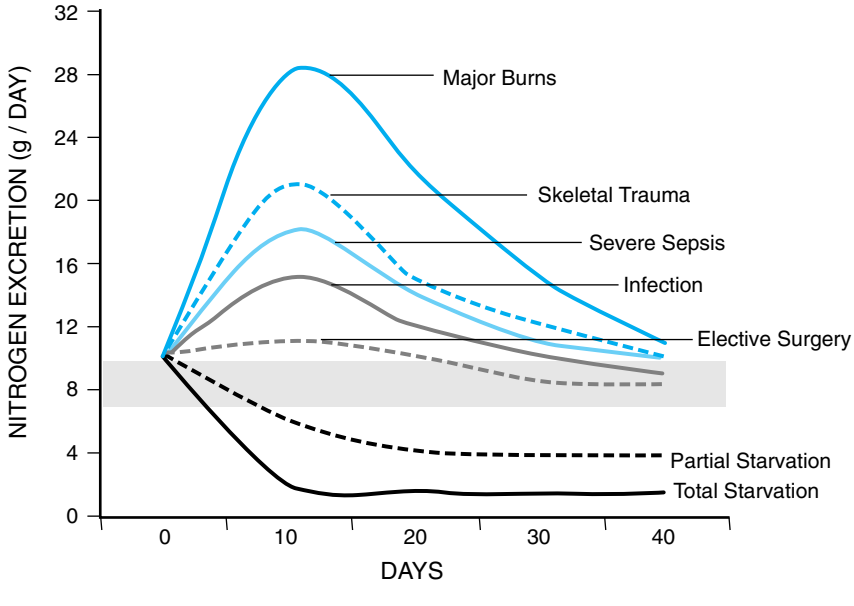

FIG. 1-30. The effect of injury severity on nitrogen wasting. (*Adapted with permission from Long CL: Metabolic response to injury and illness: Estimation of energy and protein needs from indirect calorimetry and nitrogen balance. J Parenter Enteral Nutr 3:452, 1979.*)