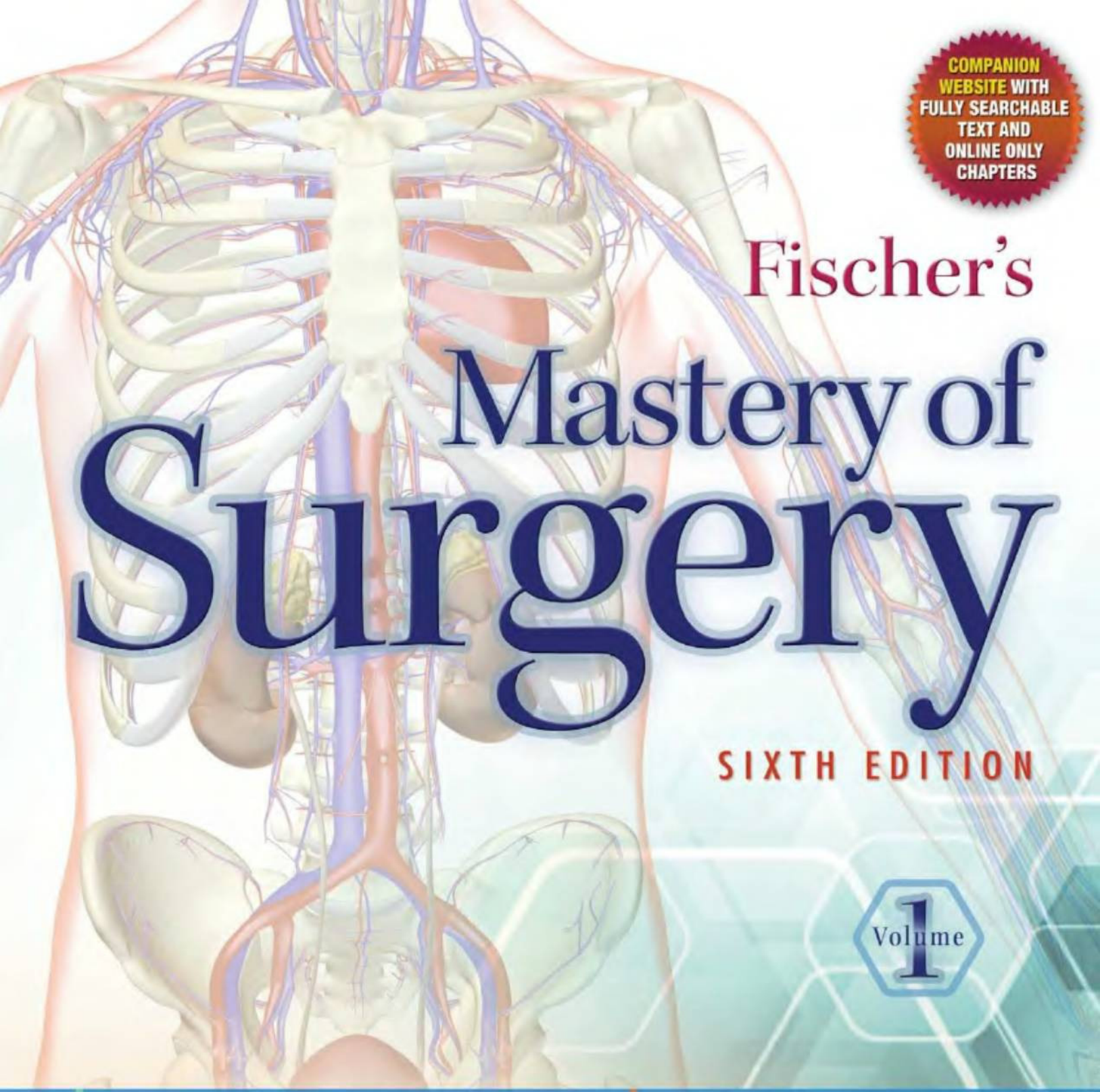

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SIXTH EDITION

Volume 1

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To Karen
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Alexandra and Peter

and

The late Dr. Howard I. Down

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Preface

This book comes at a critical time in surgery, a time the various external pressures have conspired to reduce surgery from a proud profession to a group of "employees". It was not always so. My late father-in-law, Dr. Howard I. Down, one of those to whom the book is dedicated, was born on a farm near Odebolt, Iowa in 1901, one of ten children on 640 acres of rich Missouri bottomland. All of the children survived into adulthood – a remarkable achievement. The family still holds five-year reunions on that farmland which is owned as an investment by Princeton University which generously allows the family visits. While the older boys worked the fields, as a young boy my father-in-law was assigned to help out his sisters in the house. Working in the house allowed him ample opportunities to read and develop his desire for knowledge. All of the children were offered college as an option and all but one attended at least one year. Howard decided to attend Morningside, a small Methodist college in Sioux City, then went on to medical school at Northwestern. He elected to train at the Mayo Clinic which he completed in 1932. He would tell me "they wanted to give me a room" which meant they wanted him to join the staff, but he wanted to return home to northwest Iowa to build a practice. In fact, he was the first well-trained and experienced surgeon in that vast area. On almost a weekly basis he, and later his partner, Martin Blackstone, and a nurse, rode circuit, operating in various towns; returning the following week to see how well the patients fared under the care of their general practitioner. The practice expanded and eventually he established a general medical practice and a busy surgical practice in Sioux City, population 85,000, which then and now serves as a catchment area for prosperous and relatively well-to-do farmers. Appointments were made for "the day" not for a "specific time". Patients checked in, went shopping downtown and returned at the appropriate time. When Dr. Down died at the age of 91 we found his account books. An office visit was 50¢. Many of the patients could not pay and later sent bushels of potatoes, wine, butter, etc., which were offered as payment and were duly noted in that account book. Some did not pay at all. When he died in 2001, Karen and I went through the house and found some of the most interesting gifts, and I might add, some of the worst liquor, obviously given as payment. For the most part he operated daily, came home for dinner with the family, and then returned to make rounds. The only way Dr. Down could get away on vacation was to get out of town. It took me a long time before I could live up to the two trips Karen made with the family when she was eleven and thirteen traveling to a variety of states so that he could get away from his practice.

Dr. Down lived very modestly in a three-bedroom, two-story house with one full-bath in a very nice neighborhood. He was highly respected and beloved. He sat on a number of boards while his wife was the president of a number of organizations including the YWCA and Planned Parenthood. He loved music and was on the Board of the Sioux City Symphony. In this capacity as a board member, Karen and I were invited to dine with Dr. Down and soprano Victoria de Los Angeles. One of Karen's fondest memories was watching Dr. Down "conduct" Tchaikovsky's Symphony #5 in the family living room. He continued to operate until late in life and then practiced as a general internist until he was 80 years old. He was a tall, attractive and quiet man who never said much yet dominated a room whether or not he spoke. During his long career he served as governor of the College and President of the Iowa Surgical Society. Every six months he returned to the Mayo Clinic – his equivalent of CME.

He never told Karen whether he approved of me as a son-in-law. Probably the closest he came to doing so was after I gave grand rounds at one of his hospitals in Sioux City. As he walked me out to the tarmac and just before I boarded the plane to return to Boston, without a word he stuffed a quart of Johnny Walker Black Label under my arm. I must have done something right! Speaking at his memorial service I reflected that Dr. Down terrified colleagues, nurses and at least one son-in-law without saying much; everyone knew his standards were extremely high. On the day of his funeral his brother and best friend Charles, a lawyer, told me that Howard was indeed very proud of me and he asked if he could get copies of the articles I had written and that his brother had discussed with him. As you can imagine, it was wonderful to hear this from his best friend but it would have been better to hear it while he was alive.

We were fortunate enough to obtain his vast library which consisted of a large number of medical books among which were three books: Jergen Thorwald, "*The Century of the Surgeon*"; Owen and Sarah D. Wangensteen, "*The Rise of Surgery: From Empiric Craft to Scientific Discipline*"; and Knut Haeger, "The Illustrated History of Surgery".

This was a time when surgeons were revered for their daring, their inventiveness, their interest in patients and what they did to cure disease. Dr. Francis D. Moore, longtime chief at Brigham & Women's Hospital, made the cover of *Time* magazine with the caption "You're lucky if they can operate". They were feared but committed. They were respected. They were surgeons! One of my mentors, Dr. Edward D. Churchill, my first-year chief and long time chair of the department of surgery at Massachusetts General Hospital (MGH), believed in surgery and felt that surgery was the answer to disease. Dr. Claude Welch, Dean of Boston Surgeons and another one of my mentors believed that an exploratory laparotomy was merely an extension of the physical exam. Dr. Welch was a remarkable surgeon who performed the first 10 aneurysmectomies at the Massachusetts General Hospital and some of the first parathyroidectomies, in addition to being a superb and busy GI surgeon. Dr. Robert Linton, another mentor and a giant in the field of vascular surgery, was a meticulous surgeon and taught me a great deal about the technique of surgery. He taught me to own my instruments. He sharpened his own scissors so that he would "feel with the scissors the differences in tissue and be careful". I have taken that

much to heart and find that having my own familiar scissors and other instruments enabled me to be a better technical surgeon.

Dr. Churchill was one of the wisest men I have ever met. If you asked him about the chicken—and you could commit to the time to listen—he would begin with the creation of the egg at the birth of the world. He is not adequately credited for taking the daring stance that he could recognize an applicant at the beginning of the surgical program and commit to finish them five years later. His rectangular program finally became the surviving form of the American Surgical Residency Program. This is not to take anything from Dr. Stewart Halsted and Johns Hopkins Hospital but Dr. Halsted was not interested in meeting the surgical needs of the United States. He was interested in producing elite professors. In Cincinnati, Dr. George Heuer, a direct descendent of the Hopkins system and the first Christian Holmes professor, Dr. Mont Reed, Dr. B. Nolan Carter and Dr. Gunderson, who filled in during the war waiting for Dr. Carter to return - they were all giants and products of the Hopkins program. They made enormous contributions to surgery: Dr. Heuer to neurosurgery, Dr. Reed to wound healing and general physiology and, Dr. Carter to early cardiothoracic surgery and performing some of the first cardiac perfusion operations in the United States.

While I dedicate this volume in part to my late father-in-law, Dr. Howard Down, I dedicate it to all of those surgeons who dominated American medicine for a century – the century of the surgeon as Dr. Thorwald put it. They were surgeons who believed in the discipline, they were at the top of their game and looked up to by all as being inventive, courageous and making American surgery the envy of the world as Germanic surgery was destroyed by World War II. I mourn the passing of that time.

We are no longer at the top of the heap. We are no longer the adventurous and rigorous group that were simultaneously feared and admired, who did things under difficult conditions, but kept at it until they had perfected operations that have since saved thousands of lives. In the early and middle stages of my career surgeons were independent professional who firmly advanced ideas they believed in. Now, more than 50% of surgeons are employed by hospitals. Surgical training has been constricted so that surgical residents perform 50% fewer operations due to the 80-hour work week. Yet the diseases for which we operate are the same and most of our patients are older with a greater number of co-morbidities. Greater technical and analytical skills are required to ensure a live patient at the end of an operative procedure. When will our surgical residents learn these skills? This the driving reason for this book. We need this book to teach how operations are performed – so that residents and young attendings can have some understanding of the intricasies of operative procedures.

Much has changed in the past five years as evidence of our results leads to decreased mortality and morbidity and better outcomes for our patients. Many changes in surgery have occurred since our work on the 5th edition began eight years ago. The Roux-en-y reconstruction following gastrectomy is generally agreed to be the best reconstruction, better than the gastroduodenostomy (Billroth 1) and gastrojejunostomy (Billroth 2). The fall in parathyroid hormone is no longer utilized by everyone as the sine qua non for parathyroidectomy although it does seem it is necessary to achieve a 99% cure. Thyroid carcinoma is being treated as a malignancy and node dissection is part of the best practice. Cancer of the head and neck is being treated with chemotherapy and radiation even if nodes are negative – with a better outcome – and operations are less destructive. Patients with carcinoma of the lung can undergo less extensive resections with no sacrifice of outcome and with minimally invasive techniques less pain and disability. In vascular disease, minimally invasive techniques done to a considerable extent by vascular surgeons are accompanied by less pain and disability. Eighty-five percent of vascular cases are done endovascularly.

I owe immense gratitude to too many people and undoubtedly will inadvertently miss mentioning all of them. First and foremost to my family: although I was often absent, it was kept stable by my lovely wife Karen whom my friends call "my better 7/8th". To our children, Erich and Alexandra, of whom I am immensely proud and whose interests I share and I hope partially cultivated. Our son Erich is a space and astronomy enthusiast due in part to our family's interest in astronomy. Our daughter, Alexandra, a successful practicing veterinarian, has expressed to me that this is the closest she could come to being a "3rd generation surgeon" without taking a lot of guff from being my daughter. And I must mention my daughter-in-law Hallie, and my son-in-law Peter, both of whom have enthusiastically been welcomed into our family.

Thank you to Bob Baker who was kind enough to take me, along with Dr. Lloyd Nyhus, in the 3rd edition; Dr. Baker, an attractive, urbane and, "cool hand and head" who tolerated and aided the transformation of the book from strictly an atlas to a textbook; to the various assistant and associate editors who do so well in the commentaries and in keeping the national and international views on track; to the hundreds of authors who humored me when I made "suggestions" on the first drafts of their excellent manuscripts; to the production staff at Lippincott most notably Brian Brown and Julia Seto who kept cool throughout what has been a difficult and taxing production; sincere thanks to Pat McGovern, Esq. and Richard Glovsky, Esq., both of whom enabled the production of this edition without physical interruption; and finally, thank you to a most dedicated office staff, including Edith Burbank-Schmitt now in her second year of medical school, Ingrid Johnson who always pitched in and Abigail Smith who did a magnificent job of research for the 6th edition as well as the 5th—only better. I hope we have succeeded in producing a textbook of surgery that is also an atlas reflecting the latest minimally invasive and other techniques as well as showcasing the views of many internationally known surgeons, and hopefully make up, at least partially, for the interference with adequate training.

Josef E. Fischer
November 2011
Boston, Massachusetts

Web-Only Chapters

Chapter 85: Selective Vagotomy, Antrectomy, and Gastroduodenostomy for the Treatment of Duodenal Ulcer e-1

Lloyd M. Nyhus

Selective vagotomy, antrectomy and gastroduodenostomy for the treatment of duodenal ulcer is an operation that is no longer done. Very frequently parietal cell vagotomy has largely supplanted selective vagotomy, but antrectomy and gastroduodenostomy are useful for carcinoma of the stomach with some slight modifications as pictured elsewhere in the book. This is a classic chapter, and it is included for historical reasons but also because Dr. Nyhus, one of the originators of *Mastery of Surgery* wrote a superb chapter. It can be read with profit.

Chapter 86: Selective Vagotomy and Pyloroplasty e-13

Steven D. Schwaitzberg, John L. Sawyers, and William O. Richards

Dr. Steven Schwaitzberg has written an excellent chapter on selective vagotomy and pyloroplasty. However, as Dr. Schwaitzberg pointed out to me himself, this is an operation that is no longer done very frequently, if at all. However, it is a chapter that elucidates some points concerning surgery of the stomach, unfortunately no longer carried out with any great degree of regularity. It is a chapter that can be read with significant profit.

Chapter 139: Distal Splenorenal Shunts: Hemodynamics of Total versus Selective Shunting e-21

Atef A. Salam

The distal splenorenal shunt was advocated originally as an operation for portal hypertension which had a lower rate of hepatic encephalopathy as compared to the central splenorenal shunt (which is useful in patients with significant ascites, patients on whom distal splenorenal is contraindicated), a claim which has not held up. In addition, recent data from randomized prospective trials seem to conclude that the portacaval shunt is at least as good and perhaps better as in regard to long term outcomes. (See commentaries on Chapters 137 and 138)

Chapter 145: The Continent Ileostomy e-30

Eric J. Dozois and Roger R. Dozois

This procedure was originally proposed as an alternative to Ileal Pouch Anal Anastomosis. However, as the pouch has become the standard operation for ulcerative colitis—and in some hands, familial polyposis—very few now perform this procedure.

Chapter 152: Care of Stomas e-37

Laurie Maidl and Jill Ohland

The care of stomas has become a nursing subspecialty, and the presence of a stoma nurse is a very important part of most hospitals of any size. The stoma nurse helps with preoperative planning of the operation, siting of the ileostomy or colostomy, help with difficult stomas, and care of patients with gastrointestinal cutaneous fistulas.

Chapter 180: Operations on the Ureteropelvic Junction e-53

Frank Hinman, Jr.

"Operations of the Ureteropelvic Junction" is another operation that has given way to minimally invasive and endourological procedures. Dealing with the ureteropelvic junction in open fashion is an art form that will be applied to the minority of patients. Nonetheless, it is important that one know how to do the operation if the occasion demands and the preservation of renal function is at stake.

Chapter 194: Anterior and Posterior Colporrhaphy e-60

Dionysios K. Veronikis

The chapter on anterior and posterior colporrhaphy presented here is a rather detailed chapter and one which can be read with profit. However, the vaginal floor and its repair has become much more complicated and so anterior and posterior colporrhaphy, in and of itself, are used less frequently. They may be used with operations for the prolapse of the rectum and they may be utilized in the more sophisticated approach to cystocele and urethracele.

However, the anatomy which is described in the anatomical repair, is valuable and can shed light in other specialties to the necessity for having pelvic floor repair, for example, or come in useful as stated in my commentary for repair of rectal prolapse.

Chapter 196: Bassini Operation e-75

Oreste Terranova, Luigi De Santis, and Flavio Frigo

Drs. Terranova, DeSantis and Frigo, as they have in the past, have contributed to the classic operation which started all repairs of inguinal hernia by Dr. Edoardo Bassini. "The Bassini Operation" probably is the first one that gained credence and has held for approximately 100 years or more. However, as the authors come to the conclusion that "The Bassini Operation" even carried out with repair of the transversalis fascia, as originally described by Bassini and shown here in the original pictures, has a recurrence rate anywhere from 3–22% although it may fall as they say in the text below 1.5–2%. They come to the conclusion that while of historical interest and of interest as far as the anatomy of the inguinal canal, this operation as currently described in and of itself is no longer viable.

The Shouldice operation described elsewhere in this volume may actually disagree with that particular conclusion. But according to the authors, prosthetic material must be used in order to get a reasonable recurrence rate. Thus, despite the importance of Bassini and his operation as it was originally described, this is no

longer a contemporary utilization of surgery for inguinal hernia cause of the recurrence.

It is presented on the website for historical interest as it really started everything. One may differ as to whether or not Shouldice repair is useful or whether I use a variant of the Shouldice operation, sometimes with vicryl mesh and seem to have low recurrence rates. However, the reader will decide from all of the repairs which are made available in the hernia section.

Chapter 197: Cooper Ligament Repair of Groin Hernias e-87

Robb H. Rutledge

Dr. Robb Ruttledge is an excellent practitioner who preceded me in the Massachusetts General Hospital residency by a number of years. He is an exemplary gentleman and a superb surgeon who, despite being in private practice is highly academic in his approach. I consider him a friend. The Cooper's ligament repair once was a staple of herniorraphy. Indeed, when I was a resident, the Cooper's ligament repair was the standard procedure we carried out at the Massachusetts General Hospital despite the fact that it is more painful and its primary utility is in the area of femoral hernias. Dr. Ruttledge nicely describes it. The chapter appeared in the fourth edition.

Chapter 198: The Shouldice Method of Inguinal Herniorrhaphy e-96

Robert Bendavid

The Shouldice Clinic declined to bring the operation up to date. It is still useful to review this procedure because it is, in its best sense, the descendent of the Bassini repair. It has largely been supplanted by the various mesh repairs and the Lichtenstein tension free repairs.

Chapter 199: Iliopubic Tract Repair of Inguinal Hernia: The Anterior (Inguinal Canal) Approach e-108

Robert E. Condon

A classic article on the standard repair of Inguinal Hernia.

Chapter 200: Iliopubic Tract Repair of Inguinal and Femoral Hernia: The Posterior (Preperitoneal) Approach e-118

Lloyd M. Nyhus

Chapters 172 and 173 are two classic articles appearing from a golden age in surgery, the collaboration with Dr. Robert Condon and Dr. Lloyd Nyhus. They deal with the anatomy first and foremost of the inguinal canal by two individuals who have made this a major focus of their long and distinguished academic careers. The anatomy is masterfully described and is well argued. Familiarity with this approach is essential because there are times when there is a hernia in the vicinity of the abdomen and anatomical knowledge of this area will enable a repair to be done with less difficulty, thus preventing another operative procedure.

These two classics have appeared in every previous edition and they are included here on the website. At a time when most surgical residents never learn the anatomy of the inguinal canal, which I find unfortunate, these two chapters are superb in how the knowledge of surgical anatomy can lead not only to a concept but also to performance of an excellent clinical operation at that time.

Chapter 204: Giant Prosthesis for Reinforcement of the Visceral Sac in the Repair of Groin and Incisional Hernias e-126

René E. Stoppa

The Stoppa procedure is good for bilateral hernia and has the advantage of a very low complication rate of inguinodynia, which occurs in as many as 10% of groin prosthetic repairs. Patients with severe inguinodynia are incapacitated and operative repair is successfully only in up to 80% of patients.

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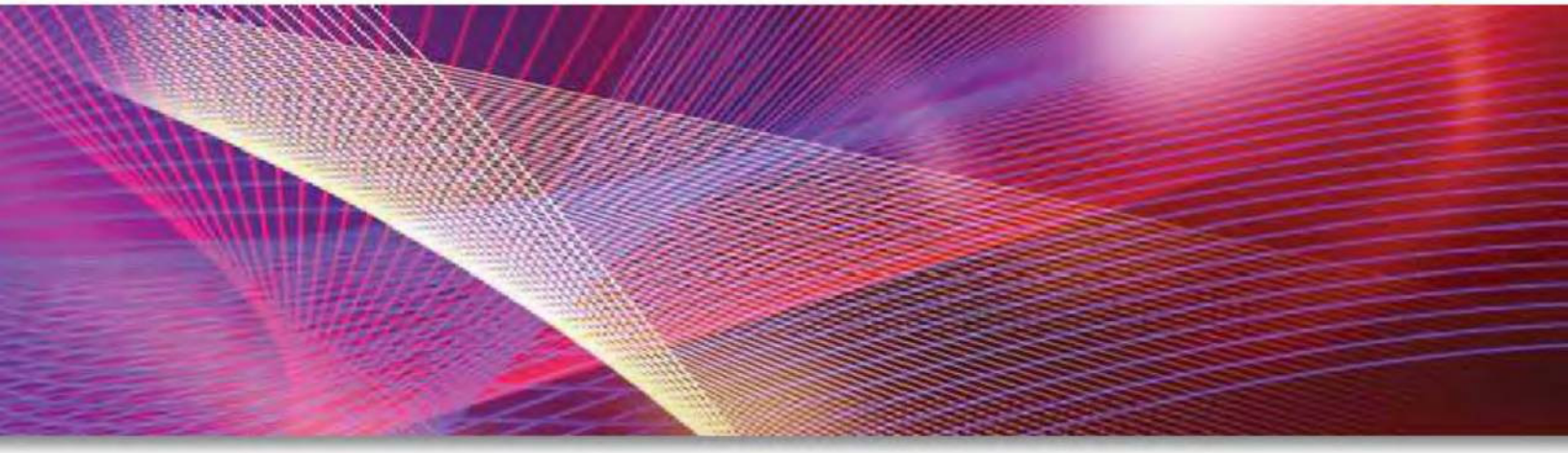

1 Metabolic and Inflammatory Responses to Trauma and Infection

Naji N. Abumrad, Igal Breitman, Julia Wattacheril, William J. Hubbard, and Irshad H. Chaudry

INTRODUCTION

Surgery has its roots in providing care for those patients coping with injury or infection. In the last decade, an enormous amount of data has been published, which describes the wide spectrum of illnesses that can result following trauma or infection—from a minor, local reaction to surgery, to a systemic stress response, to sepsis, to systemic inflammatory response syndrome (SIRS), and, finally, to multi-organ failure (MOF). This information has provided the basis for many new concepts and techniques, which are now used daily in modern surgery. Having a thorough understanding of the mechanisms leading to illness following trauma and infection is crucial for any practicing surgeon. This understanding is the very hallmark of transferring knowledge gained in research to innovative surgical care at the bedside.

OVERVIEW

Following extensive tissue damage or systemic insult, such as infection, hypoperfusion, hypothermia, acid–base disturbance, pain or severe emotional stress, various physiologic and biochemical local and systemic alternations can be present and are referred to as "the stress response". The systemic alternations are mediated by a complex signaling system, including afferent and efferent nervous signals, immunological and hormonal adaptations, and a systemic washout of locally produced substances like cytokines and other mediators. The first reference to the stress response resulted from keen observations by Sir David Cuthbertson in the 1930s who described a biphasic immune, inflammatory, and metabolic response to injury. This was further modified by Francis Moore in the 1970s. The first short (<24 hours) hypometabolic phase (termed "Ebb" by Cuthbertson) represents a coordinated response directed toward immediate survival. It starts with the activation of local coagulation and innate immune system factors. While evidence of a systemic response may be minimal in subjects with mild injury, in an insult of sufficient magnitude, the local activation is followed by systemic inflammatory and endocrine responses. These can present as surges in plasma catecholamine, cortisol and aldosterone levels inflicting tachycardia, tachypnea, vasoconstriction, lower cardiac output, lower oxygen consumption, lower basal metabolic rate, sodium and water retention, translocation of blood from the peripheral to the central vital organs, and acute-phase protein (APP) production. If the organs survive, there is transition from the "ebb" phase to the "Flow" phase. The flow phase of the stress response is characterized by explosive metabolic activity, increasing immune activity, enhanced enzymatic activity, and tissue repair. This response is mediated by a massive neuroendocrine flux involving the production and secretion of catecholamines, antidiuretic hormone (ADH), cortisol, insulin, glucagon, and growth hormone (GH). The increased adrenergic stimulation causes an increase in the ratio of glucagon to insulin and, combined with the increased cortisol and cytokines, induces the state of enhanced proteolysis and lipolysis.

The supply of amino acids comes from catabolism of mostly skeletal muscle and visceral organs. Some of these amino acids are taken up by the liver as substrates for gluconeogenesis and protein synthesis. Others are reserved for enzyme synthesis and collagen deposition at the site of injury. The energy needs of most other tissues are met by the availability of free fatty acids (FFA) and ketone bodies. These are made available via enhanced lipolysis with released glycerol acting as a glucose precursor. The hepatic glucose production supplies the glucose obligatory tissues.

Clearly, this process of catabolism requires an enhancement of blood flow to the muscle, the liver, and the areas of injury. Individuals present with tachycardia and tachypnea, peripheral edema, fever, hyperglycemia, leukocytosis, increased O_2 consumption, increased CO_2 production, increased minute ventilation, elevated resting energy expenditure and negative nitrogen balance. Consequently, the liver provides substrates through gluconeogenesis and synthesis of ketone bodies, detoxifies nitrogenous waste via the synthesis of urea and elaborates a series of APPs that bind metabolic by-products or limit the activity of proteolytic enzymes secreted by activated leukocytes. Renal blood flow and glomerular filtration increase and facilitate excretion of the nitrogenous by-products. Cytokines released from macrophages and adipokines released from adipose tissue result in disruption of capillary tight junctions, leading to vascular leak allowing fluid and substrates to flow toward the avascular area of injury, as well as to the interstitium in other body parts.

Manifestations of this hypermetabolic phase can be seen clinically in every postoperative patient. Patients retain fluid and sodium via concentrated urine, and redistribute blood flow to the vital organs, as well as compensate for the intravascular depletion secondary to capillary leak and possible external losses. If allowed to go unchecked, this catabolic response would deplete endogenous resources and become maladaptive. Systemic inflammatory response, severe metabolic depletion, and possible secondary infection can all cause damage to vital organs that were not initially compromised by the injury. Adult respiratory distress syndrome (ARDS), renal insufficiency, hepatic dysfunction, loss of gut epithelial barrier function, immunoparalysis, and sepsis may develop and the multi-organ dysfunction can be fatal. Fortunately, with appropriate support measures, the stress response nearly always resolves itself without complications.

The intensity and duration of the flow phase roughly correlate to the extent and type of injury. The catabolic process usually peaks at about 48 to 72 hours post-injury. If the insult is resolved, it can lead to an anabolic state, dominated by insulin, GH, and insulin-like growth factor I (IGF-I) within 5–10 days of injury. The change is associated with a flux of protein, fluid, and electrolytes returning to depleted intracellular space, particularly the muscle. Interstitial edema fluid is reabsorbed and the excess fluid is eliminated with a brisk diuresis. As the cellular space re-expands, the need for electrochemical equilibrium mandates the movement of ions (K^+, Mg^{2+} and PO_4^{2-}) from the blood into the cells. Serum levels of these ions decrease and require repletion. Anorexia and fatigue gradually resolve, and heart rate, respirations, and plasma glucose normalize. Nitrogen balance becomes positive and homeostasis is restored.

INFLAMMATORY RESPONSE

The inflammatory response to injury involves interplay between several hormones (catecholamines and cortisol) and a large number of mediators (cytokines and chemokines). The immune and inflammatory responses to injury are predictable and well-orchestrated, and adaptive series of events evolve leading to maximize healing potential. A normal, balanced, and well-controlled inflammatory response in previously healthy patients almost always results in an uneventful recovery.

Innate Immune System

The immune response can be divided into an early innate and a later adaptive responses. The innate immune system is the first line of defense and its principal components are the epithelial barriers, immune cells (phagocytes such as neutrophils, macrophages and dendritic cells, and natural killer [NK] cells). Tissue damage, or microorganisms invading one or more of the epithelial barriers, is immediately recognized by the multiple components of innate immunity. The mechanisms used by the innate immune system to recognize nonself entities have been elucidated only recently. The innate immune response derives from preexisting recognition of pathogen-associated molecular patterns (PAMPs) or microorganism-associated molecular patterns (MAMPs). The best known examples of PAMPs are lipopolysaccharides (LPS) in gram-negative bacteria, lipoteichoic acids in gram-positive bacteria, mannose-rich oligosaccharides in microbial glycoproteins, mannans, unmethylated CpG sequences in bacteria, double-stranded RNA in replicating viruses, glucans, and N-formylmethionine (bacterial eukaryotic protein).

The receptors that have evolved to recognize these PAMPs are called pattern-recognition receptors, and these can functionally be divided into endocytic receptors, which mediate internalization and phagocytosis of microbes, and signaling receptors, which activate cellular signaling pathways that induce the expression of a variety of immune-response genes. The most important receptors that mediate endocytosis are the mannose receptors of the calcium-dependent lectin family, which recognize terminal mannose and fucose residues of glucoproteins and glycolipids that are characteristic of microorganisms, as well as the scavenger receptors that bind to bacterial cell walls. Among these signaling receptors, the two main groups of receptors are the Toll-like receptors (TLRs) and the G-protein-coupled receptors, of which the TLRs are the most prominent in the induction of immune and inflammatory responses.

Toll-like Receptors

The Toll signaling pathway was initially described in Drosophila in 1985, with the human homologue identified in 1997. This family of type I transmembrane receptors is characterized by an extracellular domain with leucine-rich repeats and a cytoplasmic domain. At least 11 human TLRs have been identified, and each is known to detect a specific PAMP and has a specific intracellular signaling pathway. TLR-1, 2, 4, 5, and 6 mainly recognize bacterial products, of which TLR2 has been implicated in the signaling process of gram-positive bacteria. TLR4 is the main receptor mediating the proinflammatory cytokines' response to LPS. TLR-3, TLR-7, and TLR-8 are specific for viral detection and TLR-9 seems to be involved in both microbial and viral recognition.

TLRs seem to play a bridging role between the innate and the adaptive immune systems. They are expressed on dendritic cells and T-lymphocytes, as well as on a variety of parenchymal cells (e.g., adrenals, liver, and spleen). The adrenal-expressed TLRs influence the systemic inflammatory response by their effect on cortisol secretion. Upon sensing danger, the TLRs are activated on immune, competent, and endothelial cells ultimately resulting in the translocation of nuclear factor (NF)-κB. NF-κB then migrates to the nucleus and mediates gene transcription and the production of inflammatory mediators, such as chemokines, adhesion molecules, growth factors, and pro-inflammatory cytokines, especially tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1). The IL-1 and TNF-α receptors, after binding to their ligand, can further activate the same signaling pathways amplifying the immune response (Figure 1). TLRs are also involved in the recognition of endogenous ligands, which are released from damaged or dying cells, or come from a depredated extracellular matrix. These molecules include lipids, carbohydrates, proteins, and nucleic acids.

Extensive research has been conducted on whether genetic variations can be used to identify patients at high risk of developing sepsis and organ dysfunction during severe infection. Increasing evidence suggests that a genetic polymorphism in TLRs may influence a patient's outcome in sepsis. For example, a single nucleotide polymorphism of TLR1 (TLR1–7202A/G) has been associated with higher organ dysfunction, increased gram-positive infections, and death by sepsis. Patients with a TLR4 gene mutation, especially those involving TLR4, $Asp^{299}Gly$ allele have a higher incidence of gram-negative infections; this polymorphism is also attributed to the severity of SIRS. Although septic patients with TLR-4 polymorphism have been shown to have reduced levels of circulating inflammatory cytokines and an increased risk of bacterial infection, the associations of mortality with polymorphism in TLRs during sepsis are still controversial. New research suggests that manipulation of TLR signaling pathways offers significant therapeutic potential, particularly in the treatment of organ injury accompanying sepsis, but this concept requires further exploration.

G-Protein-Coupled Receptors

These receptors initiate intracellular responses through the associated guanosine triphosphate (GTP)-binding G protein. These receptors are activated by chemokines, proteolytic products of complement proteins (e.g., C5a), and lipid mediators of inflammation (platelet-activating factor, prostaglandin E, and leukotriene B4).

Complement

The complement system consists of more than 30 proteins, including serum, serosal, and cell membrane proteins. Being part of the innate immune system, the complement system does not require prior immunization for activation; it is rapidly activated in a nonspecific manner in one of three main pathways: classic, alternative, and mannan-binding lectin pathways. In the classical pathway, it is activated by an IgM or IgG antibody–antigen complex. The alternative pathway does not rely on an antibody–antigen complex; it is activated directly by bacterial cell wall components. The mannan-binding lectin pathway is homologous to the classical pathway, except that the cascade is initiated by a mannan-binding lectin protein, produced by the liver that can activate complement cleavage when binding to a pathogen surface. Activation of the complement cascade results in the formation of products that act to lyse microbes, activate platelets, stimulate histamine release, recruit neutrophils by chemotactic action, and facilitate both phagocytosis and bacterial killing through opsonization of bacteria and stimulation of neutrophil degranulation.

Complement activation pathways are regulated by a large number of regulatory complement-control proteins, preventing over-activation of the whole system; systemic overwhelming activation of the system can result in changes in hemodynamic parameters, leading to shock. Persistent elevation of the complement-derived chemotaxins C3a, C4a, and C5a have been correlated with increased remote organ damage and

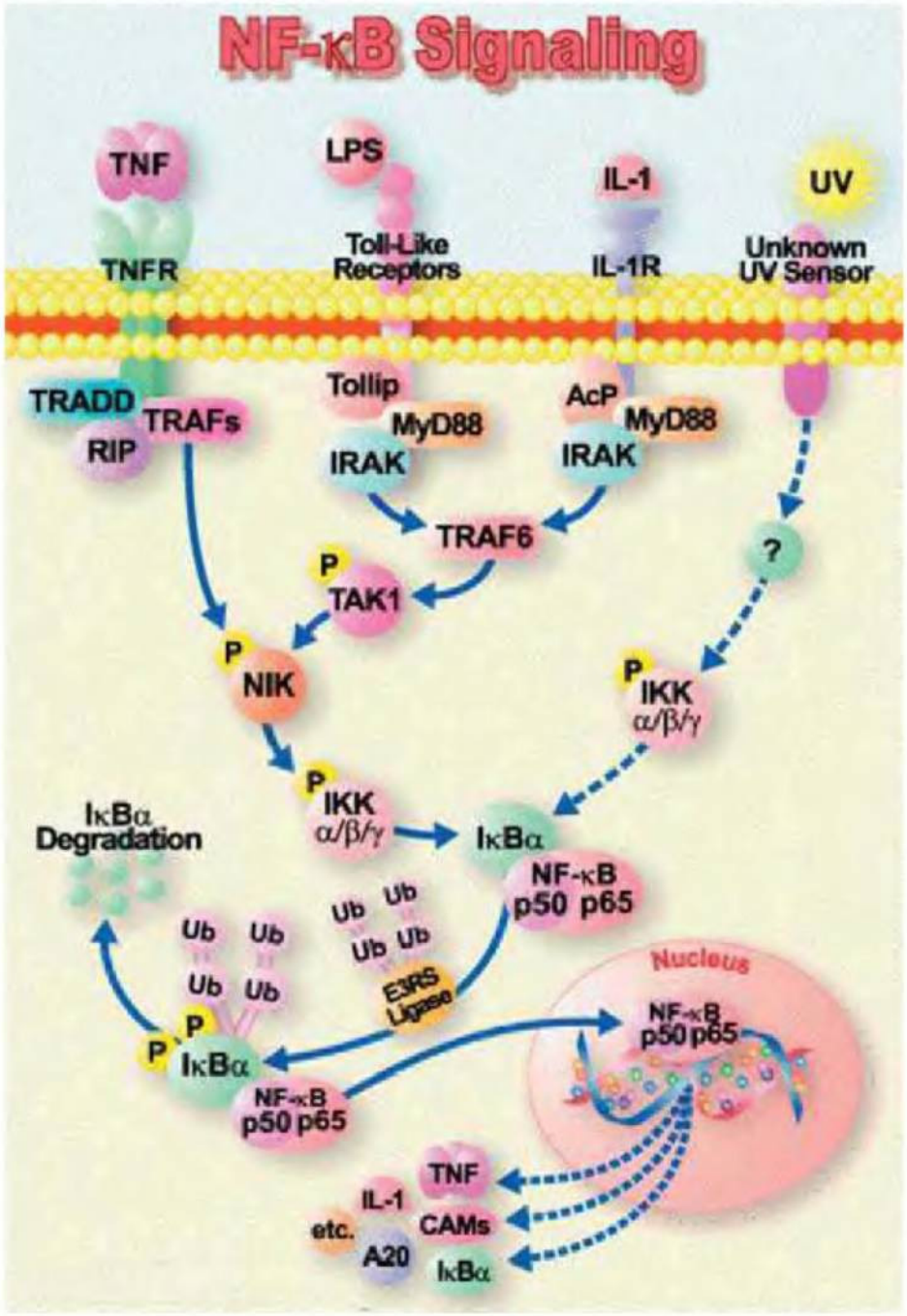

Fig. 1. The proinflammatory signal transduction pathway. ACP, accessory membrane-spanning protein; IKKα, inhibitory protein IκB kinase α; IKKβ, IκB kinase β IL-1, interleukin-1; IL-1R, IL-1 receptor; IRAK, IL-1R-activated kinase; NIK, NF-κB-inducing kinase; RIP, receptor-interacting protein; TNFR, tumor necrosis factor receptor; TRADD, TNFR and associated death-domain protein; TRAF2, TNFR-associated factor 2. (Modified from Baeuerle PA. Pro-inflammatory signaling last pieces in the NF-kappaB puzzle? *Curr Biol* 1998;8:R19, with permission.)

mortality following sepsis. Neutralization of C5a, using a monoclonal antibody, resulted in improved survival and decreased organ damage in animal models.

Alarmins

Activation of the immune system is triggered by injury or trauma without evidence of a bacterial focus. This is mediated by alarmins or PAMPs. The alarmins are released either after a nonprogrammed cell death or by cells of the immune system. Within this family of endogenous triggers are high mobility group box 1 (HMGB1), heat shock proteins (HSPs), defensins, cathelicidin, eosinophil-derived neurotoxin (EDN), and others. These structurally diverse proteins serve as endogenous mediators of innate immunity as chemoattractants and activators of antigen-presenting cells.

HMGB1 was originally identified as a chromatin-binding protein that exists ubiquitously in the nucleus of all eukaryotic cells. HMGB1 plays a critical role in stabilizing nucleosome formation and in regulating transcription; it also plays an important role in signaling following tissue damage. When present in an extracellular location, HMGB1 can activate the innate immune system and promote inflammation. It is passively released by necrotic, but not apoptotic cells as well as actively secreted by immune cells, macrophages, and NK cells upon activation with TNF. HMBG1 acts as a chemokine and is a chemoattractant for macrophages, neutrophils, and dendritic cells and causes the secretion of several proinflammatory cytokines (e.g., TNF, IL-1a, IL-1b, IL-1RA, IL-6; IL-8, MIP-1a, and MIP2b) (Figure 2).

The role of HMGB1 in multi-organ damage in severe sepsis was demonstrated in an animal model. Inhibition of HMGB1 by specific antibodies protected mice from mortality in both LPS-induced and cecal ligation and puncture-induced sepsis. Furthermore, administration of recombinant HMGB1 protein recapitulated severe sepsis by inducing lethal organ dysfunction. Several techniques have been developed to inhibit the biological activity of HMGB1 in sepsis. A protein fragment A-box, which contains the DNA-binding domain of HMGB1, competes with intact HMGB1 for binding to its cell surface receptor, and exhibited a therapeutic effect in sepsis models even when administered after the onset of the diseases. Ethyl pyruvate, a stable and nontoxic derivative of pyruvic acid, has been shown to suppress HMGB1 release from macrophages *in vitro*, reduce serum HMGB1 levels, and improve survival in sepsis models in mice.

Adaptive Immune System

Adaptive immunity constitutes the second, but more specific and efficient response to invaders. It is subdivided into cellular and humoral immunity.

Cellular Immunity

Surgical insult leads to the activation of local host responses necessary for protection against invading microorganisms and for the initiation of tissue repair. The sequence of events begins immediately after injury, with the activation of the coagulation cascade and the initiation of the inflammatory phase. Local mediators of inflammation, such as cytokines, histamine, kinins, and arachidonic acid metabolites, cause increased capillary permeability, allowing immune cell infiltration (primarily neutrophils, followed by monocyte/macrophages

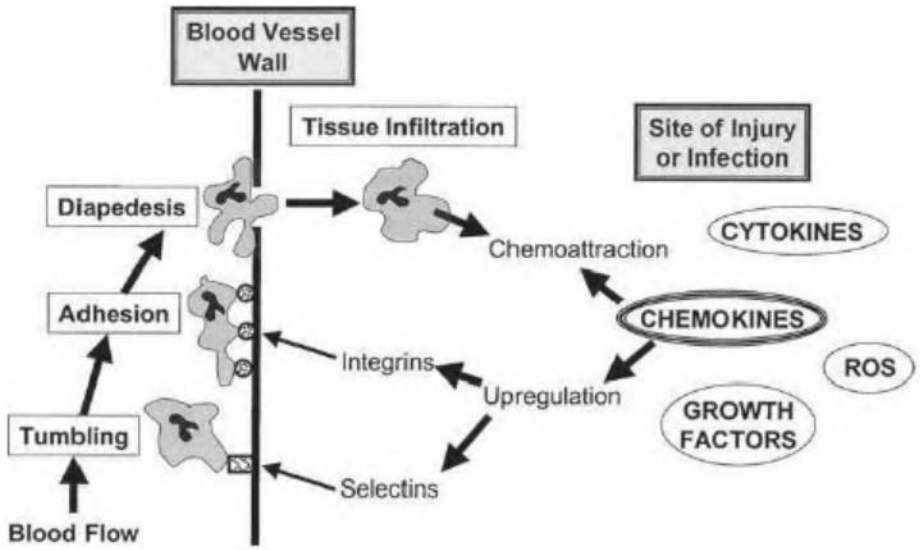

Fig. 2. Schematic of the chemokines-mediated process of polymorphonuclear leukocyte (PMN) recruitment and infiltration. Chemokines emanating from a source of injury and/or infection mediate the positively regulated expression of adhesion molecules. In this example, selectins and integrins cause tumbling and adherence, respectively, of PMNs to the endothelial lumen wall. The adherent PMN then moves through the wall by diapedesis and migrates along the chemokines gradient, eventually infiltrating in and around the focus of injury. ROS, reactive oxygen species.

infiltration). Immune cell migration is a complex process involving attachment to the endothelial cells and extravasation regulated by many substances, the most important of which are the chemokines and adhesion molecules. Most of these mediators act in a paracrine fashion and they are short-lived because of rapid metabolism. Therefore, serum measurements of these mediators may not reflect their activity in local tissues.

TLR activation causes secretion of cytokines (TNF-α and IL-1) and chemokines, especially by local macrophages. Chemokines are produced and secreted to the extracellular matrix by activated leukocytes and by various skin cells (epithelial cells, fibroblasts, and endothelial cells), and mediate cell motility. The local microcirculatory inflammatory response is reflected by a pronounced leukocyte accumulation and adherence to the endothelial lining of postcapillary and collecting venules. This response is associated with an increase in microvascular permeability, indicating the disruption of endothelial integrity.

Cytokines act on endothelial cells and induce the adhesion molecules. Leukocytes express carbohydrate ligands to bind to E and P endothelial selectins (a family of three single-chain transmembrane glucoproteins, named L, E, and P selectins), a process called "tethering." These are low-affinity interactions and the leukocytes begin to roll along to the endothelial surface due to the force of the flowing blood. Chemokine signaling on rolling leukocytes results in the modification of the structure of a family of transmembrane proteins called "integrins," allowing for firm adherence of leukocytes to the endothelial surface. Chemokines can then stimulate the extravasation and migration of the cells to the wound space.

Finally, at the time of injury, the production of pro-inflammatory cytokines and the expression of E-selectin, chemokines, and integrin ligands on endothelial cells mediate the selective recruitment of cutaneous lymphocyte antigen (CLA)-positive T-cells into the wound. There, they recognize the antigen for which their receptor is specific and become activated. The local macrophages act as antigen-presenting cells and also express the costimulatory molecules that are essential for T-cell activation. After antigen binding, T-cells differentiate preferentially into Th1 subsets, and secrete interferon-gamma (IFN-γ), the major macrophage-activating cytokine. The activated macrophages remove debris from dead cells to facilitate repair after the infection is controlled. The clearance of the debris and the infectious organisms promotes resolution of the inflammatory phase and ensuing repair responses, which include formation of granulation, reepithelialization, and neovascularization. The immune response then produces the cardinal signs of swelling, pain, erythema, and fever.

In the normal host response, these processes are mostly limited to the site of trauma; however, every substantial traumatic injury also leads to a degree of systemic inflammation. Depending on the magnitude of tissue damage, the local inflammatory process will cause washout of pro-inflammatory mediators into the systemic circulation and inflicts a systemic inflammatory process. The systemic leak of cytokines leads to further activation of immune cells, mostly polymorphonuclear leukocytes (PMN) priming, more cytokine secretion, activation of complement and the coagulation cascade, and secretion of APPs and neuroendocrine mediators. This systemic inflammation is followed by a compensatory anti-inflammatory response, creating a balance, which will have significant impact on the clinical outcome. Hence, the "right tuning" of systemic inflammation is crucial for restoration of homeostasis. Severe inflammation may lead to tissue destruction in organs not originally affected by the initial trauma by a process commonly referred to as the multiple-organ dysfunction syndrome (MODS). A lesser inflammatory response (or too much anti-inflammatory regulation) will induce a state of immunosuppression during the vulnerable time of recovery, which can result in deleterious sepsis for the host.

Cytokines

Cytokines are small proteins, secreted by systemic immune cells, macrophages, monocytes, or lymphocytes (mostly T-cells) and by diverse cell types at the site of injury. Cytokines are crucial mediators in cell immunity and inflammatory response. In healthy humans, they are produced at low constitutive levels, reaching just picograms per milliliter in plasma, and function in an endo-, para-, or autocrine manner. Cytokine receptors are expressed on the surface of the majority of human cells, and some soluble cytokine receptors are detectable in plasma at low levels. Cytokines activate intracellular signaling pathways that regulate gene transcription. Examples include NF-κB, activating protein 1 (AP-1), signal transduction- and transcription-activating factor 3 (STAT-3), and members of the CCAAT/enhancer binding protein (C/EBP) family of transcription factors, in particular C/EBP-β and δ.

The NF-κB family of transcription factors is most often studied because of its central role in the inflammatory process. Cytokines influence immune cell activity, differentiation, proliferation, and survival. These mediators also regulate the production and activity of other cytokines in a watershed manner. There is a significant overlap in bioactivity among different cytokines.

Cytokines are not antigen-specific and their effect can be stimulatory or inhibitory.

TNF, IL-1b, IL-6, IL-8, IL-12, and IFN-γ are the dominant stimulatory (or pro-inflammatory) cytokines and IL-4, IL-10, and IL-13 are considered inhibitory (or anti-inflammatory). Those compounds acting in between cells of the immune system are called interleukins, and those inducing chemotaxis of leukocytes are referred to as chemokines. Including about 50 chemokines and 30 interleukins, the number of characterized cytokines is now well in excess of 100. The number of cytokines recognized continues to grow, and a list of cytokines and their function(s), origin, target cells, and properties is provided in the Cytokine Online Pathfinder Encyclopedia (COPE) web site, created by Dr. Horst Ibelgaufts (www.copewithcytokines.de/cope.cgi).

During acute localized inflammation, connective tissue, endothelial cells, and local immune cells are first to secrete pro-inflammatory cytokines, mostly IL-1 and TNF. Cytokines may leak to the circulation and exceed the levels of soluble receptors, which results in systemic inflammation and possible development of SIRS and MODS. The monocyte/macrophage also produces the only natural and well-characterized competitive cytokine antagonist, IL-1 receptor antagonist (IL-1ra), as well as liberates soluble forms of TNF and IL-1 receptors (IL-1RI) that are able to bind and neutralize TNF and IL-1, respectively. The t½ of circulating unbound cytokines can vary from <5 minutes to a few hours.

Interleukins

One of the best-described pro-inflammatory cytokines, TNF (previously known as cachectin) is mainly produced by macrophages and monocytes, and by T-cells, endothelial cells, fibroblasts, and adipose tissues. TNF is among the early cytokines secreted after trauma with a t½ < 20 minutes. TNF acts through its receptors TNFR1 and TNFR2.

TNF, through TNF-R1, activates the caspase cascade and induces cell apoptosis, as well as induction of transcription factors (e.g., NF-κB) and activation of the mitogen-activated protein kinase (MAPK) pathways both involved in cell proliferation, transcription of inflammatory genes, and anti-apoptosis. Binding of TNF to TNFR2 leads to activation and proliferation of immune cells. TNF induces secretion of a variety of pro- and anti-inflammatory cytokines (e.g., IL-6, IL-8, IFN-γ, and IL-10), increases synthesis of nitric oxide , activates the arachidonic acid pathway and induces activation of cyclooxygenase and lipoxygenase enzymes. This leads to the production of thromboxane A2 and prostaglandins E2, which have multiple physiological effects, including increased permeability of endothelial cells. It also induces the production of adhesion molecules, such as selectins, platelet-activating factors, and intracellular adhesion molecules (ICAM). In addition, TNF increases the pro-coagulated activity of endothelial cells.

The local effects of TNF can be physiologic, but the systemic effects often lead to adverse outcomes. TNF has been identified as a principal mediator in septic shock. In the central nervous system (CNS), TNF stimulates the release of corticotropin-releasing hormone (CRH), induces fever, and reduces appetite. In the liver, it stimulates production and secretion of APPs, and also causes insulin resistance. Inhibition of TNF by either anti-TNF antibodies or soluble receptors for TNF has become a strategy in the treatment of patients with chronic inflammatory diseases, but this strategy does not work in septic patients.

IL-1 was first described as endogenous pyrogen over a half century ago, because it caused fever when injected into rabbits. After being secreted by monocytes, macrophages, or endothelial cells, it has a t½ of only 6 minutes. The two forms, IL-1α and IL-1β, are regulated by different antigens, but both bind to the same IL-1RI. Binding to this receptor activates a signaling cascade that is shared also with IL-18 and TLRs.The IL-1 is a potent pyrogen, which influences the hypothalamus to reset the temperature of the body and induces fever. It is associated with local hyperalgesia. IL-1 has similar effects to TNF on the immune system following trauma. In fact, TNF and IL-1 are often described as synergistically acting mediators.

Similar to other cytokines, IL-6 is produced by a variety of cell types. It is detectable within an hour of trauma, and peaks at 4–48 hours following surgery. The secretion of IL-6 is induced by TNF and IL-1. IL-6 induces a proliferation and differentiation of B- and T-lymphocytes, activates NK cells and neutrophils, and inhibits its apoptosis. IL-6 regulates the hepatic synthesis of APP, such as C-reactive protein (CRP), fibrinogen, complement factors, α-2 macroglobulin, α1-antitrypsin, and others. IL-6 also induces the release of soluble TNF-R and IL-I receptor antagonist, and therefore plays a dual role in the inflammatory response by acting as both a pro-inflammatory and an anti-inflammatory mediator. IL-6 has a longer t½ than TNF or IL-1, which makes it easier to monitor, and seem to correlate with the magnitude of trauma. For example, despite similar procedure times, there is a greater degree of IL-6 elevation after abdominal aortic and colorectal surgery than after hip replacement; there are lower IL-6 levels after laparoscopic than after open procedures, including cholecystectomy and small-bowel and colonic resections. It has been shown in murine models that IL-6 is an important mediator of inflammation, and blocking IL-6 increases survival. Furthermore, IL-6 is regarded as a prognostic marker of trauma patients with SIRS, sepsis, or MODS and as such has been used in the intensive care unit (ICU) setting as an indicator for the severity of the inflammatory responses that is relatively independent of bacterial infections.

Chemokines

Overall, 18 chemokine receptors and 43 chemokines have been described, demonstrating a sharing of receptors. Chemokines acts as attractants to almost all blood cell types of the innate and adaptive immune response. In lower doses, chemokines act mostly as chemoattractants, while in increased concentrations they can lead to cell activation, including cytotoxicity and even respiratory burst. Their receptors have also been detected in endothelial cells, keratinocytes, and fibroblasts, suggesting that some chemokines also contribute to the regulation of epithelialization, angiogenesis, and tissue remodeling. The chemokine receptors belong to the family of G-protein-coupled receptors, and binding to these receptors leads to effects, including both chemotaxis and activation.

IL-8 is a typical chemotactic cytokine and its secretion is induced by IL-1, TNF-α, C5a, microbes and their products, hypoxia, hyperoxia, and reperfusion. Interferons attenuate the expression of IL-8. It can be produced in an early state of inflammation following trauma and can persist over a long period of time, even weeks. It has the ability to act as potent angiogenic factor, as a potent chemoattractant, and as an activator of immune cells. IL-8 signaling also induces the shedding of L-selectin from the neutrophil cell surface, and together with TNF-α and IL-6 is responsible for the regulation of adhesion molecules on endothelial cells. It is not the concentration of IL-8, itself, but the development of a concentration gradient that directs the cellular recruitment to the site of inflammation. There is also evidence that IL-8 can protect neutrophils against apoptosis, which could be one reason for prolongation of the inflammatory response at the site of injury or infection. It has also been shown that IL-8 plays an important role in the development of the ARDS.

Recently, a group of so-called silent chemokine receptors has gained more attention. These receptors can bind chemokines,

but do not evoke chemokine-related cell responses, suggesting a role as decoy or scavenger receptors. One member of this family is the decoy receptor D6. D6 binds most inflammatory chemokines, except IL-8, and is now known to be important in limiting the inflammatory response in different animal models, allowing degradation of chemokines. Another important member is the Duffy Antigen Receptor for Chemokines (DARC). DARC, first described as a blood group antigen, is also expressed by red blood cells and endothelial cells. It binds angiogenic chemokines, including IL-8. While D6 eliminates the cellular response to chemokines, the DARC receptor seems to act more to differentiate this response, and chemokines retain their biological activity after binding to this receptor. DARC on red blood cells seems to capture chemokines and is, therefore, supposed to prevent leukocyte activation in the systemic circulation. On the other hand, DARC on endothelial cells is required for leukocyte recruitment.

Cytokines Post-elective Surgery

Elective surgery followed by an uneventful clinical course may induce only minor systemic inflammatory changes. As one could expect, the acute-phase response, post-elective surgery, is proportional to the surgery-related tissue trauma or to the severity of the procedures. Virtually, all mediators of inflammation (cellular, cytokines, and APPs) peak post-injury at about day 1 to 2 and then return to baseline levels by post-injury days 6 to 7. Persistent postoperative pain, stress, or a second insult will change that pattern.

THE NEURO-IMMUNE AXIS

The systemic and even local inflammatory responses posttrauma are regulated by the nervous system. Considerable attention has been given to the effectiveness of parasympathetic nerve stimulation in suppressing the magnitude of the proinflammatory response, leading to coining of the term "inflammatory reflex." Like other reflex arcs, the inflammatory reflex is comprised of a sensory afferent arm and an efferent motor arm.

Afferent/Sensory Input to the Brain

During stress, afferent signals from the injury site can reach the CNS through two main routes: the neural route, mostly by afferent vagal fibers, and through blood-borne inflammatory mediators.

Neural Route

The neural afferents present a rapid means to activate the CNS; the mechanism of their activation remains unclear. Various investigators demonstrated the effects of complement (C5a) fragments, PGE_2, coagulation factors (Factor XII), kinins (bradykinin), and cytokines (TNF, IL-1, and IL-6). Increasing evidence has suggested that vagal pathways are utilized as the communication link between the peritoneal cavity and the CNS, especially during episodes of intraabdominal infection. It has been shown that many CNS effects induced by intraperitoneal administration of LPS or IL-1 (fever, increased elaboration of adrenocorticotrophic hormone [ACTH]) can be blocked or attenuated by subdiaphragmatic vagotomy. This sensory arm can be activated by the presence of IL-1 in peripheral tissues. Specific IL-1 binding sites have been revealed on glomus cells adjacent to the vagus nerve. IL-1 binding and an intact vagus nerve are both required for the development of fever following intraperitoneal administration of low quantities of IL-1.

Humoral Route

Cytokines are lipophobic molecules and do not have ready access to the CNS, since the blood brain barrier (BBB) excludes entry of such proteins. An exception is in regions where the BBB is not well formed, such as around the circumventricular organs (CVOs), the meninges and the choroid plexus. There may be active transport into specific regions of the brain of circulating cytokines by the vascular endothelium. Alternatively, cytokines may damage the integrity of the vascular endothelium that forms the BBB, enter the brain, and stimulate central neural circuits. Several factors have been implicated, most notably IL-1 and IL-6. Prostaglandins, mostly PGE_2, locally produced in the hypothalamus in reaction to cytokines, play a crucial role in inducing pyrexic reaction, as known for many years from the ability of cyclooxygenase inhibitors to prevent fever.

Efferent Regulation

Following integration of afferent signals the CNS has two major effector/efferent arms that are used to regulate physiologic responses. The first is the activation of the hypothalamus-pituitary-adrenal (HPA) axis, and the second is the direct activation of the sympathetic system while suppressing the other parasympathetic "half" of the autonomic nervous system. The CNS regulates the "level of ongoing inflammation" through multiple pathways, both pro- and anti-inflammatory. The anti-inflammatory effect was studied more thoroughly. The inflammatory opposing response suppresses the immune system through at least two main routes: by increasing corticosteroid hormone levels (activation of the HPA axis) and by activation of the cholinergic anti-inflammatory pathway. Evidence exists that hormones and cytokines interact at several levels. For example, TNF-α, IL-1, and IL-6 stimulate the HPA axis resulting in the release of ACTH and glucocorticoids (Figure 3). IL-1 also has a direct enhancing effect on the adrenals. The glucocorticoids secreted down-regulate cytokine release from macrophages in a negative feedback mechanism. The negative feedback between glucocorticoids and cytokines is one of the main mechanisms protecting the organism from the possible damage from over inflammation.

Reduced triiodothyronine (T_3) levels after treatment with TNF-α or IL-1 demonstrate another link between hormones and cytokines. Hormones can also influence each other, as catecholamines increase cellular uptake of T_3. The "low T_3 syndrome" in sepsis and following trauma may be due to a combination of cytokine and catecholamine effects. The complex interactions among different mediators may explain, at least in part, why treatment directed against individual mediators following trauma or sepsis has not been successful.

Immunosuppression Following Trauma

More and more evidence is emerging that the neurologic system plays a major role in the coordination of inflammatory and anti-inflammatory immune response. While minor surgery is suggested to stimulate components of the immune system, it is generally agreed that after the acute-phase response, major surgery, and to a higher extent, major trauma cause immunosuppression that may render the host anergic to opportunistic infections. The initial response to surgical trauma is characterized by activation of the specific and nonspecific immune system's release of pro-inflammatory cytokines (TNF, IL-1β, IL-6, IL-18, and HMGB1 and more), neutrophil activation, microvascular adherence, as well as PMN and macrophage oxidative burst, but this rapidly gives way to a state of depressed immune function.

The production of immunoglobulins fall and many patients become anergic as assessed by delayed hypersensitivity skin testing. Defects in neutrophil chemotaxis, phagocytosis, and lysosomal enzyme content and respiratory burst have all been reported. This condition is referred to as a compensatory anti-inflammatory response syndrome; it is induced by multiple mediators and affects all subtypes of immunity. The counter anti-inflammatory mechanism is as complex and multi-factorial as the pro-inflammatory one. It includes cytokines

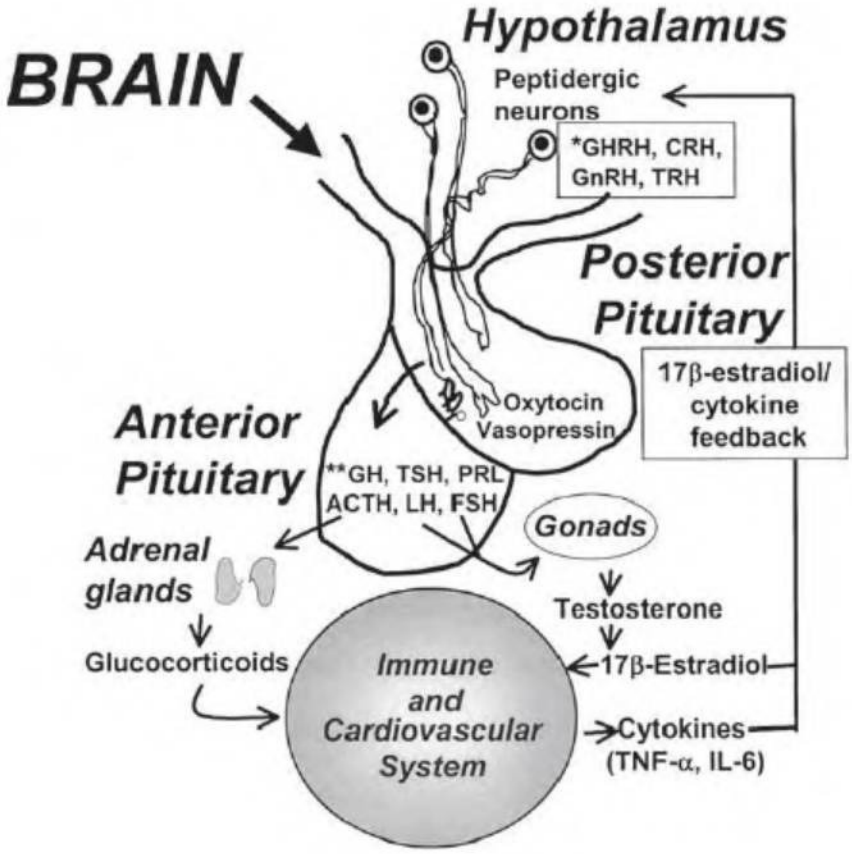

Fig. 3. Relationship between the hypothalamus–pituitary–gonad-adrenal (HPA) axis and the immune system in physiological responses to injury. The HPA is a neuroendocrine system that also has bidirectional communication with the immune system in homeostasis and in times of injury, giving the brain a major role in regulating endocrine and immune functions. The hormonal responses are apparent at three levels: the hypothalamus, the pituitary, and the adrenals. It can be seen that organs are coupled with one another (functioning as a biologic oscillators), with the coupling being mediated by neural, hormonal, and cytokine networks. Notably, cytokines and sex hormones are closely coupled in a counterregulatory fashion, which sheds light on the beneficial effects of sex hormones, especially β-estradiol, in responses to injury.

such as IL-10, TGF-β, TNF-binding protein, and hormones such as corticosteroids, adrenaline, and α-melanocyte stimulating hormone (α-MSH). These act in concert with local effectors, such as PGE_2, HSPs, and APPs. These factors interact to inhibit macrophage activation and down regulate the synthesis of pro-inflammatory cytokines.

The Cholinergic Anti-inflammatory Pathway

The activation of the cholinergic pathway leads to acetylcholine release in the reticuloendothelial system that includes the spleen, liver, lymphoid tissue, and GI tract. Acetylcholine binds to an α7 subunit of the nicotinic acetylcholine receptor, expressed on tissue macrophages, to inhibit the release of pro-inflammatory (TNF, IL-1β, IL-6, and IL-18), but not the anti-inflammatory cytokine IL-10. In macrophages, signaling through α7 attenuates TNF production through a mechanism dependent upon inhibition of NF-κB nuclear translocation and activation of Jak-STAT pathways. Direct electrical stimulation of the peripheral vagus nerve *in vivo* during lethal endotoxemia in rats inhibited TNF synthesis in liver, attenuated peak serum TNF amounts, and prevented the development of shock. Several reports have confirmed that the activation of this pathway, either by electrical stimulation of the vagus nerve or by administration of α7 selective drugs, is effective in ameliorating inflammation and improving survival in a number of experimental models, such as sepsis, hemorrhagic shock, pancreatitis, and postoperative ileus.

IL-6, As an Immunosuppressor

The massive and continuous IL-6 release accounts for the up-regulation of major anti-inflammatory mediators, such as glucocorticoids, PGE_2, IL-10, and TGFβ. IL-6 stimulates the macrophage expression of anti-inflammatory mediators, such as IL-1RI antagonist and soluble TNF receptors. These bind to the pro-inflammatory cytokines TNFα and IL-1β and truncate the inflammatory response.

Cell-Mediated Immune Dysfunction

Cellular immuno-incompetence (also called "immune paralysis") is induced by elevated PGE_2, IL-10, and other anti-inflammatory mediators, mainly caused by the deactivation of monocytes. The central role of IL-10 and TGFβ in inducing monocyte "immune paralysis" is demonstrated by the up-regulation of HLA-DR expression on monocytes following the application of an IL-10 neutralizing antibody and the restoration of macrophage antigen presentation by using TGF-β neutralizing antibodies.

Lymphocyte Dysfunction

Major surgical interventions are associated with a significant decrease in total systemic lymphocyte counts, including both $CD4^+$ and $CD8^+$ cells. This lymphocyte depression correlates with the duration of the surgical procedure and the volume of blood loss, however, is not associated with the extent of the trauma, the age of the patient, or the type of intensive care intervention. These events are accompanied (within 24 h) with elevated IL-10 and increased frequency of apoptosis of $CD4^+$ and $CD8^+$ cells accompanied by marked down-regulation of anti-apoptotic factors such as Bcl-2. The impact of this immune dysfunction was underscored by the fact that the rate of apoptotic $CD8^+$ cells significantly correlated with the manifestation of infectious complications during the postoperative course.

A considerable number of studies have shown that modulation of T-helper lymphocytes (Th cells) is also involved in the development of immune suppression following surgical trauma. The cells can be subdivided into two functionally distinct subsets: Th1 and Th2, according to individual functional parameters. Th1 cells may support an inflammatory response by producing IL-2, IL-12, and IFN-γ, while Th2 cells act as anti-inflammatory agents by secreting IL-4, IL-5, IL-6, IL-10, and IL-13. Major trauma is associated with a shift of the Th1/Th2 balance toward a Th2 response. Lymphocyte dysfunction may present as a complete lack of response to external stimuli, that is, anergy.

The Second Hit Phenomenon

The so-called two-hit model of inflammatory insult has become a commonly accepted paradigm. It takes place in many common scenarios in which the patient has to undergo a surgical procedure following initial trauma or suffers further insults due to a complication. The second hit may be

sterile- (operation after trauma) or pathogen-induced infection post-surgery.

Although influenced by many factors, the inflammatory and metabolic response is relatively predictable. The immune reaction to further insults is not as consistent. Variations in the competence of innate and adaptive immune defenses become evident; there is an innate immune tolerance and diminished adaptive immune capacity of response to a new antigen. On the other hand, the recurrent immunological activation causes a persistent systemic pro-inflammatory activity that may lead to SIRS and MOF. The persistent inflammation could take place only in some aspects of immunity and not in others. An example of this is the, continuation of coagulation system activation, even while other pro-inflammatory activity is waning. Not infrequently, a prolonged stress state manifests diminishing amplitude, frequency, and efficiency of autonomic and neuroendocrine signaling. Disturbances in circadian rhythmicity of neuroendocrine hormone secretion are also observed during prolonged inflammatory illness. The attenuated hormone rhythmicity and signal amplitude may contribute to disordered metabolic and immune functions.

Systemic Inflammatory Response Syndrome and Multiple Organ Dysfunction Syndrome

Cytokine-mediated inflammation is usually short-lived and is resolved. In some cases, however, cytokine production can become excessive, and rather than resolving, inflammation persists or even spreads, causing damage in adjacent tissues. This hypermetabolic response, often called the SIRS, encompasses excessive whole body inflammation and is considered a major determinant in the development of multiple organ dysfunctions (MODs), often with a lethal result. The pathophysiology of SIRS and MODS is explored in Chapter 8.

Endocrine Response

Role of the Central Nervous System

The CNS response consists primarily of three parallel, coordinated effects: fever, HPA axis activation, and sickness behavior (such as anorexia or somnolence). Following integration of afferent signals, the hypothalamus has two major effector arms that are used to regulate physiological responses. The first is the activation of the HPA axis and the second is the direct activation of the sympathetic system, while suppressing the other parasympathetic "half" of the autonomic nervous system. At rest, the hypothalamus secretes, in a pulsing manner, CRH, thyrotrotropin-releasing hormone (TRH), gonadotropin-releasing hormone (GnRH), growth hormone-relapsing hormone (GHRH), and dopamine. During stress, the afferent signals from the injury site reach the hypothalamus through the neural route (impulses are transferred from the cephalad to the ventral-posterior nucleus of the thalamus) mostly by afferent vagal fibers or through blood-borne inflammatory mediators. Humoral mediators reach the hypothalamic-hypophysial portal capillaries in the median eminence through the anterior hypophyseal arteries. The cytokines can diffuse into the portal capillaries, areas that are free from the BBB.

Endogenous Opioids (Endorphins)

Many of the mediators released during inflammation of peripheral tissue are known to elicit pain by activation of specialized primary afferent neurons called "nociceptors" (defined as "neurons preferentially sensitive to a noxious stimulus or to a stimulus which would become noxious if prolonged"). Nociceptor stimuli propagate through the dorsal horn of the spinal cord to the supraspinal sites where a sensation of pain is eventually elicited. Various opioid peptides, such as β-endorphin, met-enkephalin, dynorphin, and endomorphins are produced and secreted by the hypophysis, hypothalamus, and, as demonstrated most recently, locally by leukocytes. Opioid peptides can bind to opioid receptors. The most studied opioid receptor groups are μ, κ, and δ. These receptors are part of the G-protein-coupled receptors, which are synthesized in dorsal root ganglia and are transported intraaxonally. The opioid receptors are represented in the brain, spinal cord, sensory peripheral nerve endings, and in the intestinal tract. Agonist binding elicits potent analgesia, a quality often used to treat pain, with induction of external opioids.

The balanced activation of sympathetic and parasympathetic pathways, as well as HPA axis, in response to injury is crucial in dynamic regulation of a host's defense mechanisms. The endorphins are part of the counterregulatory system activated in a state of shock. The opioids enhance the parasympathetic tone, balancing the increased sympathetic drive. A meta-analysis review of the literature concerning the use of opioid antagonist (Naloxone) in clinical setup indicates that opiate antagonist treatment does improve mean arterial blood pressure in shock patients. The mechanism involved in mediating the salutary effects of opiate antagonists has not been completely elucidated.

Immune cells carry all three opioid receptors. Opioids have been shown to modulate a number of aspects of the immune response, including antibody responses *in vitro* and *in vivo*, phagocytic cell function, NK-cell activity, chemokine-induced chemotaxis, the development and function of T-cells in the thymus, and cytokine and cytokine receptor expression. Opiate-mediated immune effects have been postulated to result from either direct interaction with opioid receptors on cells of the immune system or indirectly through the activation of opioid receptors within the CNS, and the resulting modulation of HPA axis (cortisol) and the sympathetic nerve system activities. Although alternations in various aspects of immune function in patients exposed to opioid treatment were demonstrated in clinical practice (post-elective abdominal surgery, orthopedic surgery, and in healthy volunteers), there are no actual prospective clinical studies exploring the possible interaction between exposure to opiates and rates of infection.

Hormonal Changes During Acute and Chronic Surgical Illness

There is a biphasic neuroendocrine response to critical illness. The acute phase is characterized by an actively secreting pituitary; whereas, in prolonged critical illness, there is a hypothalamic suppression of the neuroendocrine axes.

Glucocorticosteroids

In a stress-free healthy human, cortisol is secreted from the zona fasciculata of the adrenal cortex, according to a diurnal pattern. Cortisol release is controlled by ACTH produced by the pituitary, in turn under the influence of the hypothalamic CRH. Cortisol itself exerts negative-feedback control on both hormones. Approximately 10% cortisol is found free in the plasma. Of the remainder, 20% is bound to albumin, and 70% is bound to cortisol-binding globulin. Only the free hormone, however, is biologically active. Glucocorticoids exert their effects by binding to and activating an intracellular receptor protein. The cortisol–glucocorticoid receptor complex moves to the nucleus where it binds as a homodimer to DNA sequences located in the promoter regions of target genes. In addition, the cortisol–glucocorticoid receptor complex may affect cellular function indirectly by binding to and modulating the transcriptional activity of other nuclear transcription factors, such as NF-κB.

Cortisol During Stress

Cortisol levels usually rise in the early phase of critical illness. The excited neurons in the hypothalamus release CRH and arginine vasopressin (AVP) from their terminals

into the capillaries of the hypothalamo-hypophysial portal system. CRH and AVP act on CRH-1 and vasopressin-1β receptors on the anterior pituitary to stimulate ACTH secretion. Plasma ACTH levels rise directly due to increased secretion and due to resistance to or inhibition of the negative-feedback mechanism exerted by cortisol. Several of the elevated cytokines have been shown to modulate cortisol production, either by directly affecting the hypothalamus/pituitary (IL-1α, IL-1β, IL-6, and TNF-α) or by direct stimulation of the adrenal cortex (IL-1α, IL-1β, and IL-6). Cytokines can also influence glucocorticoid receptor numbers and affinity. During severe illness, corticosteroid-binding globulin levels are decreased, resulting in proportionate increases in the free hormone. The diurnal variation in cortisol secretion is lost in response to any type of acute illness or trauma. An appropriate activation of the HPA axis and cortisol in response to critical illness is essential for survival. The adrenal gland does not store cortisol; therefore, increased secretion arises due to increased synthesis of cortisol from its principal precursor, cholesterol.

Cortisol Influence on Post-trauma Physiology

The stress-induced hypercortisolism fosters the acute provision of energy. Glucocorticoids increase blood glucose concentrations by increasing the rate of hepatic gluconeogenesis and inhibiting adipose tissue glucose uptake. Hepatic gluconeogenesis is stimulated by increasing the activities of phosphoenolpyruvate carboxykinase and glucose-6-phosphatase as a result of binding of glucocorticoids to the glucocorticoid response elements of the genes for these enzymes. Glucocorticoids also stimulate free fatty acid release from adipose tissue and amino acid release from body proteins. Major roles of these processes are to supply energy and substrate to the cell, which are required for the response to stress and repair to injury.

The rise in glucocorticoids also protects against excessive inflammation. The rise in glucocorticoids during acute illness plays a crucial role in preventing hazardous overstimulation of the immune system, including lymphocytes, NK cells, monocytes, macrophages, eosinophils, neutrophils, mast cells, and basophils. Glucocorticoids decrease the accumulation and function of most of these cells at inflammatory sites. Most of the suppressive effects of glucocorticoids on immune and inflammatory reactions appear to be a consequence of the modulation of production or activity of cytokines, chemokines, eicosanoids, complement activation, and other inflammatory mediators. Glucocorticoids control mediator production predominantly through inhibition of transcription factors, such as NF-κB. Glucocorticoids also produce anti-inflammatory effects by enhancing release of factors, such as IL-1RI antagonist, soluble TNF receptor, and IL-10. Glucocorticoids also block the transcription of messenger RNA for enzymes required for the synthesis of some mediators (cyclooxygenase-2 and iNOS).

A rise in glucocorticoid concentrations plays an important role in improving hemodynamic levels, by inducing fluid and sodium kidney retention. Glucocorticoids are also required for the needed increased sensitivity of the cardiovascular system to vasoconstrictors. The reactivity to angiotensin II, epinephrine (Epi), and norepinephrine (Norepi) contributes to the maintenance of cardiac contractility, vascular tone, and blood pressure. These effects are mediated partly by the increased transcription and expression of the receptors for these hormones. Glucocorticoids are required for the synthesis of Na+, K+-ATPase, and catecholamines. The effects of glucocorticoids on synthesis of catecholamines and catecholamine receptors are partially responsible for the positive inotropic effects of these hormones. Glucocorticoids also decrease the production of nitric oxide, a major vasorelaxant and modulator of vascular permeability.

During surgical procedures, such as laparotomy, serum corticotropin and cortisol rise rapidly, peaking in the immediate postoperative period. The magnitude of the postoperative increase in serum cortisol concentration is correlated with the extent of the surgery. From a normal secretion rate of 10 mg/day, cortisol production rate increases to 75 to 150 mg/day following major surgery and can reach to 250 to 300 mg/day in severe stress. Unless there is a repeated insult, such as sepsis, the glucocorticoid concentrations decline to baseline levels over the next 72 hours. This decline can often be noticed clinically as increased diuresis, improved glucose control, and, occasionally, increased pain. In critical illness, the kinetics of the response differ from those mentioned above: pain, fever, hypovolemia, hypotension, and tissue damage all result in a sustained increase in corticotropin and cortisol secretion and a loss of the normal diurnal variation in these hormones. During severe illness, serum cortisol concentrations tend to be higher than even in patients undergoing major surgery (~30 μg/dL vs. 40–50 μg/dL).

Adrenal Insufficiency

Critical illness is associated with activation of the HPA axis; however, many factors can impair the integrity of the HPA axis, such as blunt normal response leading to either transient or, rarely, permanent adrenal insufficiency. This scenario can lead to a potentially lethal condition. Refractory hypotension is the most common aspect of acute adrenal insufficiency. Adrenal insufficiency should be suspected in any critically ill patient who has persistent hypotension and hemodynamic instability that persists despite adequate fluid resuscitation and/or requires vasopressor support. Other nonspecific signs can include multiple organ dysfunction, otherwise unexplained hypoglycemia, hyponatremia, hyperkalemiametabolicacidosis,eosinophilia, hyperdynamic circulation, and other pituitary deficiencies (gonadotropin, thyroid, and diabetes insipidus). Recently, much attention had been focused on the so-called relative or functional adrenal insufficiency of critical illness, a condition defined as subnormal adrenal corticosteroid production in the absence of any structural defects of the HPA axis. The explanation for the development of this condition is hypothetical exhaustion of the secretory adrenocortical reserve as a result of ongoing near-maximal stimulation. Other contributing factors may include the suppression of cortisol and ACTH production by circulating cytokines and other inflammatory mediators, as well as the development of target tissue resistance to glucocorticoids and/or adrenal cortex resistance to ACTH action. Currently, the clinical significance of this condition is not clear and was only demonstrated in a setup of septic shock. Although corticosteroid replacement therapy might also be beneficial to patients who have other critical illnesses in which there is evidence of relative hypoadrenalism, no high-quality data from large randomized studies is available.

As mentioned earlier, there is no clear or current threshold definition for physiological "normal" and low cortisol plasma concentration during critical illness. Since about 90% to 95% of plasma cortisol is bound to protein, the routine decrease in cortisol-binding protein and albumin following critical illness makes it difficult to calculate and interpret the meaning of total cortisol concentration. While the plasma proteins are low and there is a peripheral increased resistance to cortisol, as often happens in critical illness, the free cortisol levels are not a reliable reflection of either total cortisol secretion or action. Many thresholds, below which adrenal insufficiency is likely to be present, have been suggested, ranging widely from 10 to 34 μg/dL. Many textbooks and published articles state that the normal circulating cortisol

response to stress is a level >18 to 20 μg/dL. However, the choice of 18 to 20 μg/dL is based primarily on the response to exogenous high-dose ACTH stimulation and the response to insulin-induced hypoglycemia in nonstressed patients.

The high-dose (250 μg) ACTH stimulation test, instead of random cortisol levels, is traditionally used in ICU setup and is regarded as the "gold standard" for adrenal testing. One should be aware, however, that although this test can be informative as it relates to adrenal ability to react to excessive ACTH (cortical reserve), it does not reflect the integrity of the entire hypothalamic pituitary adrenal axis. As a result, it may not be able to properly diagnose secondary adrenal insufficiency. A low-dose (1 μg) cosyntropin stimulation test has been used to a small extent to diagnose secondary insufficiency in ICU setup. Other methods that have been suggested include calculated free cortisol index, measuring salivary cortisol, or measuring other ACTH-dependent adrenal steroids (DHEA, DHEAS). None have yet become the gold standard in the clinical setup. The Surviving Sepsis guidelines currently endorse the use of corticosteroids (200 mg of hydrocortisone/day in divided doses) in patients who have refractory septic shock. Although a reasonable recommendation, the authors would point out that this is essentially based on a single study from a single center that has not yet been confirmed adequately.

Vasopressin

Vasopressin, also known as ADH, is synthesized as a large prohormone in the hypothalamus. The prohormone complex is transported to the posterior pituitary where it is stored in granules. Vasopressin is released mainly in response to hyperosmolality, hypotension, and hypovolemia, and has vasopressor and antidiuretic effects. Vasopressin levels increase rapidly in the early phase of certain stressful situations, such as hemorrhagic and septic shock. With persistence of the septic shock state, however, vasopressin falls to very low levels.

Thyroid

TRH secreted by the hypothalamus stimulates the pituitary to produce thyrotropin (TSH), which, in turn, regulates the synthesis and secretion of thyroid hormones in the thyroid gland. The thyroid hormones, in turn, exert feedback control on both TRH and TSH secretions. The early response of the thyroid axis to a severe physical stress consists of a rapid decline in the circulating levels of T3 and a rise in rT3 levels, predominantly as a consequence of altered peripheral conversion of T4 to T3, a reaction that is catalyzed by 5′ monodeiodinase (or type 1 deiodinase) located in the kidney, the liver, and the muscle. TSH and T4 levels are elevated very briefly and subsequently return to "normal," although in more severe illness, T4 levels can be decreased .The low T3 levels persist beyond TSH normalization, a condition referred to as "the low T3 syndrome." The severity of illness is reflected in the degree of the fall in serum T3 during the first 24 hours after the insult. Furthermore, an inverse correlation between T3 levels and mortality has been demonstrated. Other factors involved in the low-T3 syndrome at the tissue level include low concentrations of thyroid hormone-binding proteins, and inhibition of hormone binding, transport, and metabolism by elevated levels of glucocorticoids, FFA, and some commonly used medications (amiodarone, iodine contrast). It remains controversial whether development of the aforementioned changes in thyroid metabolism reflects a protective mechanism (attempt to reduce the elevated energy expenditure), or a maladaptive process during illness.

In prolonged critical illness, a state of euthyroid sick syndrome is usually present, in which the pulsatile TSH secretion is dramatically reduced and serum levels of both T4 and T3 are low. Reduced *TRH* gene expression in the hypothalamus has been observed in chronically ill patients who died, which is in line with the predominantly central origin of the suppressed thyroid axis. Since the presence of euthyroid sick syndrome is associated with an increased mortality among critically ill patients, it could indicate an aberration that may delay recovery from acute illness and, therefore, would require intervention. To date, however, a routine thyroid hormone therapy has not been demonstrated to improve clinical outcomes in critically ill patients with normal previous thyroid function. If hypothyroidism is suspected clinically (hypothermia, bradycardia, respiratory acidosis, pleural effusions, and failure to wean), thyroid function should be measured and corrected. In a critically ill patient with hypothyroidism, central hypothyroidism should be ruled out.

Growth Hormone

The regulation of the physiological pulsatile release of GH by the somatotrope cells in the anterior pituitary is highly complex. Hypothalamic GHRH stimulates, while somatostatin inhibits the secretion of GH. But many other stimulating (ghrelin, androgens, estrogen, hypoglycemia, sleep, fasting, and exercise) and inhibiting (circulating GH and IGF-I, hyperglycemia, and glucocorticoids) factors have been identified. GH exerts both direct and indirect effects. It directly promotes muscle mass increase through sarcomere hyperplasia, lipolysis, protein synthesis, and liver gluconeogenesis. The indirect effects are mediated by increases in IGF-I. IGF-I bioactivity is regulated by several IGF-binding proteins and it has growth stimulation effects on a wide variety of tissues. The pulsatile nature of GH secretion consists of peak serum GH levels alternating with virtually undetectable troughs. During the first hours to days after an acute insult, the GH profile changes dramatically. The amount of circulating GH rises, with increased pulsatile peak secretion and frequency. Concomitantly, a state of peripheral GH resistance develops, in part, triggered by cytokines such as TNFα and IL-6. These events are preceded by a drop in circulating GH-binding protein, which presumably reflects the functional GH receptor status. Theoretically, this constellation could enhance the direct lipolytic and insulin antagonizing effects of GH, resulting in elevated fatty acid and glucose levels in the circulation, whereas the indirect, IGF-I-mediated somatotropic effects of GH are attenuated. As a result, costly anabolism, largely mediated by IGF-I and considered less vital at this time, could be postponed. Hence, from a teleologic point of view, this response to acute injury within the GH axis seems appropriate in the struggle for survival.

In contrast with the observations during the acute phase of critical illness, the pulsatile release of GH is suppressed in patients who are critically ill for a prolonged time. The loss of pulsatile GH release contributes to the low levels of IGF-I in prolonged critical illness.

The administration of GH secretagogues has been shown to increase IGF-I- and GH-dependent IGF-binding protein levels. Since the robust release of GH in response to GH secretagogues excludes a possible inability of the somatotropes to synthesize GH, the origin of the relative hyposomatotropism is probably situated within the hypothalamus, through induced GHRH deficiency. The "relative hyposomatotropism" is thought to contribute to the pathogenesis of the "wasting syndrome" that characterizes prolonged critical illness. The "wasting syndrome" is believed to increase the rate of organ dysfunction, muscle weakness, prolonged mechanical ventilation, and length of stay in the ICU. Recombinant GH supplementation in surgical trauma and burn injury patients has demonstrated nitrogen retention, increased IGF-I levels, decreased length of stay, and improved survival. As a result, GH became widely used in the ICU, until two

large randomized trials in 1999 noted increased mortality associated with infection and organ dysfunction. Currently, the possible use, correct dosage, and method of administration of GH/ILG-I in critically ill patients are under investigation.

The Gonadal Axis

GnRH, secreted in a pulsatile pattern by the hypothalamus, stimulates the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the gonadotropes in the pituitary. In men, LH stimulates the production of androgens (testosterone and androstenedione) by the Leydig cells in the testes, whereas the combined action of FSH and testosterone on Sertoli cells supports spermatogenesis. In women, LH also mediates androgen production by the ovary, whereas FSH drives the aromatization of androgens to estrogens in the ovary. Sex steroids exert a negative feedback on GnRH and gonadotropin secretion.

Acute stress brings along an immediate fall in the serum levels of testosterone, even though LH levels are elevated. The enhanced release of CRH and β-endorphin suppresses GnRH release directly and indirectly through the release of glucocorticoids, which in turn also produce gonadotropin resistance at the gonads. Clinical data on the changes within the gonadal axis are scarce in critically ill women, as most patients are older and thus in the menopausal state. It seems that in the days directly following surgery, the FSH, LH, and estradiol levels decline, while the progesterone and prolactin levels do not change significantly. The state of relative hypogonadism is often expressed in premenopausal women by an unexpected metrorrhagia shortly after trauma.

With prolongation of the disease, a more substantial hypogonadotropism in both men and women ensues. The circulating levels of testosterone become extremely low and are often even undetectable; yet the mean LH concentrations and pulsatile LH release are suppressed. Total estradiol levels in women are relatively low. Since exogenous GnRH is only partially and transiently effective in correcting these abnormalities, the profound hypoandrogenism must result from combined central and peripheral defects.

Prolactin

Prolactin is synthesized and secreted by lactotrophs in the anterior pituitary gland. Prolactin levels are higher in females than in males, and the role of prolactin in male physiology is not completely understood. It is physiologically secreted in a pulsatile and diurnal pattern. Plasma concentrations of prolactin are highest during sleep and lowest during the waking hours. Prolactin release is predominantly under tonic inhibition by dopamine derived from hypothalamic dopaminergic neurons. Prolactin release is affected by a large variety of stimuli, the most important being suckling, increased levels of estrogen, and stress. Several neuropeptides have been identified as prolactin-releasing factors. These include TRH, oxytocin, vasoactive intestinal peptide (VIP), and neurotensin.

Prolactin is a well-known stress hormone and is presumed to have immune-enhancing properties. It increases the synthesis of IFN-γ and IL-2 by Th1 lymphocytes, and induces pro-inflammatory responses and antibody production. While the main physiological functions of prolactin are related to the mammary glands and the ovaries, it has been shown to also have an important role in the innate and adaptive immune response. Prolactin receptors can be found throughout immune system cells. Binding of prolactin to its receptor activates several signaling pathways, which include the Janus kinase-signal transducer and activator of transcription (Jak-Stat), the MAPK, and the phosphoinositide 3 kinase (PI3K). Activation of these cascades results in endpoints such as differentiation, proliferation, survival, and secretion.

Sympathetic Stress Response

Physiology of Sympathetic Activation

The sympathetic reaction is activated by a vast range of stressful stimuli, including both psychological and physical stressors. Afferent neurons of the sympathetic system are multiple in quantity and quality (chemoreceptors, baroreceptors, and visceral receptors). The activity of autonomic nerves is dependent on descending excitatory and inhibitory inputs from several brain regions, including the cortex and the hypothalamus. A major source of excitatory drive to sympathetic preganglionic neurons comes from the rostral ventrolateral medulla in the medulla oblongata. This region of the brain stem contains the cardiac, respiratory, and vasomotor autonomic centers, and connects the upper brain area to the spinal cord. Medullary neurons project to the spinal cord to inhibit or excite sympathetic activity. In addition, many brain stem nuclei that feed directly into these pathways can modulate these activities. In contrast to the parasympathetic nervous system with its predominantly selective innervation of single effector organs, the sympathetic system often reacts with a "massive none organ specific discharge." Increased traffic down the spinal cord via the lateral funiculi causes an increased activity in the sympathetic preganglionic nerve fibers, which results in burst-pattern release of norepinephrine from the sympathetic postganglionic nerve terminals, as well as epinephrine (about 80% of the secretion), norepinephrine, and dopamine from the adrenal gland. The secretion of norepinephrine from nerve terminals is immediate following the trigger (some of it originating from a spinal reflex arc). After secretion into the synaptic gap, norepinephrine is cleared by reuptake into the nerve endings, degradation by the catechol-*o*-methyltransferase or diffusion into the extra-synaptic space and blood. During stress, the latter mechanism is the main source of circulating norepinephrine. In view of its richness in sympathetic nerve endings, the intestinal tract is the main producer of norepinephrine (40% of total body norepinephrine) and dopamine (>50% of total body dopamine). Circulating epinephrine and norepinephrine are degraded 5 to 10 times more slowly than when secreted into the synaptic gap (20 to 30 s). Mechanisms of degradation of circulating catecholamine are nonenzymatic (extra-neural uptake in the lung, kidney, and intestines, and neural uptake into postsynaptic sympathetic nerve endings), and enzymatic (cytoplasmic monoamine-oxidase in sympathetic nerve endings, the liver, kidney, stomach, and jejunum).

Adrenal catecholamine secretion is also very rapid and it takes place within seconds of stimulation. Norepinephrine and epinephrine are stored in granules within the adrenal medulla and their exocytosis is initiated by acetylcholine stimulation from by the preganglionic sympathetic fibers that innervate the medulla. The normal resting rate of secretion by the adrenal medulla is about 0.2 μg/kg/min of epinephrine and ~0.05 μg/kg/min Norepinephrine. These quantities give rise to circulating levels of catecholamines that in basal conditions are enough to maintain the blood pressure near normal, even if all direct sympathetic pathways to the cardiovascular system are removed. During severe physical stress or sepsis, both plasma epinephrine and norepinephrine rise significantly.

Medullary epinephrine secretion is dependent not just on neural acetylcholine stimulation, but also on the hormonal HPA axis. The activity of phenylethanolamine *N*-methyltransferase (the rate-limiting enzyme in the conversion of norepinephrine to epinephrine) is enhanced by high doses of glucocorticoids. The medulla is exposed to uniquely high doses of glucocorticosteroid directly through a cortical-medullary, intra-adrenal portal vascular system.

The sympathetic system plays a crucial role in the maintenance of homeostasis during the stress response, and the changes to this system affect almost every possible body system. The cardiac output increases by β-receptor enhancement of heart rate and myocardial contractility. Blood pressure increases by α-receptor-mediated vasoconstriction, and blood flow is redistributed in favor of the more vital functions. Bronchodilatation, through the β2 influence, eases the need for increased minute ventilation. Thermoregulation is reset. The kidneys retain water and sodium, and secrete renin. Bowel motility decreases. Based on these effects, Walter Cannon called the emergency-induced discharge of the noradrenergic system the "preparation for flight or fight."

Adrenergic tone also plays a significant role in regulating intermediary metabolism in the body. Epinephrine's capacity to influence metabolism is 5 to 10 times greater than norepinephrine. Catecholamine-related hyperglycemia is induced by increased liver glucose secretion, on one side, and by decreased peripheral intake of glucose, due to insulin resistance and inhibition of insulin secretion, on the other. Catecholamines induce catabolism, leading to extensive lipolysis and protein breakdown, which are needed to supply energy for vital functions and substrates for synthesis of various enzymes, antibodies, and glucose.

Autonomic Dysfunction

The sophisticated sympathetic-parasympathetic balance is maintained by several reflex arches: arterial baroreflex, peripheral arterial chemoreflex, central arterial chemoreflex, and pulmonary stretch reflex. These reflexes represent the major components of blood pressure control and breathing regulation. Aside from massive stimulation, during critical illness, defects in the afferent and central pathways of the autonomic nervous system may develop. This condition is referred to as "autonomic dysfunction." This is seen mostly in ICU patients suffering from MODS, sepsis, severe head and brain injuries, as well as Guillain–Barré syndrome or myocardial infarction. Clinically, the heart rate, which is strongly influenced by the impact of sympathetic and parasympathetic tones, is usually the most sensitive measure of autonomic dysfunction. Autonomic dysfunction is usually expressed as restricted heart rate variability. Long recording (24 h) or short recording (5 to 20 min) recording of heart rate will show narrow heart rate variations. Autonomic nerve function could also be evaluated by baroreflex sensitivity (increased vagal and reduced sympathetic tone following sudden increase in blood pressure) and by chemoreflex sensitivity (sympathetic reaction to peripheral hypoxic or hypercapnic stimulus). It is not clear whether this phenomenon is an integral part of MODS or secondary to sedation, neuromuscular blocking agents, catecholamines, and mechanical ventilation, all frequently used in ICU setup. The reduction in physiological heart rate variability is one of the strongest predictors of death in critically ill patients.

Adverse Effects of Adrenergic Stress

It is undisputable that the adrenergic reaction is crucial to survive the insult of major trauma or injury. However, in critical illness, an overshooting influence of the sympathetic nervous system can become hazardous. This hazardous influence is exacerbated in the traditional setup of the ICU for patients requiring high-dose sympathetic support. Several organ systems may be affected. The heart seems to be most susceptible to sympathetic overstimulation: detrimental effects include impaired diastolic function, tachycardia and tachyarrhythmia, myocardial ischemia, apoptosis, and necrosis. Adverse catecholamine effects have also been observed in other organ functions, such as the lungs (pulmonary edema and elevated pulmonary arterial pressures), coagulation (hypercoagulability and thrombus formation), GI (hypoperfusion and inhibition of peristalsis), endocrinologic (decreased prolactin, thyroid, and GH secretion) immune systems (immunomodulation and stimulation of bacterial growth), metabolism (increase energy expenditure, hyperglycemia, catabolism, lipolysis, hyperlactatemia, and electrolyte changes), bone marrow (anemia), and skeletal muscles (enhanced protein degradation and apoptosis). Catecholamines are known to increase O_2 consumption mainly through β1 and β2 receptors. In addition, epinephrine-induced "overstimulation" of β-mediated-aerobic glycolysis through Na/K-ATPase stimulation contributes to hyperlactatemia, independent of the presence of hypoxia. Apart from their metabolic effects, catecholamines are known to have effects on the transcellular shift of electrolytes. Epinephrine causes, at first, a transient increase in potassium (mediated by α1 and α2 receptor stimulation of hepatic calcium-dependent potassium channels), but shortly thereafter, β2 and β3 receptor stimulation of membrane-bound Na/K-ATPase in skeletal muscle and other tissues, as well as activation of the renin–angiotensin–aldosterone system, causes a decrease in serum potassium and magnesium concentrations. The electrolyte disturbances that increase the risk of cardiac arrhythmias can contribute to or induce neuromuscular weakness and result in difficulty weaning from mechanical ventilation. Other effects may include changes in renal (polyuria), gastrointestinal (intestinal paralysis), and metabolic (alkalosis) functions.

The point where the beneficial effects of adrenergic stress are limited by adverse consequences varies individually depending on age and the presence of preexisting comorbidities. It seems that prolonged sympathetic stimulation carries a myotoxic and apoptotic effect on skeletal and cardiac muscles. This contributes to myopathy, muscle wasting, and difficulty in ventilatory weaning.

Metabolic Alterations

Injury and infection induce substantial changes in carbohydrate, lipid, and protein metabolism in most organs and tissues. The short initial ebb response is characterized by an enhanced gluconeogenesis, glycogenolysis, and lipolysis to recruit the much needed energy. As the "stress response" continues, the energy needs, lack of dietary input, and the body's limited available resources (glycogen) mandate the hypercatabolic state, which is the focus of this section.

Hypercatabolic Syndrome

Hypercatabolic syndrome is a biochemical state induced by increased circulating catabolic hormones (cortisol and catecholamines) and cytokines (TNF, IL-1β) on one hand, and decreased anabolic insulin effects on the other. The most important metabolic consequence of hypercatabolic syndrome is the skeletal and cardiac muscle protein breakdown that releases amino acids, which, in turn, supports indispensable body energy requirements but also reduces skeletal and cardiac physiologic and metabolic functions (Figure 4).

An abundance of substrate is provided to ensure the function of essential visceral organs, supply building blocks for tissue repair, and support an upregulated and expanding immunologic system, post-injury or during infection. The total body energy requirements during the hypermetabolic period are not necessarily substantially higher than in a normal state. Although the REE is higher, the bed rest and diminished physical activity compensates for that change. Due to lack of dietary input in the immediate posttrauma period, the metabolic energy requirements must be provided by endogenous supply. Glucose is the main source of energy in normal physiologic circumstances. Endogenous glucose is supplied by the liver (to some extent also by

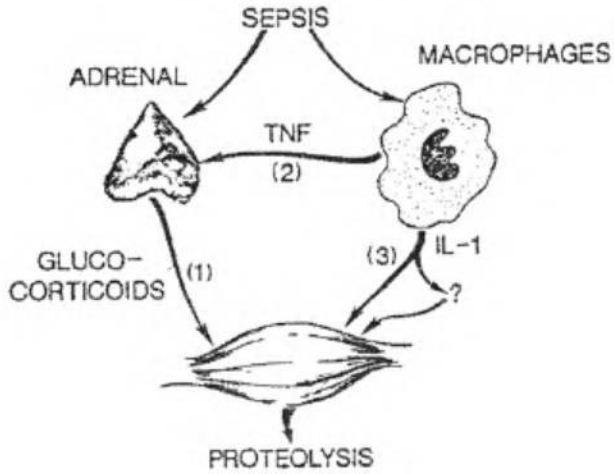

Fig. 4. Interactions among (1) glucocorticoids, (2) tumor necrosis factor (TNF), and (3) interleukin-1 (IL-1) in the regulation of sepsis-induced muscle proteolysis. The effect of TNF on muscle proteolysis is mediated primarily by glucocorticoids, whereas IL-1 regulates muscle proteolysis by glucocorticoid-independent pathway(s). (From Hasselgren PO. *Protein Metabolism in Sepsis.* Austin, TX: RG Landes; 1993, with permission.)

the kidney) mostly by using the glycogen storage. The quantity of glucose stored as liver glycogen is about 65 g/kg of liver mass, which is about 100 g glycogen for a normal 1,500 g adult liver. This amount of liver glycogen is limited to approximately 1 to 1.5 days of systemic glucose supply. So, about 24 hours post-injury, the hepatic glucose production has to change from hepatic glycogenolysis to gluconeogenesis. An average human of 75 kg has roughly 15 kg of fat stored in 16 kg of adipose tissue (the rest is water) and 10 to 12 kg of protein suspended in 60 kg of lean body mass, mostly muscle. Nearly all of the body fat is expendable without serious adverse effects. Unfortunately, glucose synthesis by the liver to supply the glucose-dependent metabolism is primarily from protein, not from fat. Unlike lipids or glucose, there is no bodily "protein storage," *per se*. The body protein component consists of muscle protein, visceral organs, protein, and enzymes. Under normal circumstances, there is a continuous protein turnover, mostly of skeletal and cardiac muscles. In healthy humans under physiologic conditions, approximately 250–350 g of proteins are degraded each day. Most of the amino acids produced are reused to synthesize new proteins, but some are lost (energetic purposes, secreted in urine or feces). The depleted protein is replaced by dietary protein.

In the post-injury period, the balance between muscle degradation and synthesis is changed due to increasing influence of catabolic hormones and cytokines, and the limitations imposed by bed rest and lack of dietary input. The muscle is not merely an organ restricted to movement or contraction; it also plays an important role in maintaining the general metabolism of the human body. Muscle mass is ~45% of the dry weight of a healthy person, and most receptors for insulin, cortisol, and glucagon are located in the muscle.

With mild to moderate injury, this catabolic response causes minimal debility. In the more extensive injuries and/or infections, one can see a urinary loss of up to 30 g nitrogen/day, which represents a degradation rate of about 180 g protein or 900 g muscle a day. Utilization of body protein may prolong convalescence and even contribute to mortality.

In contrast to fat, less than one-half of the body's protein can be mobilized before death occurs, which means that only about 4 to 5 kg of protein (or 500 to 800 g of nitrogen) can be degraded. This suggests that only 1,500 to 2,400 g of glucose could be synthesized without an external source of glucose and/or proteins (1 g of nitrogen can be equated to hepatic synthesis of about 3 g of glucose). If the brain continued to oxidize 100 to 145 g of glucose each day during starvation, survival would be limited to 10 to 20 days. During "simple" fasting, the patient's body gradually adapts to use FFAs and ketone bodies as the main energy source, which decreases the daily glucose consumption to about 30 to 40 g. This enables the gradual decrease of the protein degradation rate to about 10 g/day of nitrogen after a week and about 5 g/day of nitrogen loss after 3 weeks of starvation, allowing a much longer survival period. (There are reports of up to 2 months of starvation with drinking.) Unlike in starvation, the posttrauma patients are exposed to the persistent influence of catecholamines, glucocorticoids, and glucagon. These catabolic hormones preclude a similar substantial reduction in protein degradation and the hypercatabolism of muscle and organ protein continues as part of the systemic inflammatory process.

Mitochondria: The Center of Metabolism

Although metabolic dysfunction posttrauma or as a result of infection affects critical organs in a variety of ways, its genesis is generally linked to a single organelle, the mitochondrion (Figure 5). Mitochondria are commonly referred to as the "power-

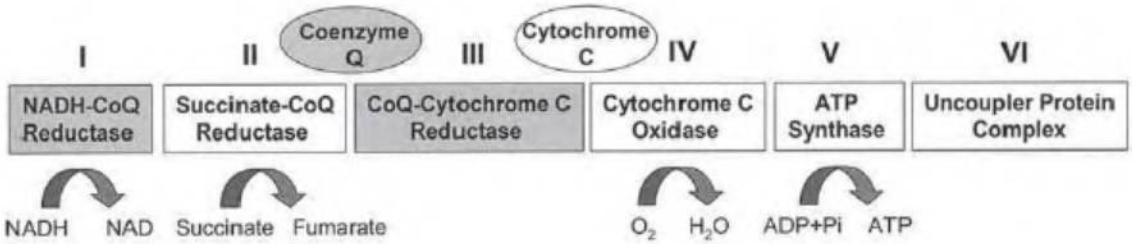

Fig. 5. Oxidative phosphorylation in mitochondria. The diagram depicts the enzymes and cofactors involved in oxidative phosphorylation employed within the mitochondrion to produce ATP from a variety of substrates. Electrons are transferred via a sequence of redox acceptors, ultimately being accepted by oxygen. The molecules that shuttle electrons are coenzyme Q and cytochrome c. Gray shading denotes the points at which reactive oxygen species (ROS) may be liberated. ROS are prominent in injury, and have the potential to do damage to biologic molecules, compromising cells and organs.

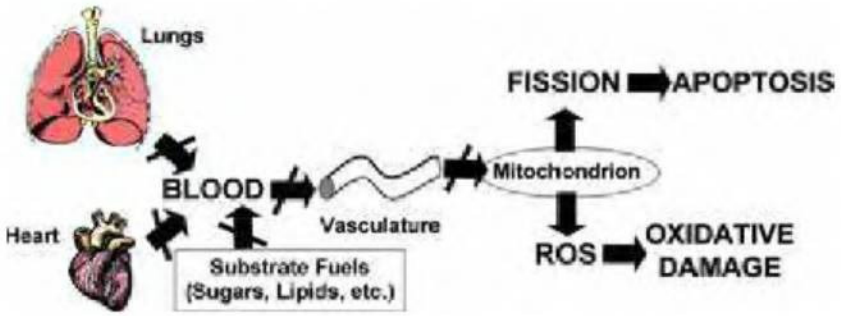

Fig. 6. Consequences of mitochondrial dysfunction in injury. Mitochondrial dysfunction has several forms, the most important of which are the generation of reactive oxygen species (ROS) and the opening of permeability transition pores. The transition pores release mitochondrial contents, which can cause severe damage to the cell, such as induction of apoptosis as mediated by mitochondrial cytochrome c. The combination of lung, heart, and vascular pathophysiology in injury can lead to mitochondrial dysfunction by virtue of inadequate respiration, poor blood flow and vascular transport and delivery, which in turn adversely affects these same organs.

house of the cell." The power is distributed via the high-energy phosphate bonds of ATP. This energy resides in the terminal phosphate of ATP. When this bond (i.e., between the second and the third phosphates) is cleaved, it releases a substantial amount of energy (~7 kcal/mol ATP). ATP is thus a safe and stable fuel, which contains a large amount of energy that may be used to facilitate a wide variety of biologic processes. The conversion of substrates (glucose, ketones, fatty acids, lactate, etc.) to ATP is accomplished via a highly efficient process that uses oxygen. Although it is extremely efficient, the process is not absolutely perfect as it has the capacity to "leak" electrons. As a consequence, these free electrons can generate oxygen-free radicals. Mitochondria can increase the output of ATP in response to a variety of triggering events. These include accumulation of ADP or the greater availability of "fuel" and oxygen. Cell-stimulatory signals, such as the presence of increased Ca^{2+} in the cytoplasm, also stimulate the mitochondria to generate more ATP. These stimuli are tied to an increased demand for work from the body, be it muscular (heart or skeletal muscle contraction), biosynthesis (production of proteins by the liver), cell division (immune responses or tissue repair), or the generation of heat (response to hypothermia). Clearly, all of these functions can be tied to the demands of dealing with infection and injury.

Mitochondrial Dysfunction

The failure of mitochondrial energy production lies not with the organelle itself, but with its various "supplies." Unlike sugars or fats, which are stored as glycogen or adipose tissue, respectively, there are no depot stores of ATP. Thus, with a failure to deliver any of the essential components (cardiac output and/or blood flow, lung oxygenation, glucose transport, etc.), there is a rapid onset of metabolic dysfunction. At the level of the mitochondrion, this dysfunction has many forms. One failure of the mitochondrion with immediate biochemical consequences is the production of reactive oxygen species (ROS). These products take numerous forms, such as superoxide, peroxides, nitric oxide, and peroxynitrite. Since ROS are constitutively produced by mitochondria, neutralizing compounds (antioxidants) such as glutathione can buffer against the damage of ROS (Figure 6). An additional consequence of mitochondrial dysfunction is spillage of the contents of the mitochondrion into the cell's cytoplasm. This is initiated at times by "permeability transition pores," which are transient structures that open in a fission response to stress, enabling molecules <1,500 Da to move between inner membranes. Mitochondrial transition pore opening can lead to swelling and rupture of the mitochondria. This ultimately will allow larger molecules, such as cytochrome C, to enter the cytosol and trigger programmed cell death (apoptosis). Thus, besides failing to produce urgently needed ATP in times of crisis, the mitochondrion generates substances that do considerable, often irreparable, damage and, in the extreme, can cause death to itself and its host cell. This is the stage in which insults of injury and infection can wreak havoc on metabolism.

Under conditions of severe injury and especially shock, there will very likely be severe morphologic damage to the mitochondria. ATP levels will decline, ROS will increase, exhausting the reserve of antioxidants and damaging not only the mitochondrion itself, but also other organelles and molecules within the cell, including DNA. There may be serious impairment of vital (renal, hepatic, lung, and cardiac) and nonvital (skeletal muscle) organ functions. These failures are exacerbated by persistent hypotension, even in the face of more than adequate volume resuscitation. In most cases, these tissues exhibit a loss of mitochondrial function. Cellular tissue ATP levels will also fall, matched by a rise in ADP and adenosine monophosphate (AMP).

Although injuries vary greatly, serious injuries have common characteristics that can unfavorably affect mitochondrial metabolism. Hemorrhage effectively produces hypoxia, which initiates a cascade of responses that are directed toward adaptation to lowered oxygen, which, at the same time, can be damaging to an already injured body. Hypoxia and ischemia-reperfusion, with their lowered oxygen availability to the tissues, will drive the cells to depend on anaerobic glycolysis for their high-energy phosphate production. This can initiate a feedback situation, wherein lactic acid increases, effectively shutting down anaerobic glycolysis as an energy source. In this setting, FFA can also increase systemically, probably from peripheral adrenergic stimulation of lipolysis. Limited oxygen also compromises β-oxidation, the principal means of converting fats to energy. This, in turn, causes a similar "stacking up" of FFA, acyl coenzyme A (acyl CoA), acylcarnitines, and so on, which compromises the heart. Under these conditions, the heart and other tissues are already at a disadvantage because, despite the high energy stored in fat, β-oxidation cannot match the efficiency of carbohydrate metabolism. Thus, reoxygenation, if it occurs, may take place in a setting in which aerobic metabolism is not possible, because of large-scale diversion of metabolism into the less efficient "backup" modes of β-oxidation and anaerobic glycolysis. There is one additional consequence of elevated lactic acid worth noting. As mentioned previously, an intracellular flux of calcium will cause a demand for increased ATP synthesis. The presence of increased lactic acid in the cell will cause calcium to enter the cytoplasm from the exterior, providing a spurious signal for increased workload at a time when the metabolic machinery is incapable of reacting appropriately. This has the untoward effect of further depleting already low supplies of ATP. Finally, regarding the lowered ATP supplies, an obvious solution for treatment would be to administer agents/drugs that increase ATP production under low-flow conditions. However, such agents will not be effective if the microcirculation is markedly impaired prior to its administration.

Carbohydrate Metabolism

Glucose plasma concentration in healthy subjects is strictly controlled. During the fed state, digested carbohydrates are delivered to the liver, with galactose and fructose rapidly converted into glucose. The glucose is either secreted to the circulation or used for storage in the form of glycogen or fat. An increased post-prandial glucose level is followed by pancreatic β-cell insulin secretion, which enhances peripheral glucose utilization, as well as glycogen and fat synthesis. In the fasted state, the plasma glucose originates mostly from hepatic output. Liver glucose production arises from glycogen breakdown, synthesis from recycled carbons (lactate and glycerol), and (to a much lesser extent) *de novo* synthesis from amino acids such as alanine. Under normal conditions, the rates of liver glucose production and peripheral incorporation of glucose is matched exactly, keeping the plasma concentration of glucose set within a very strict limit.

After being absorbed by peripheral cell tissue, the glucose is processed through glycolysis. The glycolysis yields three types of products: energy as ATP, pyruvate, and intermediates for amino acid production. The pyruvate can be further processed to water and CO_2 through the citric acid cycle for more ATP production, or be secreted to the blood stream as lactate. Most glucose uptake is completely metabolized to CO_2 and water.

Pathophysiology of Hyperglycemia in Critical Illness

Early in the course of the stress response, serum glucose levels rise. Glucose availability is needed to supply the immediate energy demand during the posttrauma hypermetabolism, especially for the explosive immune activity. Glucose utilization is increased in multiple tissues, including liver, spleen, small intestine, skin, and some muscles. A common feature of some of these tissues is a high content of macrophages. Studies have shown that in the liver, the high glucose uptake reflects increased utilization of glucose by Kupffer cells. However, because the overall rate of glucose secretion into the plasma exceeds the rate of glucose disposal, serum glucose levels are elevated.

Hyperglycemia as a sequela of critical illness commonly appears even in patients who do not have diabetes mellitus. There are many preexisting conditions (diabetes mellitus, pancreatitis, cirrhosis, advancing age, and obesity) or possible iatrogenic causes (administration of corticosteroids, sympathomimetics, total parenteral nutrition, or dextrose in excess) to hyperglycemia in the posttraumatic patient, but usually the hyperglycemia is due to alterations in glucose metabolism, secondary to the adaptive metabolic response. The synergistic activities of the HPA axis (catecholamines and glucocorticoids), pancreatic endocrine hormones (glucagon and insulin), and proinflammatory cytokines are at the heart of that change to glucose metabolism.

Increased Sympathetic Tone and Hyperglycemia

Elevated catecholamine levels post-injury have a well established effect on glucose metabolism by a number of mechanisms. Epinephrine directly promotes hepatic and skeletal muscle glycogenolysis, and hepatic gluconeogenesis independent of insulin or glucagon concentrations. Dufour et al. demonstrated that under constant insulin concentration, an increase of epinephrine plasma concentration from 100 to 2,000 pmol/L (which is equivalent to the levels observed during exercise at 60% to 80% of VO_{2max}) was followed by a 3-fold increase in glucose plasma concentration and a 2.5-fold increase in liver glucose production. During the first hour of epinephrine infusion, glycogenolysis was the source of 60% of glucose production and later gluconeogenesis accounted for about 80%.

Gluconeogenesis is further increased by catecholamines through the peripheral induction of lipolysis, which supplies the liver with glycerol. In addition, epinephrine stimulates pancreatic release of glucagon and inhibits release of insulin, further contributing to hyperglycemia. The catecholamines also affect glucose disposal through increased peripheral insulin resistance.

Hypercortisolism

Diabetes mellitus is very common (>50%) in patients with Cushing's syndrome. The typical elevated cortisol concentration found posttrauma promotes hyperglycemia through a number of mechanisms. In the liver, cortisol stimulates phosphoenolpyruvate carboxykinase, the enzyme that catalyzes the rate-controlling step of gluconeogenesis. Cortisol also stimulates the activity of the enzyme glucose-6-phosphatase, which catalyzes the completion of the final step in gluconeogenesis and glycogenolysis. Hepatic glucose production is further enhanced by the excessive flow of substrates to the liver, secondary to peripheral lipolysis and proteolysis. As with catecholamines, glucocorticosteroid not only increases the amount of glucose secreted to the blood stream, but also induces increased insulin resistance. In this manner, it contributes even more to hyperglycemia.

Insulin

Insulin levels vary depending on the phase of injury. During the ebb phase, insulin levels are reduced despite hyperglycemia. The combined effects of catecholamines, somatostatin, glucocorticoids, and reduced pancreatic blood flow may reduce pancreatic β-cell sensitivity to glucose. During the flow phase, β-cells regain their sensitivity, and insulin concentrations rise. Despite increased insulin concentrations, however, hyperglycemia may persist due to peripheral insulin resistance.

Insulin resistance: Insulin resistance is the inability of insulin to adequately stimulate glucose uptake, mainly into skeletal muscle, or to inhibit gluconeogenesis in the liver. Unlike in the case of chronic insulin resistance, such as in type 2 diabetes, which takes years and even decades to develop, insulin resistance post-injury develops within hours or minutes of insult. This form of insulin resistance is called "acute insulin resistance" and sometimes "stress diabetes" or "critical illness diabetes." There are numerous studies on the development of chronic insulin resistance, but little is known regarding the pathophysiology of acute insulin resistance. Studies suggest that acute insulin resistance is complex and might differ in a tissue-specific manner, involving multiple causative factors and intracellular signaling pathways.

Insulin signaling is initiated by binding of insulin to its receptor, followed by activation of two main intracellular insulin signaling pathways: the metabolic pathway (the IRS/PI3K/Akt pathway) and the anabolic pathway (MEK/ERK) pathway. The metabolic pathway involves the activation of glucose transporter-4 (GLUT-4), which characteristically is involved in the insulin-mediated glucose transport into the skeletal muscle, cardiac muscle, and adipose tissue.

Several tissue-specific mechanisms are involved in the development of insulin resistance including alterations related to insulin receptors, including impairment of receptor expression, or binding or inhibition of intermediaries involved in the insulin-signaling pathway for glucose uptake. Studies investigating potential mechanisms of skeletal muscle insulin resistance in experimental animal models demonstrated decreased insulin signaling via the metabolic pathway following burn injury and reduced GLUT4 mRNA and protein levels in rat adipose tissue during sepsis. Epinephrine has been reported to enhance insulin resistance through inhibition of insulin binding, GLUT-4 translocation, and IRS-1(metabolic pathway). Moreover, different tissues have been shown to develop various degrees of

insulin resistance and to be affected by different mechanisms. For instance, in rats, posttrauma, and as a result of hemorrhage, there was a severe insulin resistance in skeletal muscles, mild resistance in cardiac muscle and only minimal resistance in diaphragmatic muscle. The glucocorticoid receptor antagonist, RU486, was ineffective in blocking acute insulin resistance in the liver. However, in contrast to the liver, blocking the rise in corticosterone levels by metyrapone or blocking corticosterone action with RU486 prevents the development of acute skeletal muscle insulin resistance.

Some proinflammatory cytokines, including TNF, decrease insulin signaling via the metabolic pathway. Administration of a TNF-α neutralizing antibody following trauma and hemorrhage in rodents reverses the acute insulin-resistant state in the liver, but not in skeletal muscle.

Thus, several tissue-specific mechanisms seem to be involved in the development of insulin resistance.

Glucagon

Another counter-regulatory hormone of interest during stress of the critically ill is glucagon. Glucagon, like epinephrine, is responsible for increased glucose production through both gluconeogenesis and glycogenolysis. The action of glucagon alone is not maintained over time; however, its action on gluconeogenesis is sustained in an additive manner with the presence of epinephrine, cortisol, and GH. Likewise, epinephrine and glucagon have an additive effect on glycogenolysis. The important role of hyperglucagonemia, present during sepsis, was demonstrated in experiments in which the hormone was blocked by infusion of somatostatin in septic rats, and the elevated rate of glucose production was reduced to control levels.

Cytokines

Pro-inflammatory cytokines have a hyperglycemic affect through stimulation of the release of counter-regulatory hormones, including cortisol, epinephrine, norepinephrine, and glucagon. The most extensively studied cytokine in terms of regulation of carbohydrate metabolism is TNF. Changes in glucose metabolism during endotoxemia and sepsis can be reproduced by *in vivo* administration of TNF, which results in increased hepatic production of glucose, hyperglycemia, and stimulated glucose utilization by macrophage-rich tissues and the diaphragm. The effect of TNF on glucose kinetics is dose dependent, with relatively modest doses causing hyperglycemia and larger doses inducing hypoglycemia. The hepatic increase in glucose production secondary to TNF can be blocked by an infusion of phentolamine and propranolol, which suggests that most of the TNF effect on the liver is secondary to adrenergic activation. In addition to the effect on the counterregulatory hormones, TNF may have a direct effect on cellular glucose kinetics in muscle and adipose tissue. In myocyte and adipocytes culture cells TNF-α may hold some direct responsibility for insulin resistance at the level of the insulin receptor and through altered regulation of the insulin signaling pathway, most probably by activating an inhibitory serine phosphorylation of insulin receptor-1.

Similar to TNF, IL-1 also can influence carbohydrate metabolism. According to animal models, it seems that the IL-1β main effect is in inducing hypoglycemia by binding the hypothalamic receptors. Other factors also play a role in the regulation of metabolism during infection and injury, including nitric oxide and prostaglandins.

Glucose Control in ICU

Persistent hyperglycemia is hazardous and has been shown to impair wound healing, increase susceptibility to infections, and even increase mortality. A single-center trial in Leuven, Belgium, published in the *N Engl J Med*, emphasized the importance of tight glucose and changed the approach to glucose control in the ICU. In this study which involved 1,548 patients, most of whom had undergone cardiac surgery, patient hyperglycemia was aggressively treated with insulin, and glucose levels were kept in between 80–110 mg/dL (4.4 to 6.1 mmol/L) as compared with conventional insulin therapy, which has a target blood glucose level of 180 to 200 mg/dL (10.0 to 11.1 mmol/L). This approach significantly reduced mortality from 8% in the controls to 4.6% in the experimental group. The benefit of intensive insulin therapy is particularly apparent in those who required intensive care for more than 5 days. However, the study was criticized because of serious hypoglycemia that occurred in 5% of the patients. In addition, the study was not blinded, and the mortality in the control group was highly relative to that in other cardiac surgical centers. A subsequent study by the same group that included 1,200 medical ICU patients failed to reduce overall mortality and was associated with even a higher rate of serious hypoglycemia (18.7%). Number of additional studies including the Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial that included 6,104 patients and 42 centers failed to demonstrate a benefit in mortality and had a high rate of hypoglycemic episodes secondary to intense insulin therapy. A recent meta-analysis of 26 randomized trials that included more than 13,500 patients showed that intensive insulin therapy had no overall effect on mortality and resulted in an incidence of hypoglycemia that was six times as high as that among patients not receiving intensive therapy. In summary, the preponderance of available evidence suggests that intensive insulin therapy, as compared with standard therapy, does not provide an overall survival benefit and is associated with a higher incidence of hypoglycemia.

Lipid Metabolism

Lipids, as a class of biological molecules, are the most efficient at metabolic energy storage. The energy yield from 1 g of fatty acid is ~9 kcal, compared to 4 kcal from 1 g of carbohydrates. Moreover, since lipids are hydrophobic in nature, these molecules can be stored in a relatively water-free environment. Carbohydrates, on the other hand, are hydrophilic. This fact increases the total mass of glycogen storage. For example, 1 g of glycogen binds ~2 g of water, which translates to an actual 1.33 kcal/g stored. This means that fat can actually hold more than six times the amount of energy per weight unit than glycogen. As such, lipids, in the form of triglycerides (TGs), are the main source of stored energy. Lipids also play an important role in many other cellular functions, such as synthesis of cell membranes, and production of steroid hormones, intracellular signal mediators as prostaglandins, fat-soluble hormones, and others. Fatty acids are either derived from diet or synthesized in the liver from carbohydrates. Dietary lipids absorbed as fatty acids form into TG and are transported as chylomicrons. These newly synthesized FFAs as well as those derived from diet are converted to TG in the liver, a process called esterification. The nonsoluble esterified, hepatic TG are packaged into the soluble very low density lipoproteins (VLDL) and secreted into the blood. Triglycerides are mainly stored in adipocytes in distinct anatomic locations, such as fat tissue or diffused with other tissue types, including muscle or liver. The endothelial enzyme lipoprotein lipase hydrolyzes circulating TGs back to fatty acids, enabling their diffusion into the cells of peripheral tissues.

Hydrolysis TGs within adipocytes into FFA and glycerol is known as lipolysis, which is stimulated by various hormones. Some examples are glucagon during fasting/hypoglycemia, epinephrine, norepinephrine, and possibly cortisol during stress, and GH during anabolism. These hormones

bind to cell-surface receptors that are coupled to the activation of adenylate cyclase upon ligand binding. The result is activation of cAMP-dependent protein kinase, which, in turn, activates the intracellular version of lipoprotein lipase, known as hormone-sensitive lipase (HSL). The net result of the action of these enzymes is FFA and glycerol. The FFAs diffuse from adipose cells, combine with albumin in the blood, and are thereby transported to other tissues where they are transported into cells. Fatty acids are the most efficient source of energy for most cell types. For example, catabolism of 1 mol of a six-carbon fatty acid through the citric acid cycle to CO_2 and H_2O generates 44 mol of ATP, compared with the 38 mol generated by catabolism of 1 mol of the six-carbon carbohydrate glucose.

In the normal state, glucose is the dominant contributor of energy production. Active glucose metabolism down regulates FFA oxidation, thereby channeling those fatty acids into TG stores in the muscle, liver, and adipose tissue. However, in the fasted state, FFA is the dominant contributor of energy production. The main breakdown of fatty acids for energy happens within the mitochondria in a process called β-oxidation, as it occurs by recurrent oxidation of the fatty acid chain, at the β-carbon position. The rate of FFAs oxidation is determined by the rate of transfer into the mitochondria. Medium- and short-chain fatty acids can enter the mitochondria without difficulty, but the majority, which make up the long-chain fatty acids, must be transferred actively through the mitochondrial outer membrane. This process starts with the fatty acid reacting in the cytosol with ATP and coenzyme A to become a fatty acyl-CoA. The fatty acyl-CoA is transferred to the mitochondria via the carnitine palmitoyltransferase enzyme system (CPT-I, CPT-II). This is the crucial point in the regulation of the FFA oxidation rate. Glucose availability and metabolism control the oxidation of fatty acyl-CoA by regulating CPT-I activity via changes in malonyl CoA concentration (malonyl CoA is a regulator of CPT-I and its activity is dependent on the activity of acetyl CoA carboxylase [ACC]). ACC, in turn, is regulated by changes in the concentration of citrate, which is activator and precursor. Citrate is the intermediate product of glucose metabolism through the Krebs cycle. Once inside mitochondria, the fatty acyl-CoA undergoes β-oxidation until the entire chain is cleaved into acetyl CoA units, which, in turn, enter the citric acid cycle.

Lipid Metabolism During Critical Illness

During a critical illness, under the increased influence of hormones such as epinephrine and glucagon, and under substantial influence by pro-inflammatory cytokines, excessive peripheral lipolysis and mobilization of FFAs is observed. Likewise, a concomitant increase in the *de novo* synthesis of FFAs takes place in the liver. The FFAs are used as an alternative, available energy source for the peripheral tissue in a time of need, which spares much needed glucose reserves for use by the nervous system and erythrocytes. TNF was found to play a major role in enhancing peripheral lipolysis and hepatic synthesis of FFAs. TNF also has an inhibiting effect on peripheral lipoprotein lipase, which causes a peripheral resistance to TG resulting in increased lipemia. Other cytokines, including IL-1, IFN-α, β, and γ, may also influence lipid metabolism.

At the same time, while the organism recruits its energy sources, there is a paradoxical increase in liver esterification of FFAs to TG. A number of contributing factors play a part in this paradox:

1. FFA flux is elevated to higher level than the oxidation rate of the body, which exposes the liver to an excess of FFAs.
2. Both glucose and FFA levels simultaneously increase in blood plasma. This hyperglycemia leads to increased hepatic glucose uptake and metabolism, which leads to inhibition of CPT-I and fatty acid oxidation, leading to more accumulation of hepatic pool FFAs.
3. The increased β-adrenergic stimulation causes increased peripheral glycolysis with concomitant production of pyruvate, which exceeds its utilization by the mitochondria. The pyruvate–lactate equilibrium results in excessive secretion of lactate to the blood even without any hypoxia or hypoperfusion. This lactate is metabolized by the hepatocytes, increasing either gluconeogenesis or the citrate production through the Krebs cycle, and possibly the *de novo* fatty acid synthesis, thereby also contributing to the inhibition of FFA oxidation or TG synthesis in the liver.

The result of this process is an enhanced liver TG synthesis causing hypertriglyceridemia and often accumulation of hepatic TG that leads to a fatty liver. The reduced activity of the enzyme lipoprotein lipase in the muscle and the adipose tissue decreases the clearance of lipoproteins, leading to worsened hypertriglyceridemia. The clinical significance of this hyper lipidemia, hypertrigliceridemia, and the tendency for fatty liver during critical illness is not completely clear. However, these findings have important implications to the management of nutrition support in these patients. It has been observed with regularity that overfeeding, especially by parenteral access, causes enhanced steatohepatitis and a deteriorating prognosis for ICU patients.

Protein Metabolism

Proteins contribute to both structure (skeletal muscle) and the function (enzymes) of the body. The absolute amount of protein depends on the age, weight, disease state, and nutritional status of the patient. Skeletal muscle mass represents 30% to 50% of total body protein, is greater in men than women, and declines with age. Between the ages 20 and 80, total muscle cross-sectional area declines about 40%. Following injury, the increased urinary excretion of nitrogen from the body is roughly related to the extent of the injury. Nitrogen is primarily lost in the form of urea, which represents about 85% of the urinary nitrogen loss, although this proportion varies widely. Creatinine, ammonia, uric acid, and amino acids are also found in the urine in larger quantities than normal following injury. The nitrogen molecule is used as a surrogate marker of protein because of the fixed relation between the two substances (6.25 g protein to 1 g of nitrogen). Thus, the net loss or gain of body protein is determined by nitrogen balance, and this is a general measure of the catabolic state.

Maintenance of protein within an individual tissue is a balance between rates of protein synthesis and breakdown. Synthesis and breakdown are often mismatched during catabolic states, resulting in organ protein loss or gain. The catabolic response occurs by a relative increase of breakdown over synthesis. Protein turnover responds to injury and infection in a manner that redistributes body protein to satisfy its needs. The synthesis rate is decreased in "nonessential" tissues (e.g., limb skeletal muscle or gut) and is maintained or enhanced in tissues where work is increased (respiratory and cardiac muscle, lung, liver, and spleen). These events result in translocation of protein from skeletal muscle to the visceral organs (primarily liver, spleen, and heart), which are vital for survival.

Two amino acids, alanine and glutamine, account for approximately 50% to 75% of the amino acid nitrogen released from skeletal muscle. Alanine is used as a building block for various proteins and it is an important glucose precursor. Glutamine plays a very important role during the stress response. Similar to alanine, glutamine is also a gluconeogenesis substrate, but it mainly serves as a primary substrate for immune cells and enterocytes as both rely on glutamine for optimal function and energy production.

Glutamine also participates in acid–base homeostasis, and serves as a precursor for glutathione, an important intracellular antioxidant. In critically ill patients, the intramuscular concentration of glutamine may fall by as much as 80% to 90%. Part of this drop is due to accelerated outward transport and partly due to a decrease in glutamine *de novo* synthesis. Glutamate serves as the precursor for both glutamine and alanine. Under a variety of circumstances, the formation of alanine from glutamate is the preferred pathway, leading to depletion of glutamate availability for glutamine synthesis. It has been hypothesized that the tissue requirements for glutamine may outstrip the body's ability to produce this amino acid. Hence, a relative deficiency state exists characterized by a fall in glutamine concentrations in both plasma and tissue compartments. Thus, glutamine is considered a conditional essential amino acid.

Muscle Catabolism

The story of muscle in the stress response is the story of protein degradation and wasting. Accelerated catabolism of muscle protein is a universal problem in critically ill patients; loss of muscle mass and strength is secondary to protein breakdown due to the metabolic needs. The typical prolonged bed rest and inactivity play a large role in muscle wasting. Muscle wasting may impair recovery if severe enough and certainly limits the return of patients to normal function after recovery. Plank et al. demonstrated the changes in total body protein over a 21-day period, following onset of sepsis or major trauma. They noted that losses were greatest during the first 10 days, amounting to approximately 1.0% of total body protein per day during both sepsis and trauma. Total protein lost over the study period averaged 1.21 $\pm$ 0.13 kg in sepsis patients and 1.47 $\pm$ 0.20 kg in trauma patients. Approximately 70% of the total protein loss came from skeletal muscle. This loss occurred in sepsis patients during the first 10 days and in trauma patients in the first 5 days. After these intervals, more of the protein loss was derived from the nonmuscle tissues.

Liver

The liver plays a major role in a number of critical aspects of the stress response. It is the central metabolic organ coordinating the cardinal changes in glucose, protein, and lipid metabolism. The hepatic cell types that are involved in liver response to sepsis and SIRS include Kupffer cells, hepatocytes, and sinusoidal endothelial cells. These cell types communicate in a paracrine fashion and with bidirectional signaling via different mediators. These mediators modify the metabolic pathway of hepatocytes to support amino acid uptake, ureagenesis, increased synthesis of coagulant factors, complement factors, APPs, and anti-proteolytic enzymes

Immunological Function

The liver contains the largest mass of macrophages (Kupffer cells) in the body and it plays a crucial role in the inflammatory response, both as a source of inflammatory mediator and as a target organ for the effects of the inflammatory mediators. The interaction between hepatocytes and Kupffer cells plays a key role in the regulation of the acute-phase response. Kupffer cells are pivotal in the hepatic response to sepsis. Once activated, Kupffer cells are a major source of soluble mediators of sepsis, including pro-inflammatory cytokines, chemokines, nitric oxide, reactive oxygen products, and eicosanoid mediators. Kupffer cells are also important in preventing the dissemination of bacteria and endotoxins from the portal circulation to the systemic circulation. In an animal model, 5 minutes after intravenous injection, 50% of radiolabeled endotoxin is localized in the Kupffer cells. Hepatocytes play not only a crucial metabolic role, but also an immune role. Hepatocytes exhibit receptors for most of the soluble mediators of sepsis, including endotoxin, cytokines, inflammatory mediators, and vasoactive substances. Studies in rats showed that treatment with gadolinium chloride, which blocks Kupffer cell function, resulted in clearance of circulating endotoxin with endotoxin secreted in bile, where it was inactivated and secreted in the feces. The liver is also a major site for removal of bacteria from the systemic circulation. About 70% of radio-labeled *E. coli* and 96% of *P. aeruginosa* are localized in the liver 10 minutes after intravenous injection.

Hepatic endothelial cells are in contact with Kupffer cells and hepatocytes and interact with both. The endothelial cells participate in the inflammatory reaction by secreting pro-inflammatory cytokines (IL-1 and IL-6). They also play an important role in the regulation of the hepatic, and to some extent, systemic circulation. The liver sinusoids, which are analogous to tissue capillaries, are lacking smooth muscle cell; therefore, the liver capillary flow is instead regulated by NO and CO, which are released by the sinusoidal endothelium.

APP are plasma proteins primarily of hepatic origin; their plasma levels increased by at least 25% following sepsis, injury, or inflammation. The APPs consist of coagulation and anti-coagulation (α2-macroglobulin), complement system components, and inflammatory (CRP, serum amyloid A), anti-inflammatory (α1-antitrypsin and α1-antichemotrypsin), and various other proteins (e.g., haptoglobin and ceruloplasmin). The concentration of other liver-derived proteins, particularly albumin, is reduced in sepsis (negative APP). In a rat model of chronic sepsis, studies showed that albumin synthesis was actually increased within 4 days of initiation of sepsis. It seems that the decreased circulating levels of albumin reflect increased leak of albumin to the extravascular compartment and possibly an increased rate of degradation, but not a reduced synthesis. The enhanced synthesis of all these APPs is regulated by the Kupffer cell-derived cytokines and is a part of the complex systemic and local changes needed to defend the host. For instance, α1-antitrypsin has anti-proteinase activity and inactivates excess extracellular elastase and other proteases that are produced by activated leukocytes in sepsis. Additional hepatic APP scavengers include ceruloplasmin and α2-macroglobulin, which inactivate reactive oxygen radicals. One of the key factors of APP is the CRP. CRP functions as part of the innate immune system. Its main role is in binding to a phosphocholine expressed on the surface of dying cells and some bacteria, causing activation of the complement system (classical pathway) and promotion of phagocytosis by macrophages. The CRP level is elevated within hours of the insult; it peaks at about 48 hours post-injury. The measurement of CRP plasma level has become a common and reliable tool for the evaluation of the extent of a patient's inflammatory process.

Hypercoagulation

During the stress response, the liver promotes a hypercoagulable state by the enhanced synthesis of coagulation factors, such as fibrinogen, prothrombin, factor VIII, von Willebrand, and, at the same time, decreased synthesis of protein C and antithrombin III. The increased CRP plasma level also promotes the expression of tissue factor, the initial activator of the extrinsic clotting system, by mononuclear cells and neutrophils. Promotion of coagulation capacity by the liver is needed in case of tissue injury and possible excess consumption of coagulation factors, but it is also responsible for many fatal thrombotic and thromboembolic complications.

Liver Dysfunction During Critical Illness

The unusually high metabolic and inflammatory needs present during severe illness must be addressed by a liver that may already be

compromised due to stress (shock and sepsis), a situation that may lead to liver dysfunction. Liver dysfunction can be divided into two: primary and secondary. In normal physiologic conditions, post-prandial splanchnic blood flow accounts for up to 30% of total cardiac output. During the stress response period after a severe tissue trauma or sepsis, the portal flow, which arises from the splanchno-mesenteric vascular bed, is subject to disproportionate vasoconstriction (under the influences of α-adrenergic and renin–angiotensin stimulus). A physiologic compensatory process (referred to as hepatic arterial buffer response) of inverse changes in hepatic blood flow in response to changes in portal flow takes place, but this response of the hepatic artery is often altered during severe sepsis or shock, compromising hepatic blood flow. Hepatic dysfunction that occurs in the hours after the insult or onset of sepsis can be viewed as a primary dysfunction and is most likely linked to hypoperfusion. The outcome of such acute liver dysfunction can be catastrophic with disseminated intravascular coagulation, reduced hepatic lactate and amino acid clearance with metabolic acidosis, decreased gluconeogenesis, and glycogenolysis with subsequent hypoglycemia. These effects are potentially fatal.

Secondary hepatic dysfunction is believed to be caused by spillover of bacteria or endotoxin and the subsequent activation of inflammatory cytokines and mediators in the absence of circulatory changes. Mild cholestasis is a common sign of secondary liver dysfunction during critical illness. It is often an isolated finding secondary to intrahepatic cholestasis caused by rapid down-regulation of transporter proteins, such as NTCP (a basolateral sodium-dependent bile salt transporter) and multidrug-resistant protein 2 (MRP2), which is a canalicular anionic conjugate transporter, and a bile salt pump.

Heat Shock Proteins

One of the hepatic mechanisms to deal with the stress and avoid a secondary liver dysfunction is dramatic up-regulation of liver synthesis of HSPs. The HSPs are a group of proteins discovered during the 1960s in drosophila cells that were exposed to sublethal temperature. Although named heat shock proteins after their discovery, HSPs actually serve as general survival proteins by increasing cellular resistance against a vast range of stressors and not just elevated temperatures. In normal physiological conditions, HSPs act as regulatory intra-cellular proteins, stabilizing other proteins in proper formation by chaperoning proteins across cell membranes. HSPs have the capacity to repair denatured/injured proteins and serve as part of the cells' own repair system. HSPs serve as one of the most highly conserved mechanisms of cellular protection, are found in virtually all living organisms, and are a key part of cellular response to stress. Enhanced HSP expression, using transgenic mice or by a mild stress before the insult, has been shown to be cytoprotective in experimental models of sepsis and other types of stress. Increased expression of HSPs has been detected in a variety of clinical settings. In patients with severe trauma, a correlation was shown between survival and the ability to mount a higher HSP.

Glutathione

Cellular glutathiones play an important role in the cells' ability to reduce cellular damage, which is initiated by the typically high oxidative stress present during severe illness. In an animal model of sepsis, a six-fold increase in *de novo* synthesis of glutathione by hepatocytes was demonstrated in the first 2 days of sepsis. In contrast to acute phases proteins, persistence of stress response throughout the course of sepsis in rats (4 days after infection) led to depletion of liver glutathione. The mechanism of late glutathione depletion is not clear; one hypothesis is that it is secondary to selenium depletion. Selenium is an essential cofactor for glutathione peroxidase activity and it has been shown that depletion of that micronutrient in sepsis is associated with increased morbidity and mortality. The selenium requirement in sepsis increases in parallel with increased glutathione peroxidase activity and glutathione turnover. Recent randomized and placebo-controlled trials indicated that high-dose selenium supplementation can improve outcome in sepsis and septic shock.

Steatohepatitis

Another important factor related to liver dysfunction in critically ill patients is steatohepatitis. The liver in critically ill patients faces an increased flux of FFA, amino acids, and carbon-3 compounds, such as lactate and glycerol, together with conditions of hyperglycemia and hyperinsulinemia. The hepatic capacity of FFA oxidation and secretion seems to be inhibited, and TGs accumulate in hepatocytes leading to steatosis. Steatohepatitis in critically ill patients has been reported mostly in relation to artificial nutrition, especially total parenteral nutrition. Torgersen et al. have recently reported in a retrospective study the pathological findings of a postmortem exploration performed on 235 patients who died in ICU due to sepsis. They found steatosis in 33.2% patients, signs of hypoxic liver damage and cholestasis in 13.2% and 14% respectively. Koskinas et al. reported on end-stage pathologic changes in the liver of 15 septic patients dying in the ICU. Histology of liver biopsy specimens showed portal inflammation in 73.3%, centrilobular necrosis in 80%, lobular inflammation in 66.7%, and hepatocellular apoptosis in 66.6%. Various degree of steatosis was observed in 11/15 (73.3%) of patients.

Intestine

Our understanding of intestinal barrier function biology, its potential clinical importance, as well as the pathophysiology and consequences of gut barrier failure has changed considerably over the course of time. Now, it is clear that the intestinal mucosa functions physiologically as a local defense barrier to prevent bacteria and endotoxin, which normally are present within the intestinal lumen, from escaping and reaching extra-intestinal tissues and organs. More recently, it has become apparent that the gut can become a pro-inflammatory organ and that gut-derived factors, liberated after periods of splanchnic hypoperfusion, can lead to acute distant organ dysfunction, playing a role in the development of multiple organ failure.

Initial interest in gut barrier failure and bacterial translocation was based on clinical observations that trauma, burn, and critically ill patients, especially those developing MODs, frequently had life-threatening bacteremias with enteric organisms in the absence of an identifiable focus of infection. These clinical observations resulted in a large body of work investigating the relationships among gut barrier function, intestinal bacterial flora, systemic host defenses, and injury in an attempt to delineate the mechanisms by which bacteria contained within the GI tract can translocate to cause systemic infections. From these and subsequent studies, the current role of the gut and gut barrier function in the prevention and potentiation of systemic infections and MODS have evolved.

Gut Barrier and Bacterial Translocation

Intestinal barrier function can be seen to be of major importance when one considers that the distal small bowel and colon contain enormous concentrations of bacteria and endotoxin. Under certain clinical circumstances, intestinal barrier function becomes impaired, resulting in the movement

of bacteria and/or endotoxin to the systemic tissues. This process of bacteria and their products crossing the intestinal mucosal barrier and spreading systemically has been termed bacterial translocation. The underlying mechanisms of how and under what circumstances bacteria contained within the gut translocate across the mucosal barrier have been studied extensively in a number of animal models. Although both an intact epithelial barrier and a normal functioning immune system are important for adequate gut barrier function, it appears that an intact mucosa will prevent bacterial translocation even in rats with selectively impaired cell-mediated immunity. Reduced splanchnic blood flow, leading to an ischemia–reperfusion-mediated gut injury has been shown to be a key factor in the loss of mucosal barrier function and bacterial translocation in models of thermal injury, hemorrhagic shock, and endotoxemia. In these models, mucosal injury appears secondary to a gut ischemia–reperfusion injury, which is mediated, in part, by xanthine oxidase-generated oxidants.

Nutrition and Gut Barrier

The area of nutrition received increasing clinical and experimental attention during the past two decades. In fact, the recognition of the concept of gut barrier failure and bacterial translocation was one of the major impetuses leading to the initiation of early enteral feeding of patients shortly after injury. The optimal functional and structural integrity of the GI tract depends on whether or not the gut is fed enterally. Enteral feeding supports intestinal structural integrity by maintaining mucosal mass, stimulating epithelial cell proliferation, maintaining villus height, and promoting the production of brush border enzymes. Functional integrity of the mucosa also is supported by enteral feeding in several ways, through the maintenance of tight junctional integrity between the intestinal epithelial cells, stimulation of blood flow to the gut, and the production and release of a variety of endogenous agents, such as cholecystokinin, gastrin, bombesin, and bile salts, all of which exert major trophic effect on the intestinal epithelium. In fact, experimental evidence exists that nutrition has a profound impact on gut barrier function. Enteral feeding preserves intestinal barrier function better than parenteral feeding. Enterally fed animals survived a septic challenge better than animals fed an identical diet parenterally. This experimental observation has been verified in several prospective randomized clinical studies involving burn and trauma patients. These studies indicate that the route by which patients are fed may influence the immune-inflammatory and metabolic response to injury as well as the incidence of infectious complications and thereby modulate clinical outcome. Although bacterial translocation has been demonstrated consistently in experimental animal models, results of clinical human trials failed to find bacteria or endotoxin in the portal blood of severely injured patients and its occurrence in humans is uncertain. One possible explanation to resolve these discordant results is that gut-derived factors contributing to systemic inflammation and organ injury is reaching the systemic circulation via the mesenteric lymphatics rather than the portal venous system. One important conceptual consequence of the gut–lymph hypothesis is that the lung rather than the liver would be the first major vascular bed to be exposed to gut-originated mesenteric lymphatic factors (mesenteric lymph reaches the systemic circulation via the thoracic duct, which empties into the subclavian vein and hence the pulmonary circulation). There is extensive clinical and experimental evidence showing that after hemorrhagic shock, trauma, or a major burn injury, the gut releases pro-inflammatory and tissue injurious factors that lead to acute lung injury.

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EDITOR'S COMMENT

This is an encyclopedic chapter concerning the metabolic and inflammatory components of trauma and infection. It is probably the most complete and encyclopedic chapter that has ever been written in any literature including both surgical and medical literature. As will be clear to the reader, there are an enormous number of components to the inflammatory and metabolic response to trauma and infection. To a considerable extent, they are synergistic. The most prominent of the classics that we deal with are the cytokines, interleukins and transporting factors, if you will, such as NF-kB. Many of them have very short half-lives, such as TNF with a half-life of 20 minutes and then among the cytokines IL-1 with a half-life of 6 minutes. The entire process is to a considerable extent integrated and combines to have a series of responses, which indicate in the response what the organism perceives, in this case the human organism, is the degree of insult. For ordinarily elective surgery, for example, of rather small invasiveness, there is a programmed response, which I will discuss, but it is small, and it is temporary. If the surgery is larger, or if there is an infectious postoperative complication, or if this is a moderate traumatic episode, the cytokines, interleukins, Toll receptors and other processes begin to bring about a response which is close to life-threatening.

On the other hand, a number of these very same factors which bring about the response, which, when it gets out of hand, is deleterious, on the obverse side of the response aid in the survival mechanism of the organism, such as acute-phase protein synthesis. Other aspects of the response include the release of neutrophils over a few hours, in which it is proposed that 10 billion are released, which have a half-life of approximately a few hours and then undergo apotosis or programmed cell death, which brings about a utilization of some of the components of neutrophils to participate in synthesis of various proteins and other components which aid in the healing and in the positive response to trauma and the metabolic and inflammatory response which helps the organism survive. In the initial complex from a rather minor injury or comparatively minor surgery, or even slightly more major surgery which goes well and does not have any postoperative complications, the entire duration is 1–2 days. It then subsides.

One of the problems in this area is what I call the "holy-grail syndrome". It will be obvious after reading this chapter that it is highly unlikely that there is a "holy grail". There may be some components of the inflammatory response which are critical or central to the response, but, to my way of thinking, there is no central or essential component, although there may be components without which the inflammatory response will not take place, or at least will not resemble what we actually see now. Therefore I get a little depressed, when I go to surgical meetings, and particularly when I see a bright young man or woman presenting a paper as if to say that this is the holy grail of inflammatory and metabolic response to injury or trauma. It is highly unlikely that it is, and some bit of modesty probably should be maintained. Let us go through the components in outline form and point out some of the issues that have come to light. I would urge the reader to bear in mind that, as the result of these various components which seemingly come together, MODS (multiple organ dysfunction syndrome) and SIRS (systemic inflammatory response syndrome) accrue. This is covered nicely in Chapter 8 by Dr. Marshall, and I do like his approach, that much of what happens to patients we in fact create by the way we take care of them.

In the overview, the authors present a list of the immune, inflammatory and metabolic responses to injury. It starts as a local activation but then is followed shortly thereafter by a systemic inflammatory and endocrine response. These can be manifest to us as surges in plasma catecholamine, cortisol and aldosterone levels resulting in tachycardia, tachypnea, vasoconstriction, reduced cardiac output, lower oxygen consumption, lower basal metabolic rate, sodium and water retention, translocation of blood from the peripheral to the central vital organs, and acute-phase protein production. This is the "ebb" phase originally proposed by Sir David Cuthbertson in the 1930s. If the organism and the organs survive, we then transition to a "flow" phase. The duration and the number of organs involved really depends on, first, how extensive the injury or insult is and, second, whether or not the organs have survived the initial ebb phase. The stress response here is, as the authors say, "characterized by explosive metabolic activity," which is "mediated by a massive neuroendocrine flux involving the production and secretion of catecholamines, antidiuretic hormone, cortisol, insulin, glucagon and growth hormone. The increased adrenergic stimulation causes an increase in the glucagon to insulin ratio and, combined with . . . cortisol and cytokines, induces the state of enhanced proteolysis and lipolysis." This is the nub of the issue. There are other parts that will be covered by Dr. Hasselgren in Chapter 2 and by Dr. Marshall in Chapter 8.

Furthermore, a critical part of the issue here is that there is no inactive store of protein. The storehouse for protein, as we know it, is the muscle. The protein content of organs such as heart, liver or kidneys may also "store this protein", when the stress is high enough, and may lead to the failure of the organ and then the organism, as in liver failure. Massive destruction, catabolism of skeletal muscle to the point where the abilities of the patient to move and breathe are threatened is also part and parcel of this response. I assume that in the evolutionary component, skeletal muscle is seen as less valuable to the organism than, for example, heart, brain, kidneys and liver; however, continued destruction of lean body mass, of which these latter are all part, is part and parcel of the hypermetabolic response.

The other major destructive impulse, at least it seems to me it is, is the widespread capillary leak and the opening up of tight junctions of the capillaries and also perhaps enlargement of the pores or the spaces in the endothelium, which keep material in the circulating compartment. The capillary leak would deplete if allowed to go on, and if it does go on, endogenous resources and is maladapted as the author says. The systemic inflammatory response, severe metabolic depletion, and possible secondary infection all cause damage to vital organs, but were not initially compromised by the injury. These include adult respiratory distress syndrome, which I believe has two components, the first is the capillary leak and the second is the use of excessive crystalloid in resuscitation. Happily, many people taking care of patients with severe injury and with infection now realize that the continued resuscitation of patients who are suffering from a capillary leak is not helpful and contributes not only to ARDS but renal insufficiency, hepatic dysfunction, loss of duct epithelial-barrier function, immunoparalysis and the multi organ dysfunction after sepsis develops, which can be fatal. The stress response, however, with the appropriate support and provided the stress response is not complicated by later infection usually resolves without complication. The catabolic process usually peaks at 48 to 72 hours post injury.

If the catabolic response is resolved it then leads to the beginnings of an anabolic state with insulin, growth hormone, insulin like growth factor 1, and perhaps insulin like growth factor 2 within five days of injury, as the author says. The mechanistic change is a flux of protein, fluid, and electrolytes returning to the depleted cellular space, particularly muscle, and cellular space expands.

There is much that is new in this chapter, which has not made its appearance in the standard textbook of surgery. These include from this point on a number of headings, including "The Innate Immune System", which include the "Toll Like Receptors", which are the Toll-signaling pathway initially described in Drosophila in 1985, as the author says and finally recognized in humans in 1997; at least 11 human toll-like receptors have been identified. These, which have not received a great deal of recognition in the contemporary surgical literature at least appears

(*continued*)

to play an adaptive role on adaptive immune systems. They are expressed on dendritic cells, T-lymphocytes, a number of parenchymal cells, including adrenals, liver and spleen and which in the adrenal-expressed TLRs (toll-like receptors), the systemic inflammatory response. NF-$_k$B, which is a major facilitator to all of this migrates from the cytoplasm, where it usually resides with the destruction of the inhibiting I$_k$B and transmigrates to the nucleus. Here, it mediates gene transcription and the production of inflammatory mediators, such as chemokines, adhesion molecules, tumor necrosis factor, interleukin-1, and TNF-α receptors.

Other new terminology, which will be new or at least unfamiliar to the average surgeon reading this chapter includes complement, which is recognizable, except for the fact that what is new is that the complement system consists of more than 30 proteins. These are divided into three main pathways:

1. classic
2. alternative
3. mannan-binding lectin pathways.

Another relatively new term is alarmins, which is triggered by injury or trauma without evidence of a bacterial focus. They are released after a non-programmed cell death or by cells of the immune system. Heat shock proteins, defensins, cathelicidin, eosinophil-derived neurotoxin (EDN), and others. There are a number of systems which ordinarily do not receive a great deal of attention in a standard textbook version of the acute phase reaction. These are systems such as the adaptive immune system, which is a secondary and more efficient response to invaders, and which is made up of cellular immunity. The cellular immunity is the cellular response of the organism, namely the patient that is a local host response against invading organisms. Local mediators of inflammation, such as cytokines, histamine, kinins, and arachadonic acid metabolites allow increased capillary leakage, which in this sense is a good thing as it allows diapedesis of cells to infiltrate into the site of injury. These are primarily neutrophils and also to a lesser extent monocyte macrophages. The humeral community is much more diffuse and involves toll-like receptor activation, which causes secretion of cytokines including our friends TNF and IL-1 and the chemokines, especially derived from macrophages. There are a variety of other components in this including cytokine receptors, which are on the surface of the majority of human cells and intracellular signaling pathways that regulate gene transcription. We have already heard of the nuclear factor-$_k$B (NF-$_k$B) activating protein AP1 and the C/EBP family of transcription factors, in particular C/EBP-β and δ.

NF-$_k$B is studied because it is central in the inflammatory process as a transcription factor once its inhibitor has been metabolized will translocate to the nucleus. The number of cytokines is legion but the important ones for our purposes, TNF, IL-1β, IL-6, IL-8, IL-12 and IFN-λ, are pro-inflammatory cytokines and IL-4, IL-10, and IL-13 are considered to be inhibitory or anti-inflammatory. Interleukin-1 is ancient as compared with some of these other factors as it was described as a pyrogen a half century ago. It does have a short half life of six minutes, as mentioned earlier. Of the two forms, IL-1β is regulated by different antigens, IL-1β is the more common and more involved in what its role is. IL-6 is another popular cytokine, as it were, and it peaks and 4 to 48 hours. It is induced partially by TNF and partially by IL-1. Its function is operant by the proliferation and differentiation of B and T-lymphocytes. It also regulates the synthesis of another acute phase protein, such as C-reactive protein and fibrinogen and other complement factors. One of the significant findings of laparoscopic procedures is that there is less elevation of IL-6 following laparoscopic cholecystectomy as well as abdominal, aortic, and colorectal surgery. Similarly, small bowel and colonic resections carried out laparoscopically have lower elevations of IL-6. Another feature of IL-6 is that it seems to have a prognostic significance in patients with SIRS, sepsis, or MODS and has been tested in the ICU in this regard and has come to be a prognostic indicator.

Of the chemokines, these have not had much presence, on the surgical scene at least, and there are 18 chemokine receptors and 43 chemokines. Their role is still being elucidated, but some have suggested that some of these are "decoy receptors".

A major and relatively novel discussion in a surgical text is the neuro-immune axis. We remain very concerned about what the accurate sensory input to the brain is during stress. We know that there are neural routes, mostly by afferent vagal fibers and then there are blood-borne inflammatory mediators. Elsewhere in this volume we have called attention to the fact that vagal pathways pass from the peritoneal cavity to the CNS and in a paper that appeared in *Science* in 2000 as discussed elsewhere, there was a benefit to subdiaphragmatic vagotomy. The stimulus for the vagus is activated it seems, at least in part by IL-1 in peripheral tissues. IL-1 binding and an intact vagus nerve seem to be required for the generation of the fever following intraperitoneal IL-1. However, vagotomy alone does not block the effects of various cytokines on CNS despite the protective character of the blood brain barrier. However, in the third ventricle the blood brain barrier may be deficient and thus there may be places where the cytokine may damage the central blood brain barrier, giving results of continuing inflammation.

We have talked about the afferent effects of the neuro-immune axis, but one should not lose sight of the fact that there is an efferent regulation going through the sympathetic and suppressing the parasympathetic portion of the autonomic nervous system.

Another novel discussion is the immunosuppression following trauma, which we have been aware of in a vague way and find that there is a cholinergic anti-inflammatory pathway and some cytokine immunosuppressant such as IL-6. Immune dysfunction may also be cell mediated and cellular immunoincompetence, which is also defined as immune paralysis, may be induced by PGE2, IL-10 and other anti-inflammatory mediators. IL-10 and TGFβ may induce monocyte immune paralysis. Another form of dysfunction is lymphocyte dysfunction, in which T-helper lymphocytes may also be involved in immunosuppression following surgical trauma.

In the development of SIRS and MODS, the "second hit phenomenon" has become part of our normal language. For example, there may be initial trauma and a complication may result, which may be the second hit. The second hit may be sterile, for example the need for an operation in general, or it may be infectious with a pathogen induced infection. Whatever causes the second hit, however, has now become synonymous with the development of MODS. This is further covered in Chapter 8. There is a very extensive discussion of hormonal relationships in trauma and inflammation, but I do want to mention adrenal insufficiency, which may occur in prolonged stay in the ICU. The point is that one must think about this in order to rule it out. Patients with transient adrenal insufficiency basically may have a decreased blood pressure, decreased urine output, other inexplicable hypoglycemia, hyponatremia, hyperkalemia metabolic acidosis, eosiniphilia, and a hypodynamic circulation as well. To think of adrenal insufficiency should give one a very aggressive response to this. A 250 microgram ACTH stimulation test, which is recognized as being of a very high level, is probably the best way to tell whether the patient has a hypoadrenal response. This seems to be much more accurate than random cortisol levels.

Another hormonal deficiency that can occur after prolonged ICU stay is hypothyroidism. There is a low T3 syndrome, and interestingly enough, there is an inverse correlation between T3 levels and mortality. In prolonged critical illness, an "euthyroid sick syndrome" may present, in which the TSH exhaustion is what would best be identified, and there would be reduced TSH secretion and reduced levels of T3 and T4. Low TRH expression in the hypothalamus has been seen in patients who have been chronically ill, as if this particular function has been depleted.

The sympathetic nerves and the whole sympathetic system are extremely important in prolonged trauma and stress. The catecholamine immune secretion from the adrenals takes place within seconds of stimulation. Since both Norepinephrine and Epinephrine are stored in granules within the adrenal medulla and their exocytosis is initiated by acetylcholine secretion in the adrenal medulla. The sympathetic system is involved in almost every possible body system, which is important in the response to trauma, including cardiac output, myocardial contractility, maintenance of blood pressure, bronchodilatation, thermoregulation, retention of water and sodium in the kidneys, and not paradoxically—almost purposefully—decrease in bowel motility. The dysfunction of the adrenal system, such as exhaustion, probably presages a poor outcome.

Metabolic alterations are extremely important, but there is one concept here, which is also brought on in Chapter 8, that is mitochondrial dysfunction. The mitochondrial dysfunction may be the result of failure of the mitochondrial energy production but less and less likely so. The basic issue appears to be the failure of adequate supplies to the mitochondria. ATP is not contained in a depot. Any of the components such as glucose, fat, other sugars, and protein to mitochondria because of decreased cardiac output and blood flow, oxygenation by the lung, glucose transport leads to a rapid onset of mitochondrial dysfunction. If the mitochondrial transitional pore opening are open, large molecules such as cytochrome C can enter the cytosol and trigger apoptosis—programmed cell death. This results in the failure to produce ATP in a period of crisis.

The following two areas which should be emphasized are glucose control in the ICU and the liver, in particular, the failure of protein metabolism. Glucose control in the ICU is not new, but the emphasis on it is. Maintaining blood glucose in sick patients in the ICU is beneficial. However, the question is how low does the blood sugar have to be maintained. There is a gradually evolving agreement that using a superior level of 120 mg/dl of glucose leads to too frequent occurrence of hypoglycemia, which is damaging. Most of us are ready to accept the target of 150 mg/dl, although some believe it should be higher at 180 to 200 mg/dl.

Finally, hepatic failure. In addition to mitochondrial failure, probably the sine-qua-non of evolving death is due to hepatic failure. The hepatic cells, which are involved are the Kupffer cells and closely related to them and to the hepatocytes are the sinusoidal endothelial cells. These cells are in contact in a paracrine fashion, and have bidirectional signaling via different mediators. One of the most important functions of the liver is the large mass of macrophages (Kupffer cells) and the role they play in the inflammatory response. They are both as a source of inflammatory mediators and the target cells for the effects of the inflammatory mediators. They produce a large number of the soluble mediators of sepsis, including proinflammatory cytokines, chemokines, nitric oxide, reactive oxygen products, and eicosanoid mediators. Kupffer cell dysfunction in close association with hepatocytes is one of the main common pathways to death when the liver is dysfunctional. There is a nice discussion of liver dysfunction and critical illness.

Finally, I would simply like to mention that the authors concentrate on the intestine and the intestinal barrier. Despite the flood of papers in the '90s concerning the breakdown of the intestinal barrier, I remain somewhat unconvinced. I believe that the intestinal barrier remains intact until agonal times.

Summary: In short, I think we have come a long way from Sir David Cuthbertson's first description of biphasic immune inflammatory and metabolic response to injury, as it was elucidated by Dr. Frannie Moore in probably the best book and most influential surgery book *The Metabolic Care of the Surgical Patient*. We have begun to understand more of the critical components in what takes place. It is extremely complicated and there is no "A ha" moment in what happens to patients as they get critically ill. Likewise, there is no "magic bullet" to protect them from what seems to be an increasingly difficult support system as they go into a downward spiral of MODS, with or without SIRS.

As I said at the beginning of my discussion, I think this is a superb chapter, probably the best and most encyclopedic that has ever been written and I am especially pleased to have my good friend Professor Naji N. Abumrad be its author.

J.E.F.

2 Perioperative Management: Practical Principles, Molecular Basis of Risk, and Future Directions

Per-Olof Hasselgren, Jeremy W. Cannon, and Josef E. Fischer

INTRODUCTION

Preparing patients for surgery has grown increasingly complex as the severity of chronic illness within our patients has worsened even as the options for managing these conditions in the perioperative period have expanded. In addition, over the past decade, the process of surgical care in the operating room (OR) and afterwards has been refined in a number of respects aimed at improving patient safety and quality of care. Throughout this perioperative time, the patient's physiology is taxed to tolerate the surgical insult and then to heal the operative site. This chapter summarizes our perioperative management approach from the time the decision to operate is made through the operative and postoperative course. The most recent evidence on risk minimization is reviewed in order to provide surgeons a practical approach to assuring as safe a surgical course as possible. The physiologic underpinnings of the response to injury are also discussed along with areas for future investigation aimed at reducing the perioperative patient risk.

PERIOPERATIVE EVALUATION AND MANAGEMENT

The perioperative period is defined as the time from preoperative workup through the first 30 days of postoperative care. From the patient's perspective, a surgical procedure and the perioperative period are often a momentous occasion, which involves significant loss of personal control. As such, the surgeon's responsibility is to engender trust that the decision to operate is sound and that every measure to ensure the patient's safety throughout the perioperative course is taken.

A careful preoperative history, review of systems, and physical examination will reveal preexisting medical conditions and risk factors known to worsen surgical outcomes. This process can be facilitated by a screening questionnaire structured to trigger the patient's memory about significant medical illnesses or previous perioperative experiences (Table 1). Findings during this evaluation then guide the array of laboratory studies and additional tests needed to more specifically assess the patient's risk of an adverse perioperative event. Once all of this information is gathered, a perioperative management plan can be fashioned by the surgeon often with input from the patient's primary care physician and possibly other specialty consultants in fields such as cardiology, geriatrics, and anesthesiology. The following sections review many of the issues that arise during the perioperative period and provide a recommended approach based on current evidence.

SCREENING TESTS IN GENERALLY HEALTHY PATIENTS

For patients with no or few comorbidities, a selective preoperative testing approach is advised (Table 2). Laboratory testing options include a complete blood count (CBC), electrolyte and renal function tests, serum glucose, liver function tests (LFT), coagulation studies, urinalysis, and pregnancy test. With the exception of pregnancy test, these studies can be obtained within several months of the planned procedure. Patient's age has been identified as a minor predictor of morbidity and mortality although this seems to be related more to the associated comorbidities that develop with advancing age.

Table 1 Preoperative Screening Questionnaire

1. Do you usually get chest pain or breathlessness when you climb up two flights of stairs at normal speed?
2. Do you have kidney disease?
3. Has anyone in your family (blood relatives) had a problem following an anesthetic?
4. Have you ever had a heart attack?
5. Have you ever been diagnosed with an irregular heartbeat?
6. Have you ever had a stroke?
7. If you have been put to sleep for an operation, were there any anesthetic problems?
8. Do you suffer from epilepsy or seizures?
9. Do you have any problems with pain, stiffness, or arthritis in your neck or jaw?
10. Do you have thyroid disease?
11. Do you suffer from angina?
12. Do you have liver disease?
13. Have you ever been diagnosed with heart failure?
14. Do you suffer from asthma?
15. Do you have diabetes that requires insulin?
16. Do you have diabetes that requires tablets only?
17. Do you suffer from bronchitis?

Adapted from Hilditch et al. (2003).

Consequently, age alone should not be used in determining the types of preoperative tests to obtain with the exception of a baseline hemoglobin (Hb) for those over 65 years undergoing major surgery and any patient in whom significant blood loss is anticipated. The cost of an added white blood cell and platelet count is often minimal; so these are often obtained as part of the baseline Hb. Because renal insufficiency strongly correlates with poor perioperative outcomes, identifying patients with occult renal disease is essential. No consensus exists on the indications for such testing, but it has been suggested that a BUN and Cr should be obtained in patients over 50 years of age scheduled for intermediate or high-risk surgery or when perioperative hypotension is considered likely or when nephrotoxic medications are planned. Routine electrolyte, serum glucose, and LFT are not recommended in healthy patients. Patients with a history of a bleeding disorder or an associated illness, which can result in abnormal coagulation function should have coagulation studies performed. Otherwise, routine testing of the partial thromboplastin time, prothrombin time, and international normalized ratio (INR) is not recommended. Routine urinalysis testing is a matter of ongoing debate. On one hand, patients scheduled to have a surgical prosthesis implanted may be at an increased risk for wound or implant infections from a preexisting urinary tract infection (UTI). However, even with treatment, patients with an asymptomatic preoperative UTI develop more postoperative infections, and the cost–benefit ratio of prosthetic infection prevention with routine urinalysis screening does not clearly favor testing the asymptomatic patient. Patients of childbearing age should have a urine or serum pregnancy test, which many institutions require as a matter of policy.

Additional basic testing options include a 12-lead electrocardiogram (EKG), PA and lateral chest x-ray (CXR), and pulmonary function test (PFT). We reserve these tests almost exclusively for patients with prior history of cardiovascular or cardiopulmonary disease. With regards to PFT, these are only obtained in patients with dyspnea in whom a thorough history and physical examination fails to reveal the source of this complaint. Our approach to obtaining these additional tests is also summarized in Table 2.

Table 2 Preoperative Laboratory Testing Indications

Laboratory test	**Indication**
CBC	Age ≥ 65 + major surgery; anticipated significant blood loss
Renal function	Age ≥ 50 + major surgery; suspected renal disease; anticipated hypotension; planned nephrotoxic agents; poorly controlled hypertension
Serum electrolytes	Routine testing not recommended
Serum glucose	Routine testing not recommended
Liver function	Routine testing not recommended
Nutrition labs	History of unintentional weight loss; chronic GI illness
Coagulation studies	Routine testing not recommended
Urinalysis	Routine testing not recommended
Pregnancy test	Women of childbearing age
Additional basic tests	**Indication**
EKG	Vascular surgery planned; history of cardiovascular disease; poorly controlled hypertension
CXR	Age ≥ 50 + AAA or upper abdominal/thoracic surgery; history of cardiopulmonary disease
PFT	Unexplained dyspnea

CBC, complete blood count; GI, gastrointestinal; EKG, electrocardiogram; CXR, chest x-ray; PFT, pulmonary function tests.

RISK ASSESSMENT AND MANAGEMENT IN PATIENTS WITH CHRONIC MEDICAL ILLNESS

The most common preexisting medical condition requiring perioperative risk assessment and management is either known or suspected cardiovascular disease. Other common preexisting conditions that are amenable to risk modification include pulmonary diseases, renal insufficiency, liver failure, diabetes mellitus, immunosuppression, and hematologic conditions. The surgeon's goal should be to minimize the impact of these conditions on the surgical outcome while using a surgical and anesthetic approach, which avoids any further deterioration of the involved organ system and the patient. In each case, communication between the surgeon and the primary care physician or medical specialists involved in the patient's care is essential while preparing such patients for surgery.

Cardiovascular

Cardiovascular events are responsible for one-third to one-half of perioperative deaths, and of the patients who present for noncardiac surgery, nearly one-third have a known diagnosis of cardiovascular disease. Consequently, cardiovascular risk stratification and modification are fundamental to the perioperative care of many patients.

Patients with a good functional status have a low risk of perioperative cardiovascular complications. This can be assessed by determining the types of daily routines the patient can perform, which translate into multiples of the amount of oxygen consumed while seated at rest (1 MET). Patients

Table 3 Revised Cardiac Risk Index and Associated Rates of Significant Perioperative Cardiovascular Events

Risk factor	Comment
High-risk surgery	Intraperitoneal, intrathoracic, or supra-inguinal vascular procedures
Ischemic heart disease	History of myocardial infarction, history of a positive exercise test, current complaint of chest pain considered to be secondary to myocardial ischemia, use of nitrate therapy, or ECG with pathological Q waves
History of heart failure	History of congestive heart failure, pulmonary edema, or paroxysmal nocturnal dyspnea; physical examination showing bilateral rales or S3 gallop; or chest radiograph showing pulmonary vascular redistribution
History of cerebrovascular disease	History of transient ischemic attack or stroke
Insulin therapy for diabetes	
Preoperative serum Cr > 2 mg/dL	
Risk of perioperative cardiac complications including cardiac death, nonfatal MI, and nonfatal cardiac arrest based on the number of risk factors (% [95% CI]).	
0	0.4 [0.1 to 0.8]
1	1.0 [0.5 to 1.4]
2	2.4 [1.3 to 3.5]
3	5.4 [2.8 to 7.9]

Adapted from Lee et al. (1999) and Devereaux et al. (2005).
MI, myocardial infarction; CI, confidence interval.

who are unable to walk up two flights of steps or four blocks (>4 METs) have an increased risk of postoperative cardiovascular events. In addition to functional status, cardiovascular risk scoring systems are useful in quantifying the risk of a major perioperative cardiovascular event. The Revised Cardiac Risk Index (RCRI) is the tool we prefer given its simplicity and validation in multiple clinical studies Table 3.

In addition to basic laboratory studies, patients with cardiovascular disease should have a baseline EKG. Additional testing options include transthoracic echocardiography, exercise or chemical stress testing with or without supplemental echocardiography or radionuclide myocardial perfusion imaging, and coronary angiography. The 2007 American College of Cardiology/American Heart Association (ACC/AHA) guidelines reflect the most current recommended approach to the use of these additional studies (Fig. 1). Alternative algorithms have been proposed by the American College of Physicians (ACP) and by Fleisher and Eagle. In general, if the patient's cardiovascular disease warrants immediate intervention (i.e., the cardiovascular symptoms are more pressing than those that prompted surgical consultation), additional studies are warranted. Although these algorithms serve to identify and further evaluate patients deemed to be at either intermediate or high risk for adverse perioperative cardiovascular events, their use has, to date, not been shown to improve patient outcomes.

Based on the coronary artery revascularization prophylaxis (CARP) trial and the DECREASE-V pilot study, prophylactic coronary revascularization by percutaneous coronary intervention (PCI) or coronary artery bypass grafting does not appear to alter postoperative outcomes. Accordingly, the current ACC/AHA guidelines recommend preoperative PCI only in patients with an acute coronary syndrome for whom PCI is independently indicated. Patients who undergo coronary revascularization with a bare metal stent should have surgery delayed for 4 to 6 weeks but no more than 12 weeks when the incidence of stent restenosis begins to rise. Conversely, patients who have a drug-eluting stent (DES) placed should have surgery delayed for a year if possible while the patient is on dual antiplatelet therapy. Aspirin should be continued in the perioperative period if at all possible, and thienopyridine therapy (e.g., clopidogrel) should be resumed as soon as possible after surgery to minimize the risk of stent thrombosis.

Patients with unstable angina or a recent MI bear special consideration. Historic studies suggested that a significant and persistent risk of reinfarction or death existed for up to 6 months after an acute MI. However, with improved perioperative monitoring and management, the rates of such complications after subsequent noncardiac surgery have dropped significantly. A stress test after MI or an episode of unstable angina reliably identifies patients who will benefit from revascularization. Those who have no evidence for at-risk myocardium have a low likelihood of reinfarction with noncardiac surgery and can likely be taken for surgery within 4 to 6 weeks.

Preexisting essential hypertension is a common medical problem among patients facing surgery. Good blood pressure control (<140/90 mm Hg in most patients or <130/80 mm Hg in patients with DM or CKD) is ideal. However, national guidelines do not recommend delaying surgery unless the patient's blood pressure is over 180/110 mm Hg. Patients with poorly controlled hypertension have an increased risk of perioperative blood pressure lability, arrhythmias, and myocardial ischemia. Such patients should have an EKG and renal function testing and should be evaluated for secondary hypertension prior to elective surgery if this workup has not been previously performed. Then, improved blood pressure control should be pursued for 6 to 8 weeks prior to surgery if the urgency of the indicated procedure permits.

Pulmonary

Patients with a known diagnosis of chronic obstructive pulmonary disease (COPD), asthma, upper respiratory tract infections, pneumonia, or other pulmonary conditions warrant special attention. In addition to an assessment of the patient's smoking status, pulmonary functional baseline, need for supplemental oxygen, and current pulmonary medications, use of a pulmonary risk index can aid in the quantification of the perioperative risk of respiratory failure (Table 4). Patients with pulmonary risk factors should have a preoperative CXR supplemented by PFTs in those with unexplained dyspnea. There is no role for routine preoperative arterial blood gas testing. The benefits of perioperative smoking cessation are discussed below. If the patient has had a recent deterioration in pulmonary function in the recent past due to a reversible cause, elective surgery should be deferred until the patient returns to their prior baseline. Patients with COPD should be managed with an inhaled anticholinergic (e.g., ipratropium) and as needed inhaled beta-agonists. Patients with asthma should be maintained on their home medication regimen unless their current symptom control is poor. In these cases, a step-up in therapy in the perioperative period is warranted. Prophylactic administration of glucocorticoids to asthmatics is not

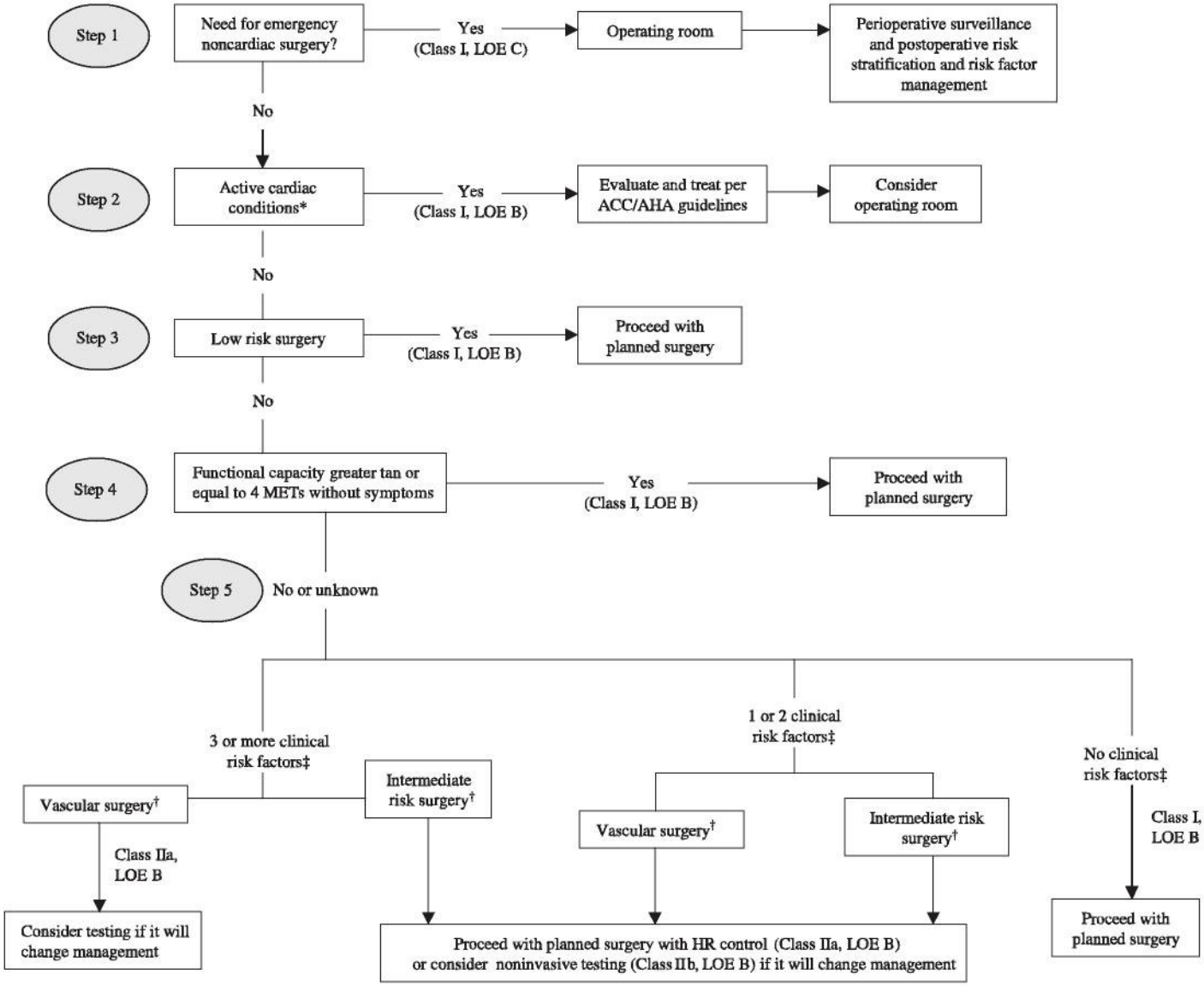

Fig 1. 2007 ACC/AHA algorithm for the perioperative cardiovascular management of patients aged 50 and above undergoing noncardiac surgery (Adapted from Fleisher et al. 2007.) *Active cardiac conditions include unstable or severe angina, MI between 7 and 30 days prior, decompensated heart failure, significant arrhythmia, severe aortic stenosis, or symptomatic mitral stenosis. †Low risk surgery includes endoscopic procedures, superficial procedures, cataract surgery, breast surgery, and ambulatory surgery; intermediate risk surgery includes intraperitoneal/intrathoracic surgery, carotid endarterectomy, head and neck surgery, orthopedic surgery, and prostate surgery; vascular surgery includes aortic and other major vascular surgery (except carotid endarterectomy) and peripheral vascular surgery. ‡Clinical risk factors are similar to the revised Cardiac Risk Index factors in Table 3 and include history of ischemic heart disease, cerebrovascular disease, compensated or prior heart failure, diabetes mellitus, and renal insufficiency.

required unless they are maintained on systemic or high-dose inhaled steroids. In patients at high risk for perioperative pulmonary complications, consideration should be given to use of spinal or epidural anesthesia over general anesthesia. Long-acting neuromuscular blockade (e.g., pancuronium) should be avoided. If a laparoscopic surgical option is available, this should be used over open surgery if possible. For postoperative risk mitigation, an epidural catheter for analgesia should be planned in these patients, and preoperative incentive spirometry teaching should be conducted so the patient is prepared to participate in early and aggressive postoperative lung expansion.

Renal

Chronic renal insufficiency with a serum Cr of ≥2 mg/dL is an independent predictor of postoperative cardiac complications. In addition, the surgical team must take special care to avoid further kidney injury in these patients by maintaining euvolemia, taking appropriate precautions to avoid contrast-induced nephropathy, and by appropriately dosing all medications while minimizing the use of those with potential nephrotoxic effects. In addition, in the perioperative period, intravascular volume status can be more difficult to gauge in this patient population; so we are aggressive with employing all available monitors to assure adequate intravascular volume to include use of a pulmonary artery catheter in some cases.

Patients with end-stage renal disease (ESRD) require coordination of perioperative care between the surgical team, the anesthesia team, and nephrology. Preoperative electrolytes should be obtained in close proximity to the procedure to ensure the serum

Table 4 Arozullah Respiratory Failure Index and the Associated Risk of Respiratory Failure[a]

Preoperative predictor		Points
Type of surgery		
Abdominal aortic aneurysm		27
Thoracic		21
Neurosurgery, upper abdominal, peripheral vascular		14
Neck		11
Emergency surgery		11
Albumin <3 g/dL		9
BUN >30 mg/dL		8
Partially or fully dependent functional status		7
History of COPD		6
Age		
>70 years		6
60 to 69 years		4
Class	**Points**	**Risk of respiratory failure (%)**
1	≤10	0.5
2	11 to 19	1.8 to 2.1
3	20 to 27	4.2 to 5.3
4	28 to 40	10.1 to 11.9
5	>40	26.6 to 30.9

Adapted from Arozullah et al. (2000).
[a]Respiratory failure is defined as either mechanical ventilation for >48 hours after surgery or reintubation and mechanical ventilation after initial postoperative extubation.

potassium is within normal limits and that there are no significant derangements in the other values. If the patient is on hemodialysis or peritoneal dialysis, the timing of pre- and postoperative dialysis should be decided upon in advance. Patients who are on the cusp of requiring renal replacement therapy (RRT) require similar surveillance and coordination in the event that transient RRT is required for postoperative electrolyte management, volume overload, or azotemia.

Liver

Patients with preexisting hepatic failure are at increased risk for complications and death after surgery. The Child–Turcotte and Child–Pugh classification schemes were originally developed to estimate the risk of death after portal-caval shunting and have since been validated as a good estimate for death following a range of other surgeries. More recently, the model for end-stage liver disease (MELD) score has also been used to assess perioperative risk in these patients (Table 5). An online calculator, which uses the patient's age, ASA class, and MELD score to calculate 7-day, 3-day, 90-day, 1-year, and 5-year predicted mortality is also available at http://www.mayoclinic.org/meld/mayomodel9.html.

In general, patients with mild cirrhosis (Child's A or MELD < 10) tolerate surgery well while patients with fulminant hepatic failure, severe hepatitis, extrahepatic complications, and advanced cirrhosis (Child's C or MELD > 15) are likely to have a poor postoperative outcome and should have surgery delayed until their liver function can be optimized or they undergo a liver transplantation if possible. Patients with moderate cirrhosis (Child's B or MELD 10 to 15) can be considered for surgery after careful preoperative evaluation. Reports of herniorrhaphy outcomes in these patients (both umbilical and inguinal) suggest that these operations can be performed safely. Similarly, cholecystectomy has been reported in patients with cirrhosis for a range of indications, and recent reports indicate that the laparoscopic approach is safe and appears to have improved outcomes when compared with open cholecystectomy. The preoperative preparation of these patients should focus on minimizing ascites, correcting vitamin deficiencies (especially vitamin K), and assessing for and correcting malnutrition.

Table 5 Use of the MELD Score for Preoperative Risk Assessment in Patients with Cirrhosis

	Mortality (%)		
MELD Score	**7-day**	**30-day**	**90-day**
0 to 7	1.9	5.7	9.7
8 to 11	3.3	10.3	17.7
12 to 15	7.7	25.4	32.3
16 to 20	14.6	44.0	55.8
21 to 25	23.0	53.8	66.7
≥26	30.0	90.0	90.0

Adapted from Teh et al. (2007).
MELD, model for end-stage liver disease.

Endocrinopathies and Obesity

Diabetes mellitus is a common medical condition present in up to 20% of surgical patients. As shown in Table 3, insulin-requiring diabetes is a marker for increased postoperative cardiac morbidity in the RCRI. Historic glycemic control is a known marker for postoperative infections (pneumonia, wound infection, UTI, and sepsis), and poor perioperative glycemic control has been shown to correlate with surgical complications and death. Thus, careful attention must be paid by the surgical team to cardiac risk modification in diabetic patients and to glucose management throughout the entire perioperative period to assure optimal outcomes.

A reliable measure of historic glycemic control over the previous 3 months is the hemoglobin A_{1C} (Hb A_{1C}). If the Hb A_{1C} is > 7%, postoperative infections are increased while a preoperative glucose level of >200 mg/dL is associated with an increased rate of postoperative deep wound infections. Perioperative management of oral hypoglycemics and insulin is discussed below (see section on "Medication Management").

Patients with hypothyroidism should continue on their baseline medication regimen throughout the postoperative period. Those who are nil per os (NPO) can have these medications safely held or converted to IV supplementation if a prolonged period of fasting is anticipated. Those with hyperthyroidism undergoing surgery should achieve a euthyroid state before surgical intervention and their antithyroid medications should be continued up until the time of surgery. If urgent surgery is required in a thyrotoxic patient, consultation with an endocrinologist is warranted.

Obesity has been extensively evaluated as a risk factor for poor perioperative outcomes. Recent evidence suggests that, in fact, there is a so-called "obesity paradox" in that such patients have fewer complications than controls. The exceptions to this paradox are wound and thromboembolic complications

including deep venous thrombosis (DVT) and pulmonary embolism (PE).

Malnutrition

Preoperative malnutrition has been recognized as an important risk factor for postoperative morbidity and mortality for over 70 years. Quantification of the degree of malnutrition and the correction of severe malnutrition preoperatively remain an important part of surgical management. Assessment of nutritional status begins with a thorough history and physical examination paying careful attention to dietary changes, evidence of malabsorption, and evidence for loss of lean body mass. The Subjective Global Assessment has been used to facilitate this evaluation. Laboratory testing should include albumin, transferrin, and prealbumin to assess the long-term, intermediate-term, and short-term nutritional state of the patient, respectively. If the patient is found to be severely malnourished, surgery should be delayed so that supplemental nutrition can be administered. Enteral supplementation is preferred if the patient can tolerate this route; otherwise, parenteral nutrition (PN) should be initiated. In this population, improvements in nutritional status are assessed at regular intervals until surgery is deemed safe (after 7 to 15 days in some studies). Supplemental nutrition is then continued postoperatively until the patient can meet their caloric needs independently.

Coagulopathy

Patients with inherited coagulopathies and those who are maintained on therapeutic anticoagulation present special challenges with regards to achieving and maintaining postoperative hemostasis. Perioperative management of anticoagulant and antiplatelet medications is discussed below (see section on "Medication Management"). The most common intrinsic coagulopathies in surgical patients are von Willebrand's disease and the hemophilias. Patients with chronic renal insufficiency also have some baseline degree of platelet dysfunction. The surgical review of systems should specifically focus on a predilection for prolonged epistaxis, easy bruising, and any bleeding complications during previous surgeries. If this evaluation is negative for a bleeding history and the physical examination does not reveal any petechiae or stigmata of chronic renal or liver disease, routine testing of coagulation studies is not indicated. If these studies are obtained and are abnormal, a mixing study is required to determine whether the abnormality is the result of a factor deficiency or an inhibitor (e.g., lupus anticoagulant). If the patient's personal family history is strongly suggestive of an undiagnosed coagulopathy, consideration should be given to testing for von Willebrand's disease using the triad of plasma von Willebrand's factor (VWF) antigen, plasma VWF activity, and factor VIII activity. Patients who carry a diagnosis of von Willebrand's disease should be pretreated in consultation with a hematologist with either desmopressin (DDAVP) for minor surgery if the patient has previously responded or with VWF concentrate for major surgery. Patients with mild hemophilia A or B can similarly be pretreated with DDAVP while those with severe hemophilia can be treated with specific factor concentrates (Factor VIII or IX) or activated Factor VII in the presence of inhibitors. Patients with thrombocytopenia (e.g., those with inherited thrombocytopenic purpura) should have a preoperative platelet transfusion targeting a minimum of 50,000/μL.

Malignancy and Immunocompromise

Patients with malignancy and those on immunosuppressive medications or with an inherited or acquired immunocompromised state frequently undergo surgery. The preoperative evaluation should proceed as described above guided by the patient's other medical conditions and nutritional status. For patients on chemotherapy, the timing of the last dose of chemotherapy, the projected cell count nadirs, and planned future therapy should be discussed with the patients and their oncologist. For patients with HIV, a history of an AIDS-defining illness and their current medication regimen should be elicited. Laboratory testing should include a CBC with differential, chemistries, renal function, and liver function studies. If malnutrition is suspected by history and physical examination, nutrition labs should be obtained. Patients with HIV should have a CD4 and a viral load obtained as the former is a surrogate for immunocompetence while the latter has been specifically correlated with increased perioperative complications at a level of 30,000 copies/mL or greater. Patients with neutropenia should have surgery delayed if at all possible. For those with neutropenia in the postoperative state, development of fever should prompt treatment with broad-spectrum antibiotics and, in some cases, an antifungal agent as well. The role of colony stimulating factors in neutropenic patients is limited to those with additional indicators that prolonged neutropenia will be poorly tolerated such as poor functional status, poor nutrition, an open wound, or active infection. It has been shown that although these stimulating factors reverse the neutropenia, they do not reliably reduce hospital length of stay or culture-positive infections.

Rheumatologic

Patients with rheumatologic diseases have a high incidence of associated cardiovascular disease as well as unique pathology, which increases the risk of perioperative complications. Patients with rheumatologic conditions are often maintained on immune-modulating medications such as glucocorticoids, methotrexate, and so-called biologic agents that interfere with the action of TNF and IL-1. The perioperative management of these medications is discussed in section on "Medication Management." In patients with rheumatoid arthritis, lateral cervical spine films with flexion and extension should be obtained within a year of surgery to assess for atlantoaxial subluxation. Patients with ankylosing spondylitis with severe kyphotic deformities may be difficult to intubate, and thoracic cavity restriction may require postoperative ventilator support. Thus, preoperative anesthesia and critical care consultations should be considered. Likewise, patients with scleroderma can present special anesthetic challenges, including a small oral aperture, difficult intravenous access, a propensity for vasospasm, prolonged response to local anesthetics, and a significant risk of aspiration due to esophageal dysmotility. In addition, preoperative detection of pulmonary or myocardial involvement is essential; so consideration should be given to obtaining PFTs, an arterial blood gas, and echocardiography in addition to a CXR and EKG. Patients with psoriatic arthritis should be advised of the risk for a psoriatic flare at both the surgical and the remote sites. In addition, these patients may be at increased risk for postoperative infection. Patients with systemic lupus erythematosus (SLE) are at increased risk for postoperative wound infection, renal insufficiency, and thrombotic complications, including pulmonary embolism. SLE patients with active disease and imminent vital organ failure can be treated with intravenous immunoglobulin in the perioperative period.

PREOPERATIVE BEHAVIORAL MODIFICATION

In addition to risk modification interventions discussed above, a number of preoperative behavioral modification strategies have been investigated in an attempt to improve surgical outcomes. The most widely published interventions include smoking cessation, preoperative weight loss, and various preoperative exercise regimens (so-called prehabilitation).

Historic evidence suggested that smoking cessation within 8 weeks of surgery actually results in increased pulmonary complications, presumably from bronchorrhea. On the other hand, several smaller studies indicate that some complications such as wound infections and seromas are reduced if smoking cessation occurs as early as 4 weeks prior to surgery although these studies have been inadequately powered to detect differences in pulmonary complications.

Although obesity is associated with an overall increase in cardiovascular disease as well as perioperative wound and thromboembolic complications, the effect of preoperative weight loss on these risks has not been well studied. In patients preparing for bariatric surgery, preoperative weight loss has been correlated with more durable postoperative weight loss. However, improved perioperative surgical outcomes in terms of fewer surgical complications, cardiovascular events, or pulmonary complications have yet to be documented for either bariatric surgery or other surgical procedures in the obese population.

Because functional status correlates strongly with cardiovascular and pulmonary complication rates, several groups have investigated the benefits of specifically targeting improved functionality in the preoperative period. Recent evidence suggests that a simple regimen of daily walking and deep breathing exercises improves exercise capacity in patients awaiting abdominal surgery, an effect that is preserved postoperatively. Similarly, preoperative inspiratory muscle training appears to result in fewer pulmonary complications and a shorter hospital stay.

MEDICATION MANAGEMENT

Adult patients facing surgery are often taking a number of medications for management of their chronic medical conditions. Prior to surgery, a complete list of all medications and herbal supplements must be obtained from the patient and reconciled with the most recent list of medications in their medical record. The most common outpatient medications and their recommended perioperative management are summarized in Table 6. In general, essential medications are continued through surgery with any doses due at the time of surgery taken with a sip of water. Essential medications and those with a significant risk of rebound effects (e.g., beta blockers and clonidine) are continued in an enteral, parenteral, transdermal, or inhaled form during the early postoperative period. As soon as feasible, the patient's outpatient medication regimen should be resumed or revised in consultation with their primary care physician or medical specialist.

Because of the risk of hemorrhage with surgical intervention, the management of outpatient therapeutic anticoagulation in the perioperative period bears special mention. Patients are maintained on anticoagulation for a range of indications from the management of thromboembolic events to anticoagulation for prosthetic heart valves. The indication for anticoagulation dictates the need for therapeutic "bridge" therapy with a short acting agent while both the surgical procedure and the indication for anticoagulation are used to develop a postoperative anticoagulation plan. For patients with mechanical heart valves, the 2006 ACC/AHA guidelines are the most straightforward to apply. In a patient with a bi-leaflet mechanical aortic valve and no additional risk factors for hypercoagulability (e.g., atrial fibrillation or previous thromboembolism among others), warfarin can be held 48 to 72 hours prior to surgery with an INR checked on the day of surgery targeting less than 1.5. All other patients (e.g., those with mechanical mitral valves and those with additional risk factors for thromboembolism or hypercoagulability) should be managed with bridge therapy. These guidelines recommend the use of therapeutic heparin during this time although therapeutic low-molecular-weight heparin is included in other guidelines. Postoperatively, in patients who do not require bridge therapy, warfarin is resumed 24 hours after surgery. Those on bridge therapy have their anticoagulation resumed as soon as the bleeding risk permits, usually at 24 hours after surgery.

In all other conditions for which patients are on therapeutic anticoagulation, the perioperative management of this regimen requires an estimate of the bleeding risk from surgery and the risk of a perioperative thromboembolic complication. There are no guidelines to inform practice, but some general practice recommendations can be made from the current literature on this topic. Patients with a recent episode of venous or arterial thromboembolism should have surgery delayed for at least 1 month if at all possible. Minor surgery (e.g., outpatient herniorrhaphy or cataract surgery) can be done safely in patients on warfarin so long as the INR is at the low end of the therapeutic range. Those undergoing major surgery should have warfarin therapy withheld approximately 5 days prior to surgery with an INR checked on the day of surgery. Those on the orally available direct thrombin inhibitor dabigatran (Pradaxa) should have this withheld 1 to 2 days before surgery if renal function is normal or 3 to 4 days with a Cr clearance <50 mL/min. Bridging anticoagulation with either intravenous heparin or therapeutic low-molecular-weight heparin should be used in patients at high or intermediate risk for a thromboembolic event. For many indications including atrial fibrillation, individual patient risk stratification should be conducted to determine the need for bridge therapy. Bridge therapy with heparin should be held 4 to 5 hours prior to surgery while low-molecular-weight heparin should be held 24 hours prior. As mentioned above, postoperative resumption of bridge therapy or oral anticoagulants depends on the risk of postoperative bleeding but generally can be considered after 24 hours.

Patients on antiplatelet therapy also commonly face noncardiac surgery. The availability of thienopyridines (e.g., clopidogrel) and the significant increase in DES implantation have also made the scenario of dual antiplatelet therapy in the surgical patient increasingly common. Patients on antiplatelet therapy should have a careful history taken to determine their indication for treatment—primary prevention versus prophylaxis against stent thrombosis. As described above, in patients with coronary stents, the timing of surgery should take into consideration the type of stent and the age of the stent. Similarly, the risk of hemorrhage from the surgery should be considered. Cataract surgery is often performed in the patient on aspirin as is coronary artery bypass grafting. If aspirin is held, this should be 7 to 10 days prior to surgery and then resumed when surgical hemostasis is assured, typically within or at 24 hours of the operation. The use of clopidogrel or another thienopyridine either alone or in combination with aspirin should be elicited as well. Some limited data in the vascular surgery literature suggests that with careful attention to hemostasis, even major vascular operations can be done on dual antiplatelet therapy if necessary with no significant increase in perioperative bleeding complications.

Patients with rheumatologic diseases as well as many other conditions ranging from reactive airway disease to inflammatory bowel disease are maintained on systemic glucocorticoids. Although historically, these patients were given additional steroid doses in the perioperative period—so-called stress dose steroids—recent evidence has called this routine practice into question. Patients who have been on prednisone doses of 20 mg/day (or the equivalent of another agent) for 3 weeks or more or who have a Chushingoid appearance should be presumed to have hypothalamic–pituitary–adrenal (HPA) suppression, which will require supplemental steroid dosing. For patients on lower doses,

Table 6 Perioperative Management of Outpatient Medications and Herbal Supplements

Medication class	Comment
Cardiovascular Medications	
Beta blockers and non-dihydropyridine calcium channel blockers	Acute withdrawal of beta blockers can increase morbidity and mortality. Continue perioperatively. Consider substituting a beta blocker in patients taking non-dihydropyridine calcium channel blockers.
Alpha-2 agonists	Acute withdrawal can precipitate rebound hypertension although this is usually at higher oral doses. Continue perioperatively.
ACE inhibitors, ARBs	Generally continue perioperatively when blood pressure is stabilized and renal function is at baseline. Consider holding one preoperative dose in patients with a low baseline blood pressure.
Dihydropyridine calcium channel blockers	Resume when blood pressure has stabilized.
Diuretics	Resume when blood pressure has stabilized and renal function is at baseline.
Statins	Withdrawal may increase perioperative cardiovascular events. Continue perioperatively.
Other lipid lowering agents	Increased risk of myopathy perioperatively with some (e.g., niacin); others interfere with GI absorption (e.g., colestipol). Hold perioperatively.
Agents Affecting Hemostasis	
Aspirin	Balance individual patient risk of cardiovascular event versus the consequences of a bleeding complication. Hold for 7 to 10 days preoperatively if bleeding would cause significant morbidity. Resume when hemostasis is adequate (e.g., within 12 to 24 hours of surgery).
Thienopyridines (e.g., clopidogrel and ticlopidine)	If given for a DES placed within the past year, consider delaying surgery. Hold for 5 to 10 days preoperatively if bleeding would cause significant morbidity. Resume when hemostasis is adequate (e.g., within 12 to 24 hours of surgery).
Dipyridamole	Hold for 2 days preoperatively if bleeding would cause significant morbidity.
NSAIDs/COX-2 Inhibitors	Hold NSAIDs for 24 to 72 hours preoperatively. COX-2 inhibitors have minimal effect on platelet function but have potential for renal toxicity and can lead to cardiovascular events.
Heparin/LMWH	Management depends on the indication and dose. Administer prophylactic doses preoperatively if indicated according to the patient's risk profile for a VTE complication; Therapeutic doses are generally held for 6 to 12 hours preoperatively and are resumed when hemostasis is assured postoperatively (usually within 12 to 24 hours).
Warfarin	See discussion in the body of the chapter for recommendations on holding and resuming warfarin.
Dabigatran	See discussion in the body of the chapter for recommendations on holding and resuming dabigatran (Pradaxa).
Pulmonary Medications	
Inhaled bronchodilators	Continue perioperatively
Leukotriene inhibitors (e.g., montelukast [Singulair])	Resume when tolerating oral medication
Theophylline	May cause arrhythmias and neurotoxicity. Hold perioperatively.
Diabetic Medications	
Insulin	See discussion in the body of the chapter. Determine the sensitivity factor for patients using an insulin pump.
Oral hypoglycemics	Hold on the morning of surgery. Resume when tolerating a regular diet and risk of returning to NPO status is minimal. Ensure normal renal function prior to resuming metformin.
Other Endocrine/Hormonal Agents	
Thyroxine (T4)	Can be safely held for 5 to 7 days postoperatively; resume when tolerating oral medications. Parenteral dose is approximately 80% of the oral dose
Oral contraceptives, HRT, and selective estrogen receptor modulators (e.g., tamoxifen)	In patients at increased risk for VTE, discontinue 6 weeks preoperatively. Resume when the risk of VTE has resolved.
Glucocorticoids	See discussion in the body of the chapter.

(*continued*)

Table 6 Perioperative Management of Outpatient Medications and Herbal Supplements (*Continued*)

Medication class	Comment
Rheumatologic Agents	
Antirheumatic agents	There is no definitive increased risk of wound complications with these agents. Methotrexate can be continued preoperatively in patients with normal renal function; sulfasalazine and azathioprine should be held for 7 days preoperatively; hydroxychloroquine can be continued periopeartively; biologic agents (e.g., etanercept [Humira] and rituximab [Rituxin]) should be held for 7 or more days preoperatively.
Gout agents	Hold on the morning of surgery. Resume when tolerating oral medications.
Neurologic Agents and Chronic Opioids	
Antiepileptic agents	Continue perioperatively. In patients at low risk of a generalized seizure, resume when tolerating oral medications. In patients at increased risk, administer a parenteral antiepileptic agent.
Anti-Parkinson agents	Anti-Parkinson agents increase the risk of perioperative hemodynamic lability and arrhythmias while abrupt withdrawal may result in neuroleptic malignant syndrome and worsening of Parkinsonian symptoms. Dopamenergic agents should be tapered to the lowest possible dose 2 weeks preoperatively and restarted at this dose postoperatively.
Chronic opioids	Patients on methadone should have their maintenance dose continued periopeartively. Methadone can be given subcutaneously or intramuscularly (at 1/2 to 2/3 of the usual dose divided into two to four equal doses) for patients who cannot tolerate oral medications.
Psychotropic Medications	
SSRI	May interfere with platelet aggregation; so balance the risk of bleeding against the risk of exacerbating the underlying disorder.
MAOI	Management of an MAOI perioperatively should involve consultation with an anesthesiologist and the patient's psychiatrist.
Lithium	Consider checking thyroid function tests preoperatively. Continue perioperatively; monitor for nephrogenic DI and serum lithium levels.
Antipsychotics	Continue with caution in patients at risk for exacerbation of psychosis; monitor QT interval; be aware of drug–drug interactions.
Anxiolytics	Continue perioperatively if used on a chronic, routine basis.
Psychostimulants (e.g., methylphenidate [Ritalin])	Hold on the day of surgery. Resume when the patient is stable.
Other	
Herbal medications	Some are associated with an increased risk of MI and stroke (ma huang), bleeding (ginko, ginseng, and garlic), hypoglycemia (ginseng), or altered drug effects. Hold for 7 days preoperatively.

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; NSAID, nonsteroidal anti-inflammatory drug; LMWH, low-molecular-weight heparin; HRT, hormone replacement therapy; VTE, venous thromboembolism; SSRI, selective serotonin reuptake inhibitor; MAOI, monoamine oxidase inhibitor; DI, diabetes insipidus; MI, myocardial infarction.

our usual approach is to resume their home dose or the equivalent in the postoperative period and observe for hemodynamic instability or significant malaise as a trigger for supplemental steroid dosing. An alternative strategy is to perform specific testing for HPA suppression using either high- or low-dose ACTH stimulation testing. Those who respond normally will likely not need supplemental steroid dosing postoperatively.

There has been some recent interest in perioperative risk reduction through initiating new medications around the time of surgery. Examples include starting a beta blocker or statin in patients with cardiovascular risk factors in the immediate preoperative period. Enthusiasm for initiation of beta blockers around the time of surgery has been recently tempered by the results of the POISE trial and a subsequent meta-analysis, which indicated that although this practice reduces the incidence of perioperative MI, the incidence of perioperative stroke is increased and all-cause mortality is either increased or, at best, unchanged (although the dose of beta blockade in the POISE trial was moderately aggressive at 200 mg of extended release metroprolol daily). In light of these results, the ACC/AHA released a focused update to their perioperative guidelines in 2009, which recommend against the initiation of high-dose beta blockade without dose titration in beta-blocker-naïve patients undergoing surgery. Similarly, the indications for perioperative statin initiation in those without classic indications for lipid lowering therapy have been clarified by recent studies. These indicate that vascular surgery patients likely benefit from this intervention with fewer episodes of myocardial ischemia and a lower perioperative cardiac death rate.

PREOPERATIVE SPECIALTY CONSULTATION

Patients with complex or refractory medical problems may benefit from preoperative consultation by a general medical internist, geriatrician, or other medical specialist. Studies evaluating patient outcomes and utilization of medical resources with this practice have generated mixed results. However, provided the consultant's role is clearly delineated in the initial request and the consultant makes evidence-based recommendations, surgeon satisfaction is high and the surgical patient's care is likely to improve. It should be evident from the discussion above that asking a medical consultant to "clear" a patient for surgery is a nonsequitur. Instead, the surgeon should ask specific questions relating to risk stratification and perioperative management of particular disease processes or medications. With this approach, the consultant's input is more likely to be useful to the surgeon and the surgical team in making decisions on surgical timing and perioperative management strategies. Postoperatively, continued involvement of these consultants or a medical hospitalist can, in some cases, improve the care of the patient and should be considered by the surgeon.

RISK REDUCTION IN THE IMMEDIATE PERIOPERATIVE PERIOD

Multiple interventions and quality improvement measures have been advanced in recent years to reduce the risk of adverse events in the OR ranging from wound infections to wrong-site surgery. This section reviews some of the processes that now routinely occur as a result of these initiatives and the management decisions that are most often made from the time the patient enters the preoperative area until the surgical intervention commences. In our view, surgeons should continue to take a leading role in directing the surgical team during this time in the patient's care as it sets the stage for the entire postoperative course.

SURGICAL CHECKLIST AND PREOPERATIVE TIMEOUT

Increased awareness of wrong-site surgery led to a summit to address this problem in 2003 and 2007. Attended by leaders from multiple surgical organizations and the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), the 2003 summit resulted in the introduction of the Universal Protocol for Preventing Wrong Site, Wrong Procedure, Wrong Person Surgery in 2004. This protocol consists of three components: preoperative verification of patient information, surgical site marking to prevent ambiguity with unilateral procedures, and conducting a presurgical timeout to review the planned procedure and resolve any concerns. Many hospitals promote use of the final presurgical time out as an opportunity for the entire OR team to review the surgical plan and to confirm that all necessary medications have been given. Despite (or perhaps because of) this increased emphasis on patient safety, the number of reported wrong-site procedures has steadily increased since the introduction of the Universal Protocol. The anticipation by proponents of this culture of safety is that as the number of reports rise and the freedom to raise safety concerns in the OR disseminates, the frequency of major errors will decrease significantly.

The Safe Surgery Saves Lives Study Group has recently evaluated an intraoperative checklist developed from the World Health Organization (WHO) guidelines for improving perioperative surgical safety. The 19-item checklist used by this group (Fig. 2)

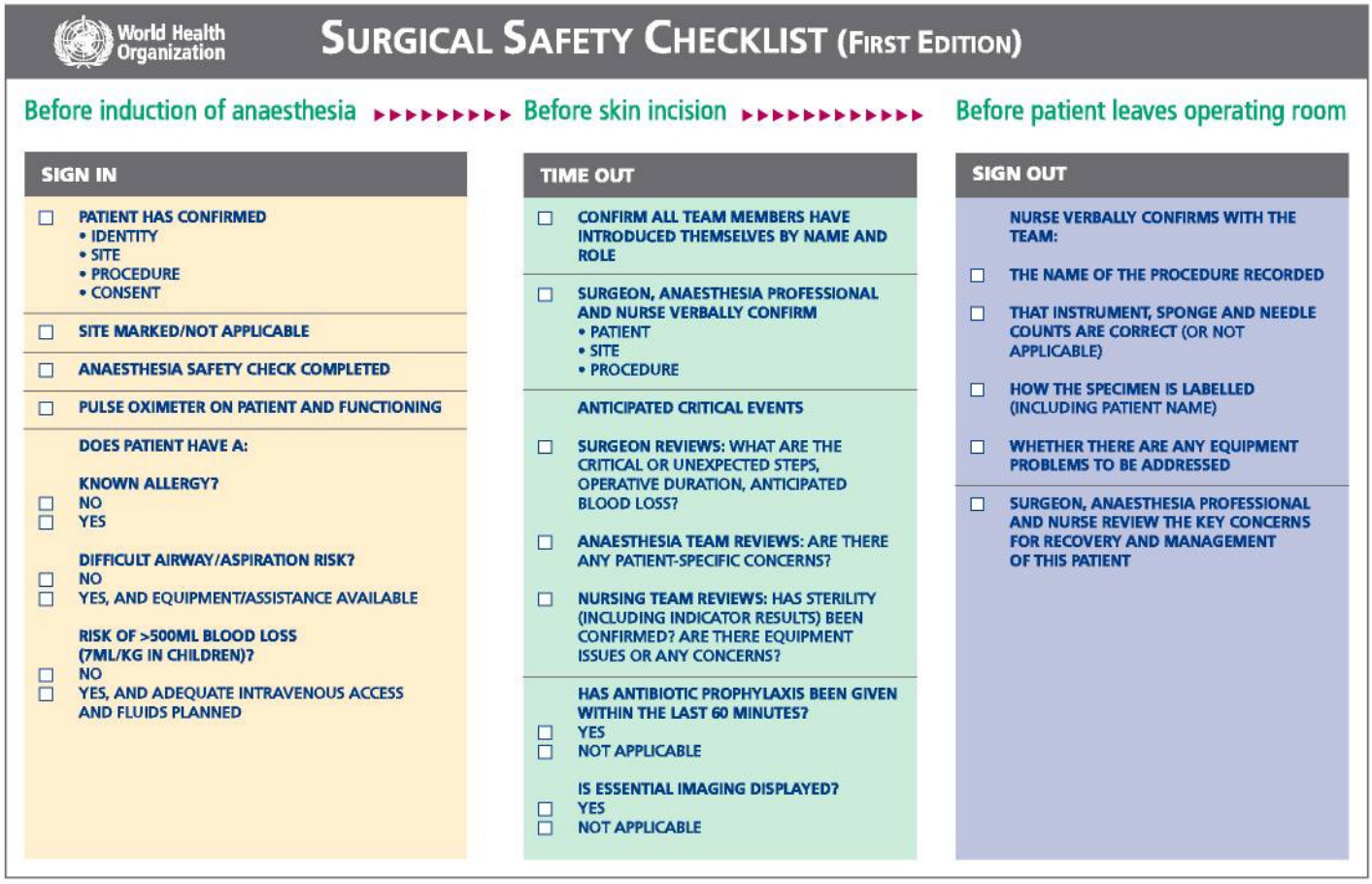

Fig 2. Perioperative checklist. (Adopted from the WHO guidelines for safe surgery, 2008.)

emphasizes communication between the patient and all the various surgical team members in the immediate preoperative period and then focuses the team on critical decisions and communication points in the OR and at the conclusion of the procedure. Use of this checklist in eight different hospitals in eight countries resulted in fewer postoperative complications, including death. This report and others highlight the importance of communication between the surgeon, anesthesiologist, OR nurse, surgical technician, and the patient to ensure that the planned surgical procedure is conducted safely and unplanned intraoperative contingencies are readily identified and well managed.

PREVENTION OF DEEP VENOUS THROMBOSIS

Venous thromboembolic (VTE) complications are an all too common perioperative complication. Over half of surgical patients are at moderate risk or greater for VTE events in the postoperative period, and PE is still the most common preventable cause of hospital death. In a recent study of surgical inpatients in 358 hospitals in 32 different countries, although 64.4% of patients were found to be at-risk for VTE, only 58.5% of patients received appropriate VTE prophylaxis. The American College of Chest Physicians Evidence-based Clinical Practice Guidelines (8th edition) on the Prevention of Venous Thromboembolism have been used to establish local policies in many hospitals and serve as a benchmark for best practice in this area (Table 7). These guidelines stratify patients into low-, moderate-, and high-risk categories based principally on the nature of the surgical procedure—an approach that relies on overall group risk assessment as opposed to individual risk assessment. Although some investigators have attempted to develop individual patient risk assessment models, to date, none of these models have been validated. In fact, it appears with few exceptions that the principal predictor of risk is the primary reason for the patient's hospitalization.

Mechanical thomboprophylaxis includes intermittent pneumatic compression devices, venous foot pumps, or graduated compression stockings. These modalities have been shown to reduce the risk of DVT in numerous patient populations. However, they have not been demonstrated to reduce the rate of PE or death, and compliance with their use is often poor in the postoperative period. Nonetheless, they are at low risk preventive measure that can be initiated prior to induction of anesthesia in most surgical patients. Those patients at moderate to high risk of VTE should be considered for chemoprophylaxis starting preoperatively within 2 hours of surgery. If the patient is to receive an epidural catheter, local policies should be developed weighing the risk of VTE versus an epidural hematoma as detailed in the American Society of Regional Anesthesia and Pain Medicine (ASRA) evidence-based guideline on regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy. In patients at moderate and greater risk of VTE perioperatively, chemoprophylaxis should be started or resumed as soon as bleeding risk is acceptably low, often shortly postoperatively. This therapy should be continued through the inpatient course in most cases. High-risk general surgical patients, who have undergone major oncologic surgery should also be considered for extended chemoprophylaxis for up to 28 days, even as an outpatient.

Table 7 Summary of the Level of Thromboembolism Risk and Recommended VTE Prophylaxis in Hospitalized Patients from the American College of Chest Physicians Evidence-Based Clinical Practice Guideline on the Prevention of Venous Thromboembolism (8th Edition)

Risk group	Group characteristics	DVT risk without prophylaxis	Suggested prophylaxis
Low	Minor surgery in mobile patients	<10%	No specific prophylaxis; early, "aggressive" ambulation
Moderate	Most general surgery patients Moderate VTE risk and high bleeding risk	10% to 40%	LMWH, LDUH BID or TID, fondaparinux Mechanical prophylaxis
High	Major trauma, SCI	40% to 80%	LMWH, fondaparinux, warfarin (INR 2 to 3)
High	High VTE risk and bleeding risk		Mechanical prophylaxis

From Geerts et al. (2008).
LMWH, prophylaxis dose low molecular weight heparin; LDUH, low-dose unfractionated subcutaneous heparin; VTE, venous thromboembolism; SCI, spinal cord injury; INR, international normalized ratio.

POSTOPERATIVE ILEUS PREVENTION

Patients undergoing bowel resection are at risk for development of a postoperative ileus. The recent availability of peripherally acting mu-opioid receptor antagonists (PAM-OR) such as alvimopan (Entereg) allows surgeons to preemptively treat patients at risk for postoperative ileus. The first dose is given orally from 30 minutes to 5 hours prior to surgery and is then continued during the inpatient course. Use of this preventive strategy appears to result in earlier return of bowel function by multiple measures and shorter inpatient hospital length of stay. Use of chronic narcotics is a contraindication to use of this medication, and hospitals that wish to offer this medication must participate in the ENTEREG Access Support and Education (E.A.S.E.™) Program.

WOUND INFECTION

The Surgical Care Improvement Project (SCIP) sought to reduce postoperative complications (primarily SSI and VTE) by 25% from 2006 to 2010. This broad-based initiative supported by numerous national organizations used a number of quality measures to achieve this goal by promoting evidence-based practice. SCIP quality measures specific to perioperative infectious complications include timely administration of prophylactic antibiotics (within 1 hour prior to the incision), use of appropriate antibiotics for SSI prophylaxis, timely discontinuation of prophylactic antibiotics (within 24 hours of the end of the operation for noncardiac surgery or 48 hours for cardiac surgery), and appropriate hair removal (no hair removal or use of clippers). Additional SCIP measures relating to infectious complications include use of intraoperative temperature management, early removal of indwelling urinary catheters, and glycemic control on the morning after surgery in cardiac patients. Evidence of the impact of compliance with these measures is just now emerging—initial reports suggest that while global compliance may result in a small reduction in SSI, compliance on individual measures results in little or no improvement in SSI rates.

Recommended perioperative antimicrobial prophylaxis regimens are periodically

updated in several publications including Treatment Guidelines from the Medical Letter (2009). The role of several additional SSI reduction strategies have been clarified in the recent literature, including topical antisepsis, the role of mechanical bowel preparation (MBP) for colorectal surgery, fascial closure techniques, and perioperative oxygen supplementation. A recent study comparing skin antisepsis with a chlorhexidine–alcohol preparation versus betadine in a range of clean contaminated surgical cases demonstrated significantly reduced SSI rates with the use of chlorhexidine–alcohol. However, there was no description of whether the betadine was allowed to dry, and a betadine–alcohol preparation was not included in the study. In addition, use of chlorhexidine-containing solutions is not recommended for preparation of exposed mucosal surfaces and alcohol-based preparations are generally considered too risky for use in emergency operations where enough time may not be afforded for the alcohol to dry prior to the use of electrocautery. Nonetheless, chlorhexidine–alcohol preparation appears to be a good choice for a range of surgical procedures.

MBP has been a mainstay of perioperative surgical practice aimed at reducing anastamotic and wound complications for decades. However, systematic study by multiple investigators and subsequent meta-analyses have not convincingly demonstrated any benefit to this practice with respect to either of these complications. In fact, there may be a slight reduction in anastamotic leakage when preoperative MBP is not performed, although, as of 2003, MBP was still widely practiced by colorectal surgeons. Current guidelines leave the use of MBP to the discretion of the surgeon for open low anterior resection and all laparoscopic colonic procedures where the site of the tumor may not be immediately obvious and where intraoperative colonoscopy may be required. For all other colonic resections, preoperative MBP can be safely eliminated.

Fascial closure techniques for abdominal operations have also been evaluated over many years searching for the optimal method, which reestablishes abdominal domain while minimizing the risk of postoperative wound complications ranging from superficial wound infections to complete dehiscence with evisceration. Most studies evaluating fascial closure methods use incisional hernia as the primary endpoint, and until recently, SSI was thought to not be affected by the technique of fascial closure. However, a recent study suggest that when using a running absorbable suture technique, relatively small (5 to 8 mm), closely spaced fascial bites resulting in a suture to wound length ratio of ≥4:1 may reduce the incidence of SSI. Likewise, there is growing interest in using antibiotic-coated suture material that may also reduce the rate of wound infections.

Oxygen supplementation in the immediate postoperative period has also been evaluated by several randomized controlled trials, including the recently published Perioperative Oxygen Fraction (PROXI) study. Although the original US-based study demonstrated increased infections in the oxygen-treated group and the PROXI study showed no benefit to 80% O_2 supplementation for 2 hours postoperatively, three other studies have shown a benefit to various types of O_2 supplementation. Consequently, pooled analysis of these results still falls in favor of perioperative hyperoxia although the likely benefit is relatively small.

INTRAOPERATIVE RESUSCITATION

Inappropriate management of intravenous fluid volumes during surgery can result in a number of postoperative complications ranging from ranging from pulmonary and renal dysfunction to anastamotic failure and sepsis. Achieving the appropriate balance of adequate intravascular volume and oxygen delivery during the surgical procedure has proven difficult, however. This difficulty arises for many reasons, mostly because direct measures of intravascular volume and end-organ perfusion are not readily available while estimates of intraoperative bleeding and insensible losses are notoriously inaccurate. Furthermore, a standard nomenclature for the various fluid administration strategies is lacking, leading to imprecise and variable definitions from study to study. Recognizing these limitations, it has become clear that either too much or too little intravenous fluid administration of any type is harmful. In major abdominal operations where additional monitoring is justified, a "goal-directed" approach based on surrogates for intravascular volume measurement (e.g., esophageal Doppler measurement of changes in peak aortic stroke velocity or arterial waveform variability) while monitoring indicators of oxygen consumption such as $ScvO_2$ is appealing. Combining this approach with a relatively restrictive (but not too restrictive) background of intravenous fluid administration (e.g., 8 to 12 mL/kg/h) appears to balance the various risks of respiratory failure, renal insufficiency, wound infections, congestive heart failure, and postoperative arrhythmia.

POSTOPERATIVE RISK MINIMIZATION

Relative to preoperative office visits and OR time, the postoperative course typically represents the time in which the patient has the most direct contact with the healthcare system. This poses both advantages and disadvantages—the patient is immediately at hand so that care can be directly monitored, although as the complexity of the system and the duration of contact increases, so to does the possibility of error. The overall goals of this phase of care should be to restore the patient to their preoperative functional level or to an even higher functional level as quickly as possible while minimizing iatrogenic events and nosocomial infections. Recent advances in postoperative care include the introduction of clinical care pathways, development of a systematic approach to care provider handoffs, recognition of the importance of early mobilization even in an intensive care unit (ICU) setting, refinement of our use of postoperative organ support devices and monitors, and clarifying the management goals for chronic illnesses (e.g., diabetes mellitus) in the postoperative time period.

CLINICAL PATHWAYS AND HANDOFFS

Clinical pathways are tools which incorporate evidence-based practice guidelines into a timeline, which is then tracked so that deviations can be monitored. Hospitals and clinical services may develop these pathways to communicate expected postoperative events to patients and support staff while ensuring the consistent use of evidence-based practice for a given disease process. They are best applied to common surgical procedures within moderate- to high-volume centers. Examples include coronary artery bypass graft surgery, laparoscopic Roux-en-Y gastric bypass, and laparoscopic cholecystectomy. Use of these pathways has been shown to standardize patient care while reducing length of hospital stay and use of resources with improved patient satisfaction.

Multiple forces within healthcare from resident work hour restrictions to changing practice models have increased the frequency of patient handoffs between providers. This represents both a time when critical information can be reviewed and summarized and a time where lapses in communication can ultimately lead to poor patient care. Approaches to minimizing the latter include use of a standardized approach to handoffs such as the Situation-Background-Assessment-Recommendation

model, specific training on how to perform a comprehensive patient handoff, and proctored simulation training on performing handoffs. There is emerging evidence that such efforts do indeed avoid lapses in patient care.

POSTOPERATIVE MONITORING AND MANAGEMENT OF CHRONIC MEDICAL ILLNESSES

Postoperatively, patients with chronic medical illnesses require monitoring of these illnesses and a plan for resuming their home medication regimen. Our general approach to postoperative medication management in patients with chronic medical conditions is included in Table 6. Regarding postoperative monitoring, selecting the appropriate level of monitoring usually depends on local hospital policies and unit expertise. In some cases, the type of surgery will dictate the level of care required such as craniotomy patients who need frequent neurologic exams or vascular surgery patients require frequent pulse checks in a specialized unit. Patients on a mechanical ventilator universally undergo postoperative care in an ICU for some period of time. For patients who do not require specialized checks or a ventilator, the patient's chronic illnesses and the extent of surgery will guide the need for postoperative monitoring. In recent years, enthusiasm for the use of pulmonary artery catheter for routine postoperative monitoring in certain patient populations has waned in the absence of any demonstrable benefit and significant risks of complications, including pulmonary artery embolism and rupture in addition to incorrect management decisions made due to misinterpretation of available data. Other monitoring decisions are discussed below individually in the context of each specific organ system.

Patients with known cardiovascular disease should be considered for telemetry monitoring. Some recommend a postoperative 12-lead EKG and a single set of cardiac enzymes in these patients as well although this practice is not universal. These patients should have beta blockers and statins resumed as soon as feasible in the postoperative period. For patients with essential hypertension, target blood pressures are relaxed to avoid hypoperfusion with intervention warranted if systolic pressures trend around 180 mm Hg or diastolic pressures rise to 100 to 110 mm Hg. These patients should have pain and other causes of elevated blood pressure, such as urinary retention ruled out as well. Patients chronically on clonidine should have this resumed early in the postoperative course. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are generally resumed when intravascular volume shifts have subsided and renal function is shown to either remain at baseline or returns to baseline. Similarly, after major surgery, diuretics are resumed when the patient is ready to mobilize fluid or the patient is determined to have little risk for becoming excessively dehydrated.

Patients with chronic pulmonary conditions should be resumed on their home regimen of inhaled beta agonists and anticholinergics via metered dose inhaler or nebulizer either orally or in-line with the ventilator. Inhaled and systemic glucocorticoids for control of reactive airway disease should similarly be continued postoperatively. Leukotriene inhibitors (e.g., montelukast [Singulair]) can be resumed when the patient is taking oral medications. Theophylline should be discontinued perioperatively given its narrow therapeutic window.

Surgical intervention can result in poor glycemic control in diabetic patients or can unmask insulin resistance in patients not previously known to be diabetic. Much attention has been given to glycemic control in the perioperative period over the past decade. Initial enthusiasm for tight glycemic control has been tempered by the recognition of the significant deleterious effects of hypoglycemic events which, in some cases, negate the benefits of tight control. Current recommendations aim for "reasonable" control over normoglycemia in the postoperative period generally defined as most readings below 180 to 200 mg/dL. One benefit of this movement is that surgeons and surgical units are now much more familiar with the management options for patients with hyperglycemia in both the fasted and the partially fasted state ranging from insulin infusions to resumption of subcutaneous insulin regimens. Patients on oral hypoglycemics can generally be managed with a short-acting insulin administered on a sliding scale until oral intake has reliably returned when most of these agents can be restarted. One exception is metformin, which should not be resumed until renal function is proven to be normal and there is little risk of significant intravascular volume shifts, which is generally proximate to the time of discharge.

Postoperative nutritional support is sometimes required if patients were severely malnourished preoperatively or if bowel function does not return within a week of surgery. Options include enteral and PN. If the patient is unable to take adequate calories due to critical illness but the gastrointestinal system is functional, enteral support is preferred. In cases where enteral support is not possible or only partial enteral support can be achieved, PN is used. When this strategy is chosen, care must be taken to meticulously care for the central venous catheter to avoid bloodstream infections, glycemic control should be maintained in a "reasonable" range as described above often with insulin added to the PN mix, protein doses are initially estimated based on the patient's diagnosis and other chronic conditions and then adjusted to avoid azotemia, and fat is used sparingly balancing the avoidance of fatty acid deficiency against the immunosuppressive effects of long-chain fatty acids and the concern that cholestasis and PN-associated hepatic injury may result from intravenous fat formulations currently available in the United States.

Patients with rheumatologic conditions should generally have their medications resumed with the initiation of a postoperative diet. Patients taking methotrexate should have normal renal function confirmed before this agent is restarted. Patients with a history of gouty arthropathy should have colchicine or any hypouricemic agents resumed when they can tolerate oral medications. If a gout flare occurs postoperatively in a patient who is an NPO, management options include intravenous ketorolac (Toradol), intra-articular steroid injections, or systemic steroids.

EARLY MOBILIZATION

Although bed rest was historically routinely prescribed after surgical interventions, the negative side effects of this practice ranging from pressure sores to osteopenia have been recognized for decades. As discussed in the next section, loss of lean body mass is associated with a range of adverse outcomes in the postoperative period, and enforced bed rest has been shown to reduce lean body mass and total body strength in healthy adults. In fact, prolonged weakness is now recognized as one of the most durable and troublesome side effects of critical illness. Efforts to minimize this complication by increasing postoperative mobility have been advanced in a number of patient populations, including cardiac surgical patients, patients undergoing elective colon resection, and in those with respiratory failure on ventilator support. These interventions range from passive range of motion exercises performed by family members and bedside nurses to lengthy training sessions with physical therapists depending