Bailey & Love's

SHORT PRACTICE of SURGERY

Edited by
NORMAN S. WILLIAMS
P. RONAN O'CONNELL
ANDREW W. McCASKIE

27th EDITION

CRC Press
Taylor & Francis Group

Bailey & Love's SHORT PRACTICE of SURGERY

Sebaceous horn
(The owner, the widow Dimanche, sold water-cress in Paris)

A favourite illustration of Hamilton Bailey and McNeill Love,
and well known to readers of earlier editions of Short Practice.

Henry Hamilton Bailey 1894–1961

Robert J. McNeill Love 1891–1974

Skilled surgeons, inspirational teachers, dedicated authors

Bailey & Love's

SHORT PRACTICE of SURGERY

27th EDITION

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CRC Press
Taylor & Francis Group

First published in Great Britain in 1932

This 27th edition published in 2018 by
CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

Printed on acid-free paper

International Standard Book Number-13: 978-1-4987-9650-7 (Pack – Paperback and eBook)
International Standard Book Number-13: 978-1-138-03166-1 (Pack – Hardback and eBook)
International Standard Book Number-13: 978-1-138-03164-7 (International Student Edition; restricted territorial availability)

Library of Congress Cataloging-in-Publication Data

Names: Williams, Norman S., 1947- editor. | O'Connell, P. Ronan, editor. | McCaskie, A. W., editor.
Title: Bailey & Love's short practice of surgery / [edited by] Norman Williams, P. Ronan O'Connell, Andrew McCaskie.
Other titles: Bailey and Love's short practice of surgery | Short practice of surgery.
Description: 27th edition. | Boca Raton, FL : CRC Press, 2017.
Identifiers: LCCN 2017015906 (print) | LCCN 2017018725 (ebook) | ISBN 9781315111087 (General eBook) | ISBN 9781351617994 (Adobe eBook) | ISBN 9781351617987 (ePub eBook) | ISBN 9781351617970 (Mobipocket eBook) | ISBN 9781138031661 (hardback : alk. paper) | ISBN 9781498796507 (pbk. : alk. paper) | ISBN 9781138031647 (international edition pbk. : alk. paper).
Subjects: | MESH: Surgical Procedures, Operative | Perioperative Care.
Classification: LCC RD31 (ebook) | LCC RD31 (print) | NLM WO 500 | DDC 617--dc23
LC record available at https://lccn.loc.gov/2017015906

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Preface to 27th Edition

When Hamilton Bailey and McNeil Love published the first edition of their venerated textbook in 1932 the surgical world was a very different place to that of today. There were no antibiotics, no joint replacement, no open heart surgery, no transplantation and many other procedures that we now take for granted had simply not been invented. Medicine as a whole and surgery in particular never stands still. Surgeons continually strive to innovate so that they can tackle conditions and diseases previously thought to be beyond reach. They do this against a background of new discoveries in both the physical and biological sciences. Such breakthroughs make some surgical procedures redundant but others stimulate new approaches. This is seen in all specialties and consequently it is important for textbooks not only to keep pace with new developments but also to ensure that a balanced view is taken of their place in the therapeutic armamentarium. In developing the 27th edition of this much-loved textbook, we have striven to keep this in the forefront of our minds and those of our contributors. Nevertheless, in addition to considering the place of innovation, it is important not to 'throw the baby out with the bathwater'. We have therefore ensured that the basic tenets of surgical practice that have stood the test of time remain where appropriate.

Since the last edition great strides have been made in certain areas and we have ensured that these have been embedded in the book. For instance, in colorectal surgery a tipping point has been reached whereby more elective surgery is performed laparoscopically than by open technique. Similarly, in vascular surgery there has been an explosion in the use of interventional radiology to treat conditions that were previously the sole province of the surgeon. Stenting of aortic aneurysms (EVAR), for instance, is rapidly replacing elective open operations and, in many instances, is being used for treating leaking aneurysms, with a concomitant marked reduction in mortality. Damage control surgery is an increasingly important part of trauma management, in both civilian and conflict settings. Such developments also highlight the important role of the multidisciplinary team and the realisation that modern surgical care can no longer be provided in isolation. This concept is reiterated throughout the book and is also why the importance of human factors is emphasised in the chapter on patient safety, which is a relatively new science of how humans behave physically and psychologically in relation to particular environments. There is no more intense environment than an operating theatre, so how a surgical team interacts is crucial to the outcome for a patient undergoing a surgical procedure. This also applies, of course, outside the operating theatre because multidisciplinary working is now paramount to the delivery of safe and effective patient care. There is no doubt that in recent years regulation of medical practice has become tighter. Whereas in certain jurisdictions some may feel that this has become stifling, there is no doubt that regulation is here to stay. Needless to say, we should all be aware of our responsibilities to patients, both morally and ethically, and, although most need no reminding, the law is continually changing as test cases are brought before the courts. Hence, we draw the attention of the reader to the revamped chapter on ethics and the law, the tenets of which we must all abide by.

Throughout the text, we have also endeavoured to point out where we and our authors think the specialty is moving. Exciting developments are on the horizon. For instance, genome sequencing will have a marked effect on how we practise in certain specialties, none more so than oncology. Robotics is likely to improve many more surgical procedures and tissue engineering will become more commonplace. In order to accommodate these advances, it has been necessary to streamline some of the more established chapters, otherwise the book would become unwieldy. As a consequence, we have ensured that the 'Further reading' list at the end of each chapter has been brought up to date, allowing readers to delve further if they so wish.

We are very conscious that the book is popular throughout the world and consequently we have ensured that those diseases that are prevalent outside Europe and North America are included. Where relevant we have involved experts who are used to dealing with such maladies. The chapter on tropical infections and infestations is such an example.

We have also endeavoured in this edition to be more consistent in its layout, ensuring that we use a similar format for tables, graphs and diagrams. Nevertheless, we have been sure to keep the biographical details of individual scientists and practitioners, which have been beloved of all readers throughout the generations. Similarly, we have retained the section on surgical instruments. Although some are now very much of historical interest, they are part of our heritage and students and indeed established practitioners will, we hope, find these vignettes fascinating. We have been told that the Summary boxes are very much appreciated by both undergraduate and postgraduate students revising, sometimes in

haste, before exams and hence our authors have ensured that these are up to date.

A book as comprehensive as this could never have been completed without the dedication and professionalism of our contributors. They have invariably answered our demands with alacrity and accuracy, appreciating the responsibility that goes with informing the readership of such a respected and established textbook. We are extremely grateful for all their efforts because we are conscious that a textbook such as this can never rest on its laurels. If it is to remain in the higher echelons of surgical tomes it must have the very best contributors and we believe that we have brought together such a cadre in the present edition. This in no way diminishes the contributions of the authors from the previous edition who are no longer involved. They, for a variety of reasons including retirement, have passed on the baton. We are grateful to them for magnanimously stepping down and making way for 'new blood' and none more so than our previous co-editor Professor Christopher Bulstrode. Chris helped revamp the 23rd, 24th, 25th and 26th Editions and these would never have been as successful without his dedicated efforts. Chris's place in the editorial team has been taken by Andrew McCaskie who has streamlined the trauma and orthopaedic sections as well as overseeing other chapters.

Readers of *Bailey & Love* have always been an integral part of the development of the book over the years and the present editorial group relish your feedback, which we know from experience will be forthcoming. Such input is vital if the book is to continue to reach the very high standards expected from each new edition. This has been a labour of love for all of us involved in this edition and we do hope it fulfils your needs, no matter whether you are an undergraduate student exploring the exciting world of surgical practice for the first time, a postgraduate trainee studying for exams or an established consultant who wishes to refresh his or her memory.

We wish you all well in your careers no matter which specialty you choose to practise in and we very much hope that the 27th and indeed subsequent editions of *Bailey & Love* accompany you on your travels through this most rewarding of professions.

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Acknowledgements

In this day and age, it is impossible to produce a book like Bailey and Love without the contribution of numerous talented individuals. Although it is impractical to mention all those who have played a part in producing the 27th Edition, it would be remiss not to express our gratitude to the following key players.

Henry Spilberg initiated the new edition as commissioning editor under the supervision of Jo Koster and was very much involved in the early planning. His role was subsequently taken over by Miranda Bromage following his departure for pastures green. Miranda's diligence and experience has been invaluable and we are enormously indebted to her wise counsel. Cherry Allen, as Editorial Assistant has been key in liaising with the editors and the contributors, ensuring manuscripts have been received on time and has been responsible for ensuring the smooth handover of the text to the production team. The latter has been headed by Paul Bennett who has provided an extremely professional service. His and his team's attention to detail has been very much valued and we hope is reflected in a first class product.

Chapter 5, *Surgical infection*, contains some material from '*Surgical infection*' by David J. Leaper. The material has been revised and updated by the current author.

Chapter 7, *Basic surgical skills and anastomoses*, contains some material from '*Basic surgical skills and anastomoses*' by David J. Leaper and William E.G. Thomas. The material has been revised and updated by the current author.

Chapter 9, *Principles of paediatric surgery*, contains some material from '*Principles of paediatric surgery*' by Mark Stringer. The material has been revised and updated by the current author.

Chapter 12, *Surgical ethics and law*, contains some material from '*Surgical ethics*' by Len Doyal. The material has been revised and updated by the current author.

Chapter 14, *Diagnostic imaging*, contains some material from '*Diagnostic imaging*' by the current authors and Gina Allen, which has been revised and updated for this edition.

Chapter 17, *Preoperative care including the high-risk surgical patient*, contains some material from '*Pre operative preparation*' by current authors Medha Vanarase-Pandit and Pierre Foex, and Kevin Tremper, Lisa Leonard and Sarah Barton, and '*Perioperative management of the high-risk patient*' by Mridula Rai, Kevin D. Johnston, Rupert M. Pearse and Richard M. Langford. The material has been revised and updated by the current authors.

Chapter 18, *Anaesthesia and pain relief*, contains some material from '*Anaesthesia and pain relief*' by current author Vivek Mehta, and Richard Langford and Jagannath Halder. The material has been revised and updated by the current authors.

Chapter 20, *Postoperative care*, contains some material from '*Postoperative care*' by Jay Kini, current author Anand Sardesai, and Alistair Pace and Nicholas C.M. Armitage. The material has been revised and updated by the current authors.

Chapter 23, *Early assessment and management of trauma*, contains some material from '*Early assessment and management of trauma*' by Dinesh Nathwani and Joseph Windley. The material has been revised and updated by the current authors.

Chapter 24, *Traumatic brain injury*, contains some material from '*Head injury*' by Richard Stacey and John Leach. The material has been revised and updated by the current authors.

Chapter 25, *Neck and spine*, contains some material from '*Neck and spine*' by Ashley Poynton. The material has been revised and updated by the current authors.

Chapter 26, *Maxillofacial trauma*, contains some material from '*Maxillofacial trauma*' by Charles Perkins. The material has been revised and updated by the current author.

Chapter 28, *Extremity trauma*, contains some material from '*Extremity trauma*' by Parminder Singh. The material has been revised and updated by the current author.

Chapter 31, *History taking and clinical examination in musculoskeletal disease*, contains some material from '*History taking and clinical examination in musculoskeletal disease*' by

Parminder Singh and current author Hemant G. Pandit. The material has been revised and updated by the current authors.

Chapter 32, *Sports medicine and sports injuries*, contains some material from '*Sports medicine and sports injuries*' by D.L. Back and Jay Smith. The material has been revised and updated by the current authors.

Chapter 33, *The spine*, contains some material from '*The spine*' by the current authors and Gavin Bowden, which has been revised and updated for this edition.

Chapter 34, *Upper limb*, contains some material from '*Upper limb – pathology, assessment and management*' by Vinay Takwale, Irfan Khan and Srinath Kamineni. The material has been revised and updated by the current authors.

Chapter 35, *Hip and knee*, contains some material from '*Hip and knee*' by Hermant G. Pandit, Andrew Bernett, current author Vikas Khanduja and Richard N. Villar. The material has been revised and updated by the current authors.

Chapter 36, *Foot and ankle*, contains some material from '*Foot and ankle*' by Mark Davies, Matthew C. Solan and Vikas Khanduja. The material has been revised and updated by the current author.

Chapter 38, *Infection of the bones and joints*, contains some material from '*Infection of the bones and joints*' by the current authors and Philip Bejon, which has been revised and updated for this edition.

Chapter 39, *Paediatric orthopaedics*, contains some material from '*Paediatric orthopaedics*' by the current author and Joanna Hicks, which has been revised and updated for this edition.

Chapter 43, *Cranial neurosurgery*, contains some material from '*Elective Neurosurgery*' by John Leach and Richard Kerr. The material has been revised and updated by the current authors.

Chapter 44, *The eye and orbit*, contains some material from '*The eye and orbit*' by Colm O'Brien, Hugo Henderson and Jonathan Jagger. The material has been revised and updated by the current author.

Chapter 45, *Cleft lip and palate: developmental abnormalities of the face, mouth and jaws*, contains some material from '*Cleft lip and palate: developmental abnormalities of the face, mouth and jaws*' by William P. Smith. The material has been revised and updated by the current author.

Chapter 46, *The ear, nose and sinuses*, contains some material from '*The nose and sinuses*' by Robert W. Ruckley and current author Iain J. Nixon, and '*The ear*' by Grant Bates. The material has been revised and updated by the current authors.

Chapter 47, *Pharynx, larynx and neck*, contains some material from '*Pharynx, larynx and neck*' by Rishi Sharma, Martin Birchall, Jonathan D. Jagger and Hugo W.A. Henderson. The material has been revised and updated by the current author.

Chapter 48, *Oral cavity malignancy*, contains some material from '*Oropharyngeal cancer*' by William P. Smith. The material has been revised and updated by the current author.

Chapter 49, *Disorders of the salivary glands*, contains some material from '*Disorders of the salivary glands*', by William P. Smith. The material has been revised and updated by the current authors.

Chapter 50, *The thyroid glands*, contains some material from '*The thyroid and parathyroid glands*' by Zygmunt H. Krukowski. The material has been revised and updated by the current author.

Chapter 51, *The parathyroid glands*, contains some material from '*The thyroid and parathyroid glands*' by Zygmunt H. Krukowski. The material has been revised and updated by the current author.

Chapter 52, *The adrenal glands and other abdominal endocrine disorders*, contains some material from '*Adrenal glands and other endocrine disorders*' by Matthias Rothmund. The material has been revised and updated by the current author.

Chapter 54, *Cardiac surgery*, contains some material from '*Cardiac surgery*' by current author Jonathan Anderson and Ian Hunt. The material has been revised and updated by the current authors.

Chapter 55, *The thorax*, contains some material from '*The thorax*' by Tom Treasure. The material has been revised and updated by the current authors.

Chapter 56, *Arterial disorders*, contains some material from '*Arterial disorders*' by John A. Murie. The material has been revised and updated by the current author.

Chapter 57, *Venous disorders*, contains some material from '*Venous disorders*' by Peter McCollum, current author Ian Chetter and Kevin Burnand. The material has been revised and updated by the current authors.

Chapter 58, *Lymphatic disorders*, contains some material from '*Lymphatic disorders*' by current author Shervanthi Homer-Vanniasinkam and Andrew Bradbury. The material has been revised and updated by the current authors.

Chapter 59, *History and examination of the abdomen*, contains some material from '*History and examination of the abdomen*', by Mohan de Silva, V. Sitaram and Simon Paterson-Brown. The material has been revised and updated by the current author.

Chapter 60, *Abdominal wall, hernia and umbilicus*, contains some material from '*Hernias, umbilicus and abdominal wall*' by Andrew N. Kingsnorth, Giorgi Giorgobiani and David H. Bennett. The material has been revised and updated by the current authors.

Chapter 61, *The peritoneum, omentum, mesentery and retroperitoneal space*, contains some material from '*The peritoneum, omentum, mesentery and retroperitoneal space*' by Jerry Thompson. The material has been revised and updated by the current author.

Chapter 64, *Bariatric and metabolic surgery*, contains some material from '*Bariatric surgery*' by John Baxter. The material has been revised and updated by the current author.

Chapter 65, *The liver*, contains some material from '*The liver*' by Rahul S. Koti, Sanjeev Kanoria and Brian R. Davidson. The material has been revised and updated by the current authors.

Chapter 69, *The small intestine*, contains some material from '*The small and large intestines*' by current author Gordon Carlson, Jonathan Epstein, Neil J. McC. Mortensen and Shazad Ashraf. The material has been revised and updated by the current authors.

Chapter 70, *The large intestine*, contains some material from '*The small and large intestines*' by Neil J. McC. Mortensen and Shazad Ashraf. The material has been revised and updated by the current authors.

Chapter 71, *Intestinal obstruction*, contains some material from '*Intestinal obstruction*' by Marc Christopher Winslet. The material has been revised and updated by the current author.

Chapter 72, *The vermiform appendix*, contains some material from '*The vermiform appendix*' by P. Ronan O'Connell. The material has been revised and updated by the current author.

Chapter 73, *The rectum*, contains some material from '*The rectum*' by Sue Clark. The material has been revised and updated by the current author.

Chapter 74, *The anus and anal canal*, contains some material from '*The anus and anal canal*' by the current author and Peter Lunniss, which has been revised and updated for this edition.

Chapter 76, *The kidneys and ureters*, contains some material from '*The kidneys and ureters*' by Christopher G. Fowler. The material has been revised and updated by the current author.

Chapter 77, *The urinary bladder*, contains some material from '*The urinary bladder*' by David E. Neal. The material has been revised and updated by the current author.

Chapter 79, *Urethra and penis*, contains some material from '*Urethra and penis*' by Christopher G. Fowler. The material has been revised and updated by the current author.

Chapter 80, *Testis and scrotum*, contains some material from '*Testis and scrotum*' by Christopher G. Fowler. The material has been revised and updated by the current author.

Chapter 81, *Gynaecology*, contains some material from '*Gynaecology*' by Stephen Kennedy and Enda McVeigh. The material has been revised and updated by the current author.

We acknowledge advice, beyond their chapter contribution, from Anand Sardesai in relation to anaesthetics, and Lee Van Rensburg, in relation to trauma.

Sayings of the great

Both Hamilton Bailey and McNeill Love, when medical students, served as clerks to Sir Robert Hutchinson, 1871–1960, who was Consulting Physician to the London Hospital and President of the Royal College of Physicians. They never tired of quoting his 'medical litany', which is appropriate for all clinicians and, perhaps especially, for those who are surgically minded.

From inability to leave well alone;
From too much zeal for what is new and contempt for what is old;
From putting knowledge before wisdom, science before art, cleverness before common sense;
From treating patients as cases; and
From making the cure of a disease more grievous than its endurance,
Good Lord, deliver us.

To which may be added:

The patient is the centre of the medical universe around which all our works revolve and towards which all our efforts trend.

J.B. Murphy, 1857–1916, Professor of Surgery,
Northwestern University, Chicago, IL, USA

To study the phenomenon of disease without books is to sail an uncharted sea, while to study books without patients is not to go to sea at all.

Sir William Osler, 1849–1919,
Professor of Medicine, Oxford, UK

A knowledge of healthy and diseased actions is not less necessary to be understood than the principles of other sciences. By and acquaintance with principles we learn the cause of disease. Without this knowledge a man cannot be a surgeon. … The last part of surgery, namely operations, is a reflection on the healing art; it is a tacit acknowledgement of the insufficiency of surgery. It is like an armed savage who attempts to get that by force which a civilised man would by stratagem.

John Hunter, 1728–1793, Surgeon,
St George's Hospital, London, UK

Investigating Nature you will do well to bear ever in mind that in every question there is the truth, whatever our notions may be. This seems perhaps a very simple consideration; yet it is strange how often it seems to be disregarded. If we had nothing but pecuniary rewards and worldly honours to look to, our profession would not be one to be desired. But in its practice you will find it to be attended with peculiar privileges; second to none in intense interest and pure pleasures. It is our proud office to tend the fleshy tabernacle of the immortal spirit, and our path, if rightly followed, will be guided by unfettered truth and love unfeigned. In the pursuit of this noble and holy calling I wish you all God-speed.

Promoter's address, Graduation in Medicine,
University of Edinburgh, August, 1876, by Lord Lister,
the Founder of Modern Surgery

Surgery has undergone many great transformations during the past fifty years, and many are to be thanked for their contributions – yet when we think of how many remain to be made, it should rather stimulate our inventiveness than fuel our vanity.

Sir Percival Pott, 1714–88, Surgeon,
St Bartholomew's Hospital, London, UK

If you cannot make a diagnosis at least make a decision!
Sir Harry Platt, 1897–1986,
Professor of Orthopaedics, Manchester, and
President of the Royal College of Surgeons England,
London, UK

If the surgeon cuts a vessel and knows the name of that vessel, the situation is serious; if the anaesthetist knows the name of that vessel, the situation is irretrievable.

Maldwyn Morgan 1938–
Anaesthetist, Hammersmith Hospital, London, UK

PART 1

Basic principles

Chapter 1

Metabolic response to injury

Learning objectives

To understand:

- Classical concepts of homeostasis
- Mediators of the metabolic response to injury
- Physiological and biochemical changes that occur during injury and recovery
- Changes in body composition that accompany surgical injury
- Avoidable factors that compound the metabolic response to injury
- Concepts behind optimal perioperative care

BASIC CONCEPTS IN HOMEOSTASIS

In the eighteenth and nineteenth centuries, a series of eminent scientists laid the foundations of our understanding of homeostasis and the response to injury. The classical concepts of homeostasis and the response to injury are:

- 'The stability of the "milieu intérieur" is the primary condition for freedom and independence of existence' (Claude Bernard); i.e. body systems act to maintain internal constancy.
- 'Homeostasis: the coordinated physiological process which maintains most of the steady states of the organism' (Walter Cannon); i.e. complex homeostatic responses involving the brain, nerves, heart, lungs, kidneys and spleen work to maintain body constancy.
- 'There is a circumstance attending accidental injury which does not belong to the disease, namely that the injury done, has in all cases a tendency to produce both the deposition and means of cure' (John Hunter); i.e. responses to injury are, in general, beneficial to the host and allow healing/survival.

In essence, the concept evolved that the constancy of the 'milieu intérieur' allowed for the independence of organisms, that complex homeostatic responses sought to maintain this constancy, and that within this range of responses were the elements of healing and repair. These ideas pertained to normal physiology and mild/moderate injury. In the modern era, such concepts do not account for disease evolution following major injury/sepsis or the injured patient who would have died but for artificial organ support. Such patients exemplify less of the classical homeostatic control system (signal detector–processor–effector regulated by a negative feedback loop) and more of the 'open loop' system, whereby only with medical/surgical resolution of the primary abnormality is a return to classical homeostasis possible.

As a consequence of modern understanding of the metabolic response to injury, elective surgical practice seeks to reduce the need for a homeostatic response by minimising the primary insult (minimal access surgery and 'stress-free' perioperative care). In emergency surgery, where the presence of tissue trauma/sepsis/hypovolaemia often compounds the primary problem, there is a requirement to augment artificially homeostatic responses (resuscitation) and to close the 'open' loop by intervening to resolve the primary insult (e.g. surgical treatment of major abdominal sepsis) and provide organ support (critical care) while the patient comes back to a situation in which homeostasis can achieve a return to normality.

Summary box 1.1

Basic concepts

- Homeostasis is the foundation of normal physiology
- 'Stress-free' perioperative care helps to preserve homeostasis following elective surgery
- Resuscitation, surgical intervention and critical care can return the severely injured patient to a situation in which homeostasis becomes possible once again

Claude Bernard, 1813–1878, Professor of Physiology, The College de France, Paris, France.
Walter Bradford Cannon, 1871–1945, Professor of Physiology, Harvard University Medical School, Boston, MA, USA.
John Hunter, 1728–1793, surgeon, St George's Hospital, London, UK. He is regarded as 'The Father of Scientific Surgery'. To further his knowledge of venereal disease he inoculated himself with syphilis in 1767.

This chapter aims to review the mediators of the stress response, the physiological and biochemical pathway changes associated with surgical injury and the changes in body composition that occur following surgical injury. Emphasis is laid on why knowledge of these events is important to understand the rationale for modern 'stress-free' perioperative and critical care.

THE GRADED NATURE OF THE INJURY RESPONSE

It is important to recognise that the response to injury is graded: the more severe the injury, the greater the response (**Figure 1.1**). This concept not only applies to physiological/metabolic changes but also to immunological changes/sequelae. Thus, following elective surgery of intermediate severity, there may be a transient and modest rise in temperature, heart rate, respiratory rate, energy expenditure and peripheral white cell count. Following major trauma/sepsis, these changes are accentuated, resulting in a systemic inflammatory response syndrome (SIRS), hypermetabolism, marked catabolism, shock and even multiple organ dysfunction (MODS). It is important to recognise that genetic variability plays a key role in determining the intensity of the inflammatory response. Moreover, in certain circumstances, the severity of injury does not lead to a simple dose-dependent metabolic response, but rather leads to quantitatively different responses.

Not only is the metabolic response graded, but it also evolves with time. In particular, the immunological sequelae of major injury evolve from a proinflammatory state driven primarily by the innate immune system (macrophages, neutrophils, dendritic cells) into a compensatory anti-inflammatory response syndrome (CARS) characterised by suppressed immunity and diminished resistance to infection. In patients who develop infective complications, the latter will drive ongoing systemic inflammation, the acute phase response and continued catabolism.

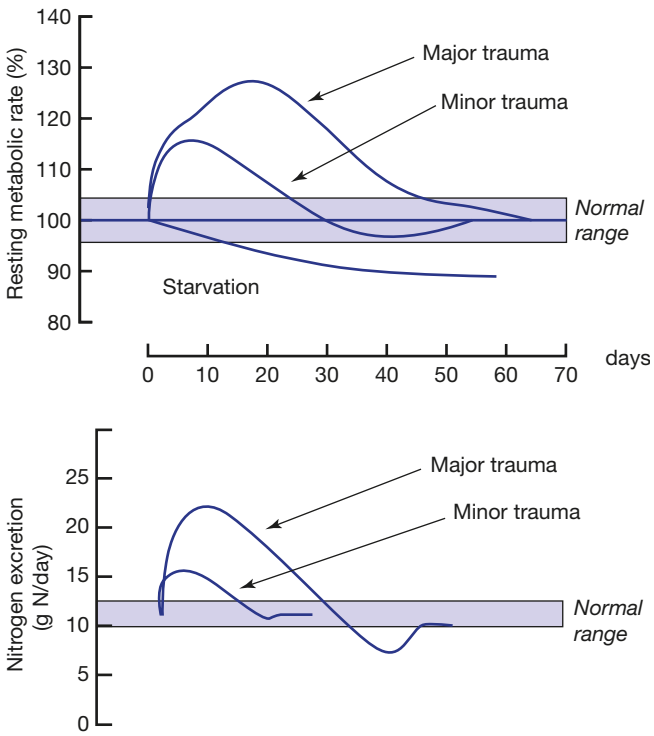

Figure 1.1 Hypermetabolism and increased nitrogen excretion are closely related to the magnitude of the initial injury and show a graded response.

MEDIATORS OF THE METABOLIC RESPONSE TO INJURY

The classical neuroendocrine pathways of the stress response consist of afferent nociceptive neurones, the spinal cord, thalamus, hypothalamus and pituitary (**Figure 1.2**). Corticotrophin-releasing factor (CRF) released from the hypothalamus increases adrenocorticotrophic hormone (ACTH) release from the anterior pituitary. ACTH then acts on the adrenals to increase the secretion of cortisol. Hypothalamic activation of the sympathetic nervous system causes release of adrenaline and also stimulates release of glucagon. Intravenous infusion of a cocktail of these 'counter-regulatory' hormones (glucagon, glucocorticoids and catecholamines) reproduces many aspects of the metabolic response to injury. There are, however, many other players, including alterations in insulin release and sensitivity, hypersecretion of prolactin and growth hormone (GH) in the presence of low circulatory insulin-like growth factor-1 (IGF-1) and inactivation of peripheral thyroid hormones and gonadal function. Of note, GH has direct lipolytic, insulin-antagonising and proinflammatory properties.

Summary box 1.2

Neuroendocrine response to injury/critical illness

The neuroendocrine response to severe injury/critical illness is biphasic:

- **Acute phase** characterised by an actively secreting pituitary and elevated counter-regulatory hormones (cortisol, glucagon, adrenaline). Changes are thought to be beneficial for short-term survival
- **Chronic phase** associated with hypothalamic suppression and low serum levels of the respective target organ hormones. Changes contribute to chronic wasting

The innate immune system (principally macrophages) interacts in a complex manner with the adaptive immune system (T cells, B cells) in co-generating the metabolic response to injury (**Figure 1.2**). Proinflammatory cytokines including interleukin-1 (IL-1), tumour necrosis factor alpha (TNFα), IL-6 and IL-8 are produced within the first 24 hours and act directly on the hypothalamus to cause pyrexia. Such cytokines also augment the hypothalamic stress response and act directly on skeletal muscle to induce proteolysis while inducing acute phase protein production in the liver. Pro-inflammatory cytokines also play a complex role in the development of peripheral insulin resistance. Other important proinflammatory mediators include nitric oxide ([NO]

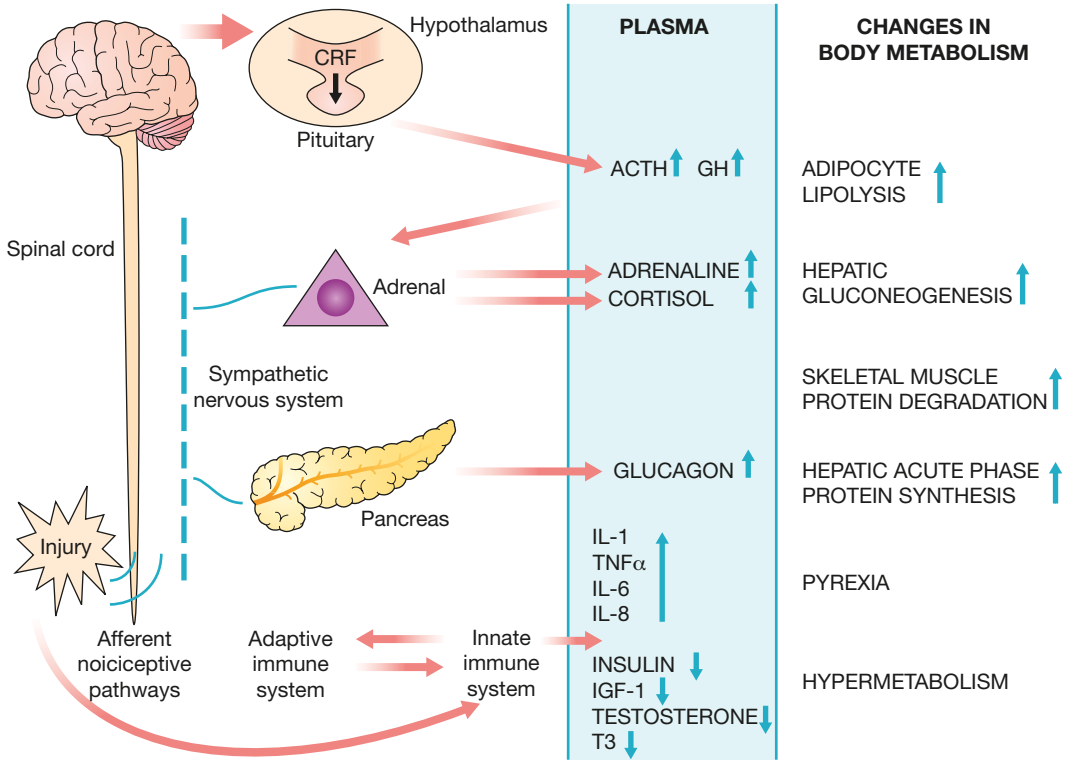

Figure 1.2 The integrated response to surgical injury (first 24–48 hours): there is a complex interplay between the neuroendocrine stress response and the proinflammatory cytokine response of the innate immune system.

via inducible nitric oxide synthetase [iNOS]) and a variety of prostanoids (via cyclooxygenase-2 [Cox-2]). Changes in organ function (e.g. renal hypoperfusion/impairment) may be induced by excessive vasoconstriction via endogenous factors such as endothelin-1.

Within hours of the upregulation of proinflammatory cytokines, endogenous cytokine antagonists enter the circulation (e.g. interleukin-1 receptor antagonist [IL-1Ra] and TNF-soluble receptors [TNF-sR-55 and 75]) and act to control the proinflammatory response. A complex further series of adaptive changes includes the development of a Th2-type counterinflammatory response (regulated by IL-4, -5, -9 and -13 and transforming growth factor beta [TGFβ]) which, if accentuated and prolonged in critical illness, is characterised as the CARS and results in immunosuppression and an increased susceptibility to opportunistic (nosocomial) infection. Within inflamed tissue the duration and magnitude of acute inflammation as well as the return to homeostasis are influenced by a group of local mediators known as specialised proresolving mediators (SPM) that include essential fatty acid-derived lipoxins, resolvins, protectins and maresins. These endogenous resolution agonists orchestrate the uptake and clearance of apoptotic polymorphonuclear neutrophils and microbial particles, reduce proinflammatory cytokines and lipid mediators as well as enhancing the removal of cellular debris in the inflammatory milieu. Thus, both at the systemic level (endogenous cytokine antagonists – see above) and at the local tissue level, the body attempts to limit/resolve inflammation driven dyshomeostasis.

Summary box 1.3

Systemic inflammatory response syndrome following major injury

- Is driven initially by proinflammatory cytokines (e.g. IL-1, IL-6 and TNFα)
- Is followed rapidly by increased plasma levels of cytokine antagonists and soluble receptors (e.g. IL-1Ra, TNF-sR)
- If prolonged or excessive may evolve into a counterinflammatory response syndrome

There are many complex interactions among the neuroendocrine, cytokine and metabolic axes. For example, although cortisol is immunosuppressive at high levels, it acts synergistically with IL-6 to promote the hepatic acute phase response. ACTH release is enhanced by proinflammatory cytokines and the noradrenergic system. The resulting rise in cortisol levels may form a weak feedback loop attempting to limit the proinflammatory stress response. Finally, hyperglycaemia may aggravate the inflammatory response via substrate overflow in the mitochondria, causing the formation of excess oxygen free radicals and also altering gene expression to enhance cytokine production.

At the molecular level, the changes that accompany systemic inflammation are extremely complex. In a recent study using network-based analysis of changes in mRNA expression in leukocytes following exposure to endotoxin, there were changes in the expression of more than 3700 genes

with over half showing decreased expression and the remainder increased expression. The cell surface receptors, signalling mechanisms and transcription factors that initiate these events are also complex, but an early and important player involves the nuclear factor kappa B (NFκB)/*relA* family of transcription factors. A simplified model of current understanding of events within skeletal muscle is shown in **Figure 1.3**.

THE METABOLIC STRESS RESPONSE TO SURGERY AND TRAUMA: THE 'EBB AND FLOW' MODEL

In the natural world, if an animal is injured, it displays a characteristic response, which includes immobility, anorexia and catabolism.

Summary box 1.4

Physiological response to injury

The natural response to injury includes:

- Immobility/rest
- Anorexia
- Catabolism

The changes are designed to aid survival of moderate injury in the absence of medical intervention.

In 1930, Sir David Cuthbertson divided the metabolic response to injury in humans into 'ebb' and 'flow' phases (**Figure 1.4**). The ebb phase begins at the time of injury and lasts for approximately 24–48 hours. It may be attenuated by proper resuscitation, but not completely abolished. The ebb phase is characterised by hypovolaemia, decreased

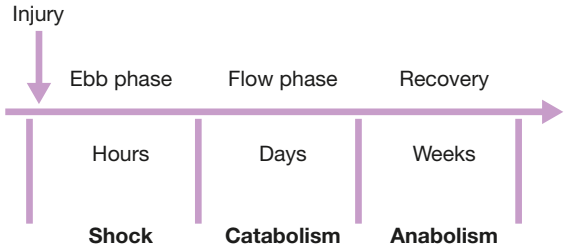

Figure 1.4 Phases of the physiological response to injury (after Cuthbertson 1930).

basal metabolic rate, reduced cardiac output, hypothermia and lactic acidosis. The predominant hormones regulating the ebb phase are catecholamines, cortisol and aldosterone (following activation of the renin–angiotensin system). The magnitude of this neuroendocrine response depends on the degree of blood loss and the stimulation of somatic afferent nerves at the site of injury. The main physiological role of the ebb phase is to conserve both circulating volume and energy stores for recovery and repair.

Following resuscitation, the ebb phase evolves into a hypermetabolic flow phase, which corresponds to SIRS. This phase involves the mobilisation of body energy stores for recovery and repair, and the subsequent replacement of lost or damaged tissue. It is characterised by tissue oedema (from vasodilatation and increased capillary leakage), increased basal metabolic rate (hypermetabolism), increased cardiac output, raised body temperature, leukocytosis, increased oxygen consumption and increased gluconeogenesis. The flow phase may be subdivided into an initial catabolic phase, lasting approximately 3–10 days, followed by an anabolic phase, which may last for weeks if extensive recovery and repair are required following serious injury. During the catabolic phase, the increased production of counter-regulatory hormones (including catecholamines, cortisol, insulin and glucagon) and inflammatory cytokines

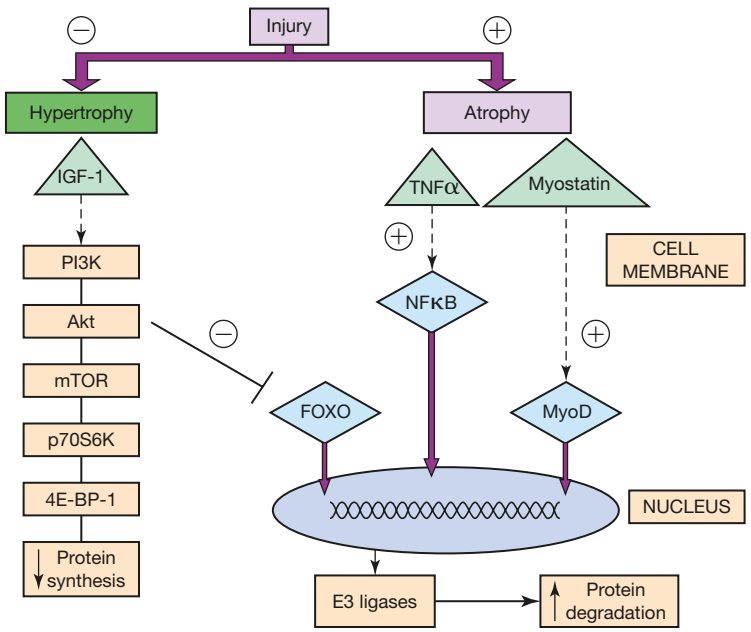

Figure 1.3 The major catabolic and anabolic signalling pathways involved in skeletal muscle homeostasis. FOXO, forkhead box sub-group O; mTOR, mammalian target of rapamycin; MyoD, myogenic differentiation factor D; NFκB, nuclear factor kappa B; PI3K, phosphatidylinositol 3-kinase; p70S6K, p70S6 kinase; TNFα, tumour necrosis factor alpha; 4E-BP-1, eukaryotic initiation translation factor 4E binding protein 1.

Sir David Paton Cuthbertson, 1900–1989, biochemist, Director of the Rowett Research Institute, Glasgow, UK.

(e.g. IL-1, IL-6 and TNFα) results in significant fat and protein mobilisation, leading to significant weight loss and increased urinary nitrogen excretion. The increased production of insulin at this time is associated with significant insulin resistance and, therefore, injured patients often exhibit poor glycaemic control. The combination of pronounced or prolonged catabolism in association with insulin resistance places patients within this phase at increased risk of complications. Obviously, the development of complications will further aggravate the neuroendocrine and inflammatory stress responses, thus creating a vicious catabolic cycle.

Summary box 1.5

Purpose of neuroendocrine changes following injury

The constellation of neuroendocrine changes following injury acts to:

- Provide essential substrates for survival
- Postpone anabolism
- Optimise host defence

These changes may be helpful in the short term, but may be harmful in the long term, especially to the severely injured patient who would otherwise not have survived without medical intervention.

KEY CATABOLIC ELEMENTS OF THE FLOW PHASE OF THE METABOLIC STRESS RESPONSE

There are several key elements of the flow phase that largely determine the extent of catabolism and thus govern the metabolic and nutritional care of the surgical patient. It must be remembered that, during the response to injury, not all tissues are catabolic. Indeed, the essence of this coordinated response is to allow the body to reprioritise limited resources away from peripheral tissues (muscle, adipose tissue, skin) and towards key viscera (liver, immune system) and the wound (**Figure 1.5**).

Hypermetabolism

The majority of trauma patients (except possibly those with extensive burns) demonstrate energy expenditures approximately 15–25% above predicted healthy resting values. The predominant cause appears to be a complex interaction between the central control of metabolic rate and peripheral energy utilisation. In particular, central thermodysregulation (caused by the proinflammatory cytokine cascade), increased sympathetic activity, abnormalities in wound circulation (ischaemic areas produce lactate, which must be metabolised by the adenosine triphosphate [ATP]-consuming hepatic Cori cycle; hyperaemic areas cause an increase in cardiac output), increased protein turnover and nutritional support may all increase patient energy expenditure. Theoretically, patient energy expenditure could rise even higher than observed levels following surgery or trauma, but several features of standard intensive care (including bed rest, paralysis, ventilation and external temperature regulation) counteract the hypermetabolic driving forces of the stress response. Furthermore, the skeletal muscle wasting experienced by patients with prolonged catabolism actually limits the volume of metabolically active tissue (see below).

Summary box 1.6

Hypermetabolism

Hypermetabolism following injury:

- Is mainly caused by an acceleration of energy-dependent metabolic cycles
- Is limited in modern practice on account of elements of routine critical care

Alterations in skeletal muscle protein metabolism

Muscle protein is continually synthesised and broken down with a turnover rate in humans of 1–2% per day, and with a greater amplitude of changes in protein synthesis (± twofold) than breakdown (± 0.25-fold) during the diurnal cycle. Under normal circumstances, synthesis equals breakdown and muscle bulk remains constant. Physiological stimuli that promote net muscle protein accretion include feeding (especially extracellular amino acid concentration) and exercise. Paradoxically, during exercise, skeletal muscle

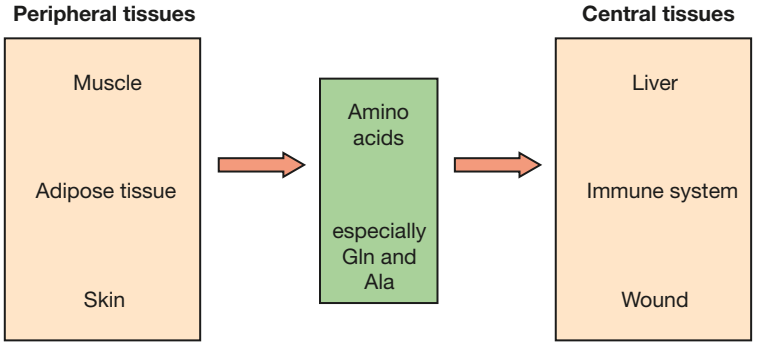

Figure 1.5 During the metabolic response to injury, the body reprioritises protein metabolism away from peripheral tissues and towards key central tissues such as the liver, immune system and wounds. One of the main reasons why the reutilisation of amino acids derived from muscle proteolysis leads to net catabolism is that the increased glutamine and alanine efflux from muscle is derived, in part, from the irreversible degradation of branched chain amino acids. Ala, alanine; Gln, glutamine.

Carl Ferdinand Cori, 1896–1984, Professor of Pharmacology, and later of Biochemistry, Washington University Medical School, St Louis, MI, USA and his wife **Gerty Theresa Cori**, 1896–1957, who was also Professor of Biochemistry at the Washington University Medical School. In 1947 the Coris were awarded a share of the Nobel Prize for Physiology or Medicine 'for their discovery of how glycogen is catalytically converted'.

protein synthesis is depressed, but it increases again during rest and feeding.

During the catabolic phase of the stress response, muscle wasting occurs as a result of an increase in muscle protein degradation (via enzymatic pathways), coupled with a decrease in muscle protein synthesis. The major site of protein loss is peripheral skeletal muscle, although nitrogen losses also occur in the respiratory muscles (predisposing the patient to hypoventilation and chest infections) and in the gut (reducing gut motility). Cardiac muscle appears to be mostly spared. Under extreme conditions of catabolism (e.g. major sepsis), urinary nitrogen losses can reach 14–20 g/day; this is equivalent to the loss of 500 g of skeletal muscle per day. It is remarkable that muscle catabolism cannot be inhibited fully by providing artificial nutritional support as long as the stress response continues. Indeed, in critical care, it is now recognised that 'hyperalimentation' represents a metabolic stress in itself, and that nutritional support should be at a modest level to attenuate rather than replace energy and protein losses.

The predominant mechanism involved in the wasting of skeletal muscle is the ATP-dependent ubiquitin–proteasome pathway (**Figure 1.6**), although the lysosomal cathepsins and the calcium–calpain pathway play facilitatory and accessory roles.

Clinically, a patient with skeletal muscle wasting will experience asthenia, increased fatigue, reduced functional ability, decreased quality of life and an increased risk of morbidity and mortality. In critically ill patients, muscle weakness may be further worsened by the development of critical illness myopathy, a multifactorial condition that is associated with impaired excitation–contraction coupling at the level of the sarcolemma and the sarcoplasmic reticulum membrane.

Summary box 1.7

Skeletal muscle wasting

- Provides amino acids for the metabolic support of central organs/tissues
- Is mediated at a molecular level mainly by activation of the ubiquitin–proteasome pathway
- Can result in immobility and contribute to hypostatic pneumonia and death if prolonged and excessive

Alterations in hepatic protein metabolism: the acute phase protein response

The liver and skeletal muscle together account for >50% of daily body protein turnover. Skeletal muscle has a large mass but a low turnover rate (1–2% per day), whereas the liver has a relatively small mass (1.5 kg) but a much higher protein turnover rate (10–20% per day). Hepatic protein synthesis is divided roughly 50:50 between renewal of structural proteins and synthesis of export proteins. Albumin is the major export protein produced by the liver and is renewed at the rate of about 10% per day. The transcapillary escape rate (TER) of albumin is about ten times the rate of synthesis, and short-term changes in albumin concentration are most probably due to increased vascular permeability. Albumin TER may be increased three-fold following major injury/sepsis.

In response to inflammatory conditions, including surgery, trauma, sepsis, cancer or autoimmune conditions, circulating peripheral blood mononuclear cells secrete a range of proinflammatory cytokines, including IL-1, IL-6 and TNFα.

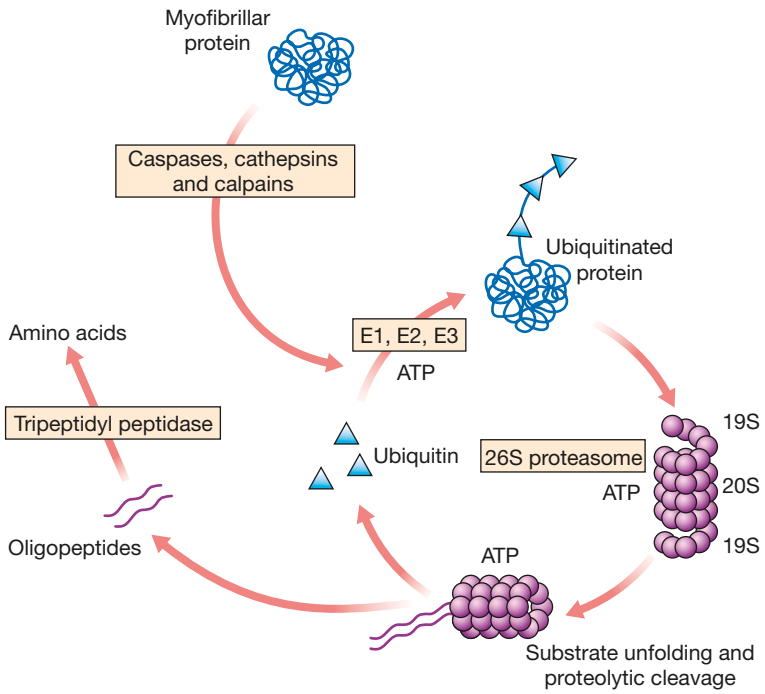

Figure 1.6 The intercellular effector mechanisms involved in degrading myofibrillar protein into free amino acids. The ubiquitin–proteasome pathway is a complex multistep process, which requires adenosine triphosphate and results in the tagging of specific proteins with ubiquitin for degradation of proteasome. E1, ubiquitin-activating enzyme; E2, ubiquitin-conjugating enzyme; E3, ubiquitin ligase.

These cytokines, in particular IL-6, promote the hepatic synthesis of positive acute phase proteins, e.g. fibrinogen and C-reactive protein (CRP). The acute phase protein response (APPR) represents a 'double-edged sword' for surgical patients as it provides proteins important for recovery and repair, but only at the expense of valuable lean tissue and energy reserves.

In contrast to the positive acute phase reactants, the plasma concentrations of other liver export proteins (the negative acute phase reactants) fall acutely following injury, e.g. albumin. However, rather than representing a reduced hepatic synthesis rate, the fall in plasma concentration of negative acute phase reactants is thought principally to reflect increased transcapillary escape, secondary to an increase in microvascular permeability (see above). Thus, increased hepatic synthesis of positive acute phase reactants is not compensated for by reduced synthesis of negative reactants.

Summary box 1.8

Hepatic acute phase response

The hepatic acute phase response represents a reprioritisation of body protein metabolism towards the liver and is characterised by:

- **Positive** reactants (e.g. CRP): plasma concentration ↑
- **Negative** reactants (e.g. albumin): plasma concentration ↓

Insulin resistance

Following surgery or trauma, postoperative hyperglycaemia develops as a result of increased glucose production combined with decreased glucose uptake in peripheral tissues. Decreased glucose uptake is a result of insulin resistance which is transiently induced within the stressed patient. Suggested mechanisms for this phenomenon include the action of proinflammatory cytokines and the decreased responsiveness of insulin-regulated glucose transporter proteins. The degree of insulin resistance is proportional to the magnitude of the injurious process. Following routine upper abdominal surgery, insulin resistance may persist for approximately 2 weeks.

Postoperative patients with insulin resistance behave in a similar manner to individuals with type II diabetes mellitus. The mainstay of management of insulin resistance is intravenous insulin infusion. Insulin infusions may be used in either an intensive approach (i.e. sliding scales are manipulated to normalise the blood glucose level) or a conservative approach (i.e. insulin is administered when the blood glucose level exceeds a defined limit and discontinued when the level falls). While some studies of postoperatively ventilated patients in the intensive care unit (ICU) have suggested that maintenance of normal glucose levels using intensive insulin therapy can significantly reduce both morbidity and mortality, others have not. The risks of adverse events following significant hypoglycaemia as a consequence of intensive insulin therapy have led most ICUs to adopt a more conventional approach to glycaemic control. It should be noted that diabetic patients whose glycaemic control has been poor prior to their critical illness pose a particular challenge.

CHANGES IN BODY COMPOSITION FOLLOWING INJURY

The average 70-kg male can be considered to consist of fat (13 kg) and fat-free mass (or lean body mass: 57 kg). In such an individual, the lean tissue is composed primarily of protein (12 kg), water (42 kg) and minerals (3 kg) (**Figure 1.7**). The protein mass can be considered as two basic compartments, skeletal muscle (4 kg) and non-skeletal muscle (8 kg), which includes the visceral protein mass. The water mass (42 litres) is divided into intracellular (28 litres) and extracellular (14 litres) spaces. Most of the mineral mass is contained in the bony skeleton.

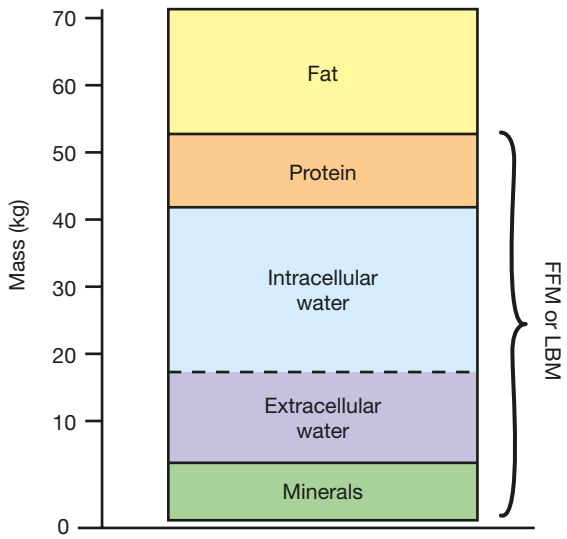

Figure 1.7 The chemical body composition of a normal 70-kg male. FFM, fat-free mass; LBM, lean body mass.

The main labile energy reserve in the body is fat, and the main labile protein reserve is skeletal muscle. While fat mass can be reduced without major detriment to function, loss of protein mass results not only in skeletal muscle wasting, but also in depletion of visceral protein status. Within lean issue, each 1 g of nitrogen is contained within 6.25 g of protein, which is contained in approximately 36 g of wet weight tissue. Thus, the loss of 1 g of nitrogen in urine is equivalent to the breakdown of 36 g of wet weight lean tissue. Protein turnover in the whole body is of the order of 150–200 g per day. A normal human ingests about 70–100 g protein per day, which is metabolised and excreted in urine as ammonia and urea (i.e. approximately 14 g N/day). During total starvation, urinary loss of nitrogen is rapidly attenuated by a series of adaptive changes. Loss of body weight follows a similar course (**Figure 1.8**), thus accounting for the survival of hunger strikers for a period of 50–60 days. Following major injury, and particularly in the presence of ongoing septic complications, this adaptive change fails to occur, and there is a state of 'autocannibalism', resulting in continuing urinary nitrogen losses of 10–20 g N/day (equivalent to 500 g of wet weight lean tissue

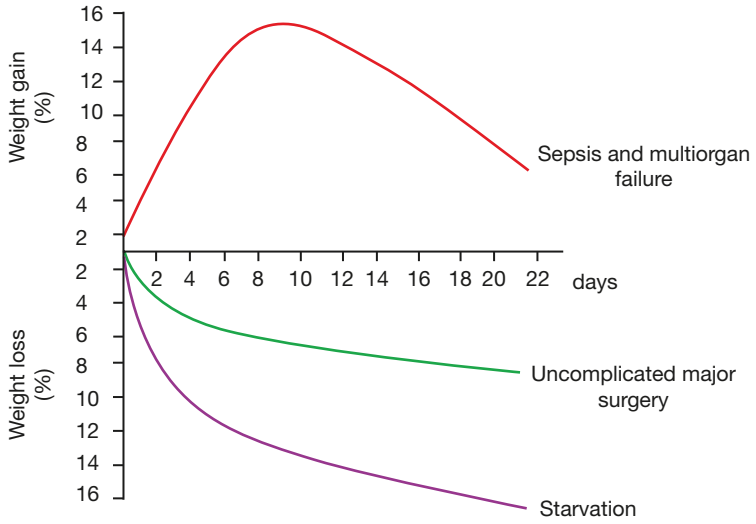

Figure 1.8 Changes in body weight that occur in serious sepsis, after uncomplicated surgery and in total starvation.

per day). As with total starvation, once loss of body protein mass has reached 30–40% of the total, survival is unlikely.

Critically ill patients admitted to the ICU with severe sepsis or major blunt trauma undergo massive changes in body composition (**Figure 1.8**). Body weight increases immediately on resuscitation with an expansion of extracellular water by 6–10 litres within 24 hours. Thereafter, even with optimal metabolic care and nutritional support, total body protein will diminish by 15% in the next 10 days, and body weight will reach negative balance as the expansion of the extracellular space resolves. In marked contrast, it is now possible to maintain body weight and nitrogen equilibrium following major elective surgery. This can be achieved by blocking the neuroendocrine stress response with epidural analgesia/other related techniques and providing early oral/enteral feeding. Moreover, the early fluid retention phase can be avoided by careful intraoperative management of fluid balance, with avoidance of excessive administration of intravenous saline.

Summary box 1.9

Changes in body composition following major surgery/critical illness

- Catabolism leads to a **decrease** in fat mass and skeletal muscle mass
- Body weight may paradoxically **increase** because of expansion of extracellular fluid space

AVOIDABLE FACTORS THAT COMPOUND THE RESPONSE TO INJURY

As noted previously, the main features of the metabolic response are initiated by the immune system, cardiovascular system, sympathetic nervous system, ascending reticular formation and limbic system. However, the metabolic stress response may be further exacerbated by anaesthesia, dehydration, starvation (including preoperative fasting), sepsis, acute medical illness or even severe psychological stress (**Figure 1.9**). Attempts to limit or control these factors can be beneficial to the patient.

Summary box 1.10

Avoidable factors that compound the response to injury

- Continuing haemorrhage
- Hypothermia
- Tissue oedema
- Tissue underperfusion
- Starvation
- Immobility

Volume loss

During simple haemorrhage, pressor receptors in the carotid artery and aortic arch, and volume receptors in the wall of the left atrium, initiate afferent nerve input to the central nervous system (CNS), resulting in the release of both aldosterone and antidiuretic hormone (ADH). Pain can also stimulate ADH release. ADH acts directly on the kidney to cause fluid retention. Decreased pulse pressure stimulates the juxtaglomerular apparatus in the kidney and directly activates the renin–angiotensin system, which in turn increases aldosterone release.

Aldosterone causes the renal tubule to reabsorb sodium (and consequently also conserve water). ACTH release also augments the aldosterone response. The net effects of ADH and aldosterone result in the natural oliguria observed after surgery and conservation of sodium and water in the extracellular space. The tendency towards water and salt retention is exacerbated by resuscitation with saline-rich fluids. Salt and water retention can result in not only peripheral oedema, but also visceral oedema (e.g. in the stomach). Such visceral oedema has been associated with reduced gastric emptying, delayed resumption of food intake and prolonged hospital

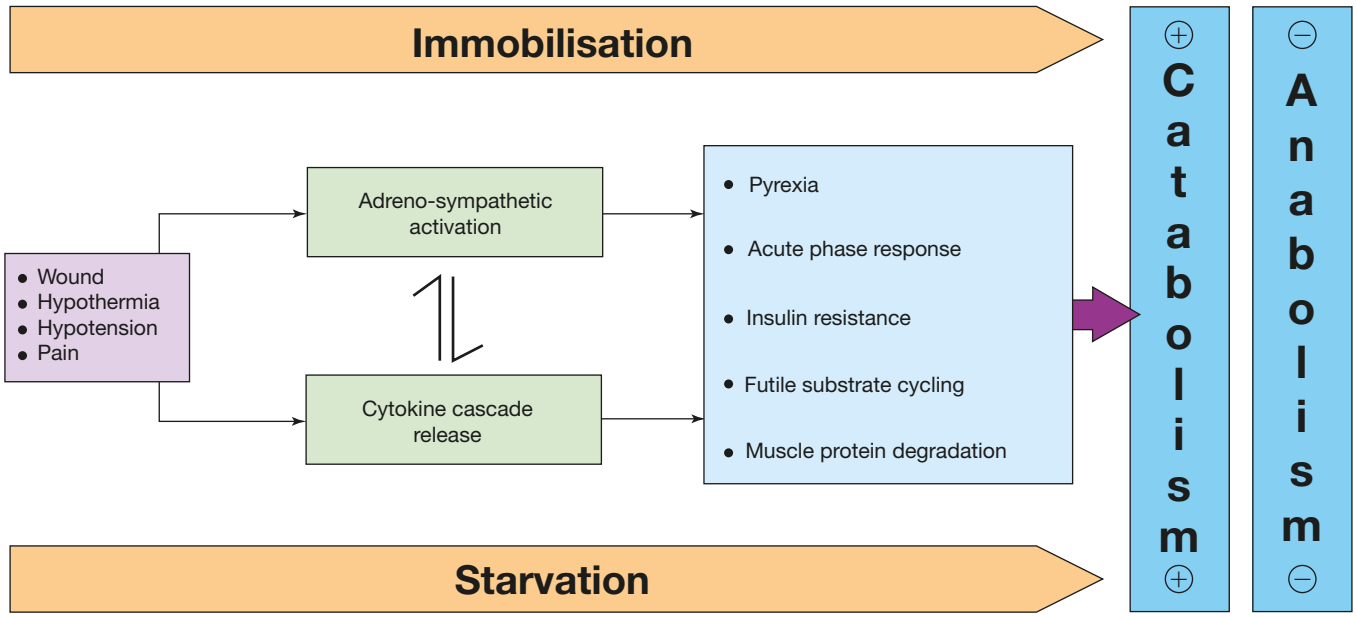

Figure 1.9 Factors that exacerbate the metabolic response to surgical injury include hypothermia, uncontrolled pain, starvation, immobilisation, sepsis and medical complications.

stay. Careful limitation of intraoperative administration of balanced crystalloids so that there is no net weight gain following elective surgery has been proven to reduce postoperative complications and length of stay.

Hypothermia

Hypothermia results in increased elaboration of adrenal steroids and catecholamines. When compared with normothermic controls, even mild hypothermia results in a two- to three-fold increase in postoperative cardiac arrhythmias and increased catabolism. Randomised trials have shown that maintaining normothermia by an upper body forced-air heating cover reduces wound infections, cardiac complications and bleeding and transfusion requirements.

Tissue oedema

During systemic inflammation, fluid, plasma proteins, leukocytes, macrophages and electrolytes leave the vascular space and accumulate in the tissues. This can diminish the alveolar diffusion of oxygen and may lead to reduced renal function. Increased capillary leak is mediated by a wide variety of mediators including cytokines, prostanoids, bradykinin and nitric oxide. Vasodilatation implies that intravascular volume decreases, which induces shock if inadequate resuscitation is not undertaken. Meanwhile, intracellular volume decreases, and this provides part of the volume necessary to replenish intravascular and extravascular extracellular volume.

Systemic inflammation and tissue underperfusion

The vascular endothelium controls vasomotor tone and microvascular flow, and regulates trafficking of nutrients and biologically active molecules. When endothelial activation is excessive, compromised microcirculation and subsequent cellular hypoxia contribute to the risk of organ failure. Maintaining normoglycaemia with insulin infusion during critical illness has been proposed to protect the endothelium, probably, in part, via inhibition of excessive iNOS-induced NO release.

Starvation

During starvation, the body is faced with an obligate need to generate glucose to sustain cerebral energy metabolism (100 g of glucose per day). This is achieved in the first 24 hours by mobilising glycogen stores and thereafter by hepatic gluconeogenesis from amino acids, glycerol and lactate. The energy metabolism of other tissues is sustained by mobilising fat from adipose tissue. Such fat mobilisation is mainly dependent on a fall in circulating insulin levels. Eventually, accelerated loss of lean tissue (the main source of amino acids for hepatic gluconeogenesis) is reduced as a result of the liver converting free fatty acids into ketone bodies, which can serve as a substitute for glucose for cerebral energy metabolism. Provision of 2 litres of intravenous 4% dextrose/0.18% sodium chloride as maintenance intravenous fluids for surgical patients who are fasted provides 80 g of glucose per day and has a significant protein-sparing effect. Avoiding unnecessary fasting in the first instance and early oral/enteral/parenteral nutrition form the platform for avoiding loss of body mass as a result of the varying degrees of starvation observed in surgical patients. Modern guidelines on fasting prior to anaesthesia allow intake of clear fluids up to 2 hours before surgery. Administration of a carbohydrate drink at this time reduces perioperative anxiety and thirst and decreases postoperative insulin resistance.

Immobility

Immobility has long been recognised as a potent stimulus for inducing muscle wasting. Inactivity impairs the normal meal-derived amino acid stimulation of protein synthesis in skeletal muscle. Avoidance of unnecessary bed rest and active early mobilisation are essential measures to avoid muscle wasting as a consequence of immobility.

CONCEPTS BEHIND ENHANCED RECOVERY AFTER SURGERY

Current understanding of the metabolic response to surgical injury and the mediators involved has led to a reappraisal of traditional perioperative care. There is now a strong scientific rationale for avoiding unmodulated exposure to stress, prolonged fasting and excessive administration of intravenous (saline) fluids (**Figure 1.10**). The widespread adoption of minimal access (laparoscopic) surgery is a key change in surgical practice that can reduce the magnitude of surgical injury and enhance the rate of patients' return to homeostasis and recovery. It is also important to realise that modulating the stress/inflammatory response at the time of surgery may have long-term sequelae over periods of months or longer. For example, β-blockers and statins have been shown to improve long-term survival after major surgery. It has been suggested that these effects may be due to suppression of innate immunity at the time of surgery. Equally, in 'open' surgery the use of epidural analgesia to reduce pain, block the cortisol stress response and attenuate postoperative insulin resistance may, via effects on the body's protein economy, favourably affect many of the patient-centred outcomes that are important to postoperative recovery. Due to the reduction in wound size and tissue trauma, it should be noted that epidural analgesia is no longer recommended for laparoscopic surgery. Patient controlled analgesia is usually sufficient. Adjuncts such as 'one shot' spinal diamorphine and/or a 6–12-hour infusion of intravenous lidocaine have been suggested to be opiate sparing, to improve gut function and enhance overall recovery.

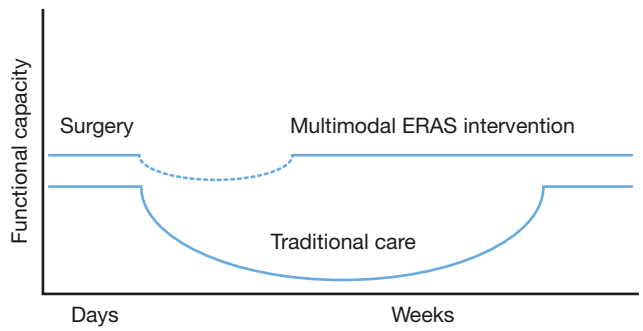

Figure 1.10 Enhanced recovery after surgery (ERAS) programmes can be modulated by multimodal enhanced recovery programmes (optimal nutritional and metabolic care to minimise the stress response).

Summary box 1.11

A proactive approach to prevent unnecessary aspects of the surgical stress response

- Minimal access techniques
- Blockade of afferent painful stimuli (e.g. epidural analgesia, spinal analgesia, wound catheters)
- Minimal periods of starvation
- Early mobilisation

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Chapter 2

Shock and blood transfusion

Learning objectives

To understand:

- The pathophysiology of shock and ischaemia–reperfusion injury
- The different patterns of shock and the principles and priorities of resuscitation
- Appropriate monitoring and end points of resuscitation
- Use of blood and blood products, the benefits and risks of blood transfusion

INTRODUCTION

Shock is the most common and therefore the most important cause of death of surgical patients. Death may occur rapidly due to a profound state of shock, or be delayed due to the consequences of organ ischaemia and reperfusion injury. It is important therefore that every surgeon understands the pathophysiology, diagnosis and priorities in management of shock and haemorrhage.

SHOCK

Shock is a systemic state of low tissue perfusion that is inadequate for normal cellular respiration. With insufficient delivery of oxygen and glucose, cells switch from aerobic to anaerobic metabolism. If perfusion is not restored in a timely fashion, cell death ensues.

Pathophysiology

Cellular

As perfusion to the tissues is reduced, cells are deprived of oxygen and must switch from aerobic to anaerobic metabolism. The product of anaerobic respiration is not carbon dioxide but lactic acid. When enough tissue is underperfused, the accumulation of lactic acid in the blood produces a systemic metabolic acidosis.

As glucose within cells is exhausted, anaerobic respiration ceases and there is failure of sodium/potassium pumps in the cell membrane and intracellular organelles. Intracellular lysosomes release autodigestive enzymes and cell lysis ensues. Intracellular contents, including potassium, are released into the blood stream.

Microvascular

As tissue ischaemia progresses, changes in the local milieu result in activation of the immune and coagulation systems. Hypoxia and acidosis activate complement and prime neutrophils, resulting in the generation of oxygen free radicals and cytokine release. These mechanisms lead to injury of the capillary endothelial cells. These, in turn, further activate the immune and coagulation systems. Damaged endothelium loses its integrity and becomes 'leaky'. Spaces between endothelial cells allow fluid to leak out and tissue oedema ensues, exacerbating cellular hypoxia.

Systemic

CARDIOVASCULAR

As preload and afterload decrease, there is a compensatory baroreceptor response resulting in increased sympathetic activity and release of catecholamines into the circulation. This results in tachycardia and systemic vasoconstriction (except in sepsis – see below).

RESPIRATORY

The metabolic acidosis and increased sympathetic response result in an increased respiratory rate and minute ventilation to increase the excretion of carbon dioxide (and so produce a compensatory respiratory alkalosis).

RENAL

Decreased perfusion pressure in the kidney leads to reduced filtration at the glomerulus and a decreased urine output. The renin–angiotensin–aldosterone axis is stimulated, resulting in further vasoconstriction and increased sodium and water reabsorption by the kidney.

ENDOCRINE

As well as activation of the adrenal and renin–angiotensin systems, vasopressin (antidiuretic hormone) is released from the hypothalamus in response to decreased preload and results in vasoconstriction and resorption of water in the renal collecting system. Cortisol is also released from the adrenal cortex, contributing to the sodium and water resorption and sensitising cells to catecholamines.

Ischaemia–reperfusion syndrome

During the period of systemic hypoperfusion, cellular and organ damage progresses due to the direct effects of tissue hypoxia and local activation of inflammation. Further injury occurs once normal circulation is restored to these tissues. The acid and potassium load that has built up can lead to direct myocardial depression, vascular dilatation and further hypotension. The cellular and humoral elements activated by the hypoxia (complement, neutrophils, microvascular thrombi) are flushed back into the circulation where they cause further endothelial injury to organs such as the lungs and the kidneys. This leads to acute lung injury, acute renal injury, multiple organ failure and death. Reperfusion injury can currently only be attenuated by reducing the extent and duration of tissue hypoperfusion.

Classification of shock

There are numerous ways to classify shock, but the most common and most clinically applicable is one based on the initiating mechanism.

All states are characterised by systemic tissue hypoperfusion, and different states may coexist within the same patient.

Summary box 2.1

Classification of shock

- Hypovolaemic shock
- Cardiogenic shock
- Obstructive shock
- Distributive shock
- Endocrine shock

Hypovolaemic shock

Hypovolaemic shock is due to a reduced circulating volume. Hypovolaemia may be due to haemorrhagic or non-haemorrhagic causes. Non-haemorrhagic causes include poor fluid intake (dehydration), excessive fluid loss due to vomiting, diarrhoea, urinary loss (e.g. diabetes), evaporation, or 'third-spacing' where fluid is lost into the gastrointestinal tract and interstitial spaces, as for example in bowel obstruction or pancreatitis.

Hypovolaemia is probably the most common form of shock, and to some degree is a component of all other forms of shock. Absolute or relative hypovolaemia must be excluded or treated in the management of the shocked state, regardless of cause.

Cardiogenic shock

Cardiogenic shock is due to primary failure of the heart to pump blood to the tissues. Causes of cardiogenic shock include myocardial infarction, cardiac dysrhythmias, valvular heart disease, blunt myocardial injury and cardiomyopathy. Cardiac insufficiency may also be due to myocardial depression caused by endogenous factors (e.g. bacterial and humoral agents released in sepsis) or exogenous factors, such as pharmaceutical agents or drug abuse. Evidence of venous hypertension with pulmonary or systemic oedema may coexist with the classical signs of shock.

Obstructive shock

In obstructive shock there is a reduction in preload due to mechanical obstruction of cardiac filling. Common causes of obstructive shock include cardiac tamponade, tension pneumothorax, massive pulmonary embolus or air embolus. In each case, there is reduced filling of the left and/or right sides of the heart leading to reduced preload and a fall in cardiac output.

Distributive shock

Distributive shock describes the pattern of cardiovascular responses characterising a variety of conditions, including septic shock, anaphylaxis and spinal cord injury. Inadequate organ perfusion is accompanied by vascular dilatation with hypotension, low systemic vascular resistance, inadequate afterload and a resulting abnormally high cardiac output.

In anaphylaxis, vasodilatation is due to histamine release, while in high spinal cord injury there is failure of sympathetic outflow and adequate vascular tone (neurogenic shock). The cause in sepsis is less clear but is related to the release of bacterial products (endotoxin) and the activation of cellular and humoral components of the immune system. There is maldistribution of blood flow at a microvascular level with arteriovenous shunting and dysfunction of cellular utilization of oxygen.

In the later phases of septic shock there is hypovolaemia from fluid loss into interstitial spaces and there may be concomitant myocardial depression, complicating the clinical picture (*Table 2.1*).

Endocrine shock

Endocrine shock may present as a combination of hypovolaemic, cardiogenic or distributive shock. Causes of endocrine shock include hypo- and hyperthyroidism and adrenal insufficiency. Hypothyroidism causes a shock state similar to that of neurogenic shock due to disordered vascular and cardiac responsiveness to circulating catecholamines. Cardiac output falls due to low inotropy and bradycardia. There may also be an associated cardiomyopathy. Thyrotoxicosis may cause a high-output cardiac failure.

Adrenal insufficiency leads to shock due to hypovolaemia and a poor response to circulating and exogenous catecholamines. Adrenal insufficiency may be due to pre-existing Addison's disease or be a relative insufficiency due to a pathological disease state, such as systemic sepsis.

Thomas Addison, 1799–1860, physician, Guy's Hospital, London, UK, described the effects of disease of the suprarenal capsules in 1849.

TABLE 2.1 Cardiovascular and metabolic characteristics of shock.

	Hypovolaemia	Cardiogenic	Obstructive	Distributive
Cardiac output Vascular resistance	Low High	Low High	Low High	High Low
Venous pressure	Low	High	High	Low
Mixed venous saturation Base deficit	Low High	Low High	Low High	High High

Severity of shock

Compensated shock

As shock progresses, the body's cardiovascular and endocrine compensatory responses reduce flow to non-essential organs to preserve preload and flow to the lungs and brain. In compensated shock, there is adequate compensation to maintain central blood volume and preserve flow to the kidneys, lungs and brain. Apart from a tachycardia and cool peripheries (vasoconstriction, circulating catecholamines), there may be no other clinical signs of hypovolaemia.

However, this cardiovascular state is only maintained by reducing perfusion to the skin, muscle and gastrointestinal tract. There is a systemic metabolic acidosis and activation of humoral and cellular elements within the underperfused organs. Although clinically occult, this state will lead to multiple organ failure and death if prolonged, due to the ischaemia–reperfusion effect described above under **Ischaemia–reperfusion syndrome**. Patients with occult hypoperfusion (metabolic acidosis despite normal urine output and cardiorespiratory vital signs) for more than 12 hours have a significantly higher mortality, infection rate and incidence of multiple organ failure (see below, **Multiple organ failure**).

Decompensation

Further loss of circulating volume overloads the body's compensatory mechanisms and there is progressive renal, respiratory and cardiovascular decompensation. In general, loss of around 15% of the circulating blood volume is within normal compensatory mechanisms. Blood pressure is usually well maintained and only falls after 30–40% of circulating volume has been lost.

Mild shock

Initially there is tachycardia, tachypnoea, a mild reduction in urine output and the patient may exhibit mild anxiety. Blood pressure is maintained although there is a decrease in pulse pressure. The peripheries are cool and sweaty with prolonged capillary refill times (except in septic distributive shock).

Moderate shock

As shock progresses, renal compensatory mechanisms fail, renal perfusion falls and urine output dips below 0.5 mL/kg per hour. There is further tachycardia, and now the blood pressure starts to fall. Patients become drowsy and mildly confused.

Severe shock

In severe shock, there is profound tachycardia and hypotension. Urine output falls to zero and patients are unconscious with laboured respiration.

Pitfalls

The classic cardiovascular responses described (*Table 2.2*) are not seen in every patient. It is important to recognise the limitations of the clinical examination and to recognise patients who are in shock despite the absence of classic signs.

CAPILLARY REFILL

Most patients in hypovolaemic shock will have cool, pale peripheries, with prolonged capillary refill times. However, the actual capillary refill time varies so much in adults that it is not a specific marker of whether a patient is shocked, and patients with short capillary refill times may be in the early stages of shock. In distributive (septic) shock, the peripheries will be warm and capillary refill will be brisk, despite profound shock.

TACHYCARDIA

Tachycardia may not always accompany shock. Patients who are on beta-blockers or who have implanted pacemakers are unable to mount a tachycardia. A pulse rate of 80 in a fit young adult who normally has a pulse rate of 50 is very abnormal. Furthermore, in some young patients with penetrating trauma, where there is haemorrhage but little tissue damage, there may be a paradoxical bradycardia rather than tachycardia accompanying the shocked state.

TABLE 2.2 Clinical features of shock.

	Compensated	Mild	Moderate	Severe
Lactic acidosis	+	++	++	+++
Urine output	Normal	Normal	Reduced	Anuric
Conscious level	Normal	Mild anxiety	Drowsy	Comatose
Respiratory rate	Normal	Increased	Increased	Laboured
Pulse rate	Mild increase	Increased	Increased	Increased
Blood pressure	Normal	Normal	Mild hypotension	Severe hypotension

BLOOD PRESSURE

It is important to recognise that hypotension is one of the last signs of shock. Children and fit young adults are able to maintain blood pressure until the final stages of shock by dramatic increases in stroke volume and peripheral vasoconstriction. These patients can be in profound shock with a normal blood pressure.

Elderly patients who are normally hypertensive may present with a 'normal' blood pressure for the general population but be hypovolaemic and hypotensive relative to their usual blood pressure. Beta-blockers or other medications may prevent a tachycardic response. The diagnosis of shock may be difficult unless one is alert to these pitfalls.

Consequences

Unresuscitatable shock

Patients who are in profound shock for a prolonged period of time become 'unresuscitatable'. Cell death follows from cellular ischaemia and the ability of the body to compensate is lost. There is myocardial depression and loss of responsiveness to fluid or inotropic therapy. Peripherally there is loss of the ability to maintain systemic vascular resistance and further hypotension ensues. The peripheries no longer respond appropriately to vasopressor agents. Death is the inevitable result.

This stage of shock is the combined result of the severity of the insult and delayed, inadequate or inappropriate resuscitation in the earlier stages of shock. Conversely, when patients present in this late stage, and have minimal responses to maximal therapy, it is important that the futility of treatment is recognised and valuable resources are not wasted.

Multiple organ failure

As techniques of resuscitation have improved, more and more patients are surviving shock. Where intervention is timely and the period of shock is limited, patients may make a rapid, uncomplicated recovery. However the result of prolonged systemic ischaemia and reperfusion injury is end-organ damage and multiple organ failure.

Multiple organ failure is defined as two or more failed organ systems. There is no specific treatment for multiple organ failure. Management is supporting of organ systems, with ventilation, cardiovascular support and haemofiltration/dialysis until there is recovery of organ function. Multiple organ failure currently carries a mortality of 60%; thus, prevention is vital by early aggressive identification and reversal of shock.

Summary box 2.2

Effects of organ failure

- Lung: Acute respiratory distress syndrome
- Kidney: Acute renal insufficiency
- Clotting: Coagulopathy
- Cardiac: Cardiovascular failure

RESUSCITATION

Immediate resuscitation manoeuvres for patients presenting in shock are to ensure a patent airway and adequate oxygenation and ventilation. Once 'airway' and 'breathing' are assessed and controlled, attention is directed to cardiovascular resuscitation.

Conduct of resuscitation

Resuscitation should not be delayed in order to definitively diagnose the source of the shocked state. However, the timing and nature of resuscitation will depend on the type of shock and the timing and severity of the insult. Rapid clinical examination will provide adequate clues to make an appropriate first determination, even if a source of bleeding or sepsis is not immediately identifiable. If there is initial doubt about the cause of shock, it is safer to assume the cause is hypovolaemia and begin with fluid resuscitation, and then assess the response.

In patients who are actively bleeding (major trauma, aortic aneurysm rupture, gastrointestinal haemorrhage), it is counterproductive to institute high-volume fluid therapy without controlling the site of haemorrhage. Increasing blood pressure merely increases bleeding from the site while fluid therapy cools the patient and dilutes available coagulation factors. Thus operative haemorrhage control should not be delayed and resuscitation should proceed in parallel with surgery.

Conversely, a patient with bowel obstruction and hypovolaemic shock must be adequately resuscitated before undergoing surgery otherwise the additional surgical injury and hypovolaemia induced during the procedure will exacerbate the inflammatory activation and increase the incidence and severity of end-organ insult.

Fluid therapy

In all cases of shock, regardless of classification, hypovolaemia and inadequate preload must be addressed before other therapy is instituted. Administration of inotropic or chronotropic agents to an empty heart will rapidly and permanently deplete the myocardium of oxygen stores and dramatically reduce diastolic filling and therefore coronary perfusion. Patients will enter the unresuscitatable stage of shock as the myocardium becomes progressively more ischaemic and unresponsive to resuscitative attempts.

First-line therapy, therefore, is intravenous access and administration of intravenous fluids. Access should be through short, wide-bore catheters that allow rapid infusion of fluids as necessary. Long, narrow lines, such as central venous catheters, have too high a resistance to allow rapid infusion and are more appropriate for monitoring than fluid replacement therapy.

Type of fluids

There is continuing debate over which resuscitation fluid is best for the management of shock. There is no ideal resuscitation fluid, and it is more important to understand how and when to administer it. In most studies of shock resuscitation

there is no overt difference in response or outcome between crystalloid solutions (normal saline, Hartmann's solution, Ringer's lactate) or colloids (albumin or commercially available products). Furthermore, there is less volume benefit to the administration of colloids than had previously been thought, with only 1.3 times more crystalloid than colloid administered in blinded trials. On balance, there is little evidence to support the administration of colloids, which are more expensive and have worse side-effect profiles.

Most importantly, the oxygen carrying capacity of crystalloids and colloids is zero. If blood is being lost, the ideal replacement fluid is blood, although crystalloid therapy may be required while awaiting blood products.

Hypotonic solutions (dextrose etc.) are poor volume expanders and should not be used in the treatment of shock unless the deficit is free water loss (e.g. diabetes insipidus) or patients are sodium overloaded (e.g. cirrhosis).

Dynamic fluid response

The shock status can be determined dynamically by the cardiovascular response to the rapid administration of a fluid bolus. In total, 250–500 mL of fluid is rapidly given (over 5–10 minutes) and the cardiovascular responses in terms of heart rate, blood pressure and central venous pressure are observed. Patients can be divided into 'responders', 'transient responders' and 'non-responders'.

Responders have an improvement in their cardiovascular status that is sustained. These patients are not actively losing fluid but require filling to a normal volume status.

Transient responders have an improvement, but this then reverts to the previous state over the next 10–20 minutes. These patients have moderate ongoing fluid losses (either overt haemorrhage or further fluid shifts reducing intravascular volume).

Non-responders are severely volume depleted and are likely to have major ongoing loss of intravascular volume, usually through persistent uncontrolled haemorrhage.

Vasopressor and inotropic support

Vasopressor or inotropic therapy is not indicated as first-line therapy in hypovolaemia. As discussed above, administration of these agents in the absence of adequate preload rapidly leads to decreased coronary perfusion and depletion of myocardial oxygen reserves.

Vasopressor agents (phenylephrine, noradrenaline) are indicated in distributive shock states (sepsis, neurogenic shock) where there is peripheral vasodilatation, and a low systemic vascular resistance, leading to hypotension despite a high cardiac output. Where the vasodilatation is resistant to catecholamines (e.g. absolute or relative steroid deficiency) vasopressin may be used as an alternative vasopressor.

In cardiogenic shock, or where myocardial depression has complicated a shock state (e.g. severe septic shock with low cardiac output), inotropic therapy may be required to increase cardiac output and therefore oxygen delivery. The inodilator dobutamine is the agent of choice.

Monitoring

The **minimum** standard for monitoring of the patient in shock is continuous heart rate and oxygen saturation monitoring, frequent non-invasive blood pressure monitoring and hourly urine output measurements. Most patients will need more aggressive invasive monitoring, including central venous pressure and invasive blood pressure monitoring.

Summary box 2.3

Monitoring for patients in shock

Minimum

- ECG
- Pulse oximetry
- Blood pressure
- Urine output

Additional modalities

- Central venous pressure
- Invasive blood pressure
- Cardiac output
- Base deficit and serum lactate

Cardiovascular

Cardiovascular monitoring at minimum should include continuous heart rate (ECG), oxygen saturation and pulse waveform and non-invasive blood pressure. Patients whose state of shock is not rapidly corrected with a small amount of fluid should have central venous pressure monitoring and continuous blood pressure monitoring through an arterial line.

CENTRAL VENOUS PRESSURE

There is no 'normal' central venous pressure (CVP) for a shocked patient, and reliance cannot be placed on an individual pressure measurement to assess volume status. Some patients may require a CVP of 5 cmH_2O, whereas some may require a CVP of 15 cmH_2O or higher. Further, ventricular compliance can change from minute to minute in the shocked state, and CVP is a poor reflection of end diastolic volume (preload).

CVP measurements should be assessed dynamically as response to a fluid challenge (see above). A fluid bolus (250–500 mL) is infused rapidly over 5–10 minutes.

The normal CVP response is a rise of 2–5 cmH_2O which gradually drifts back to the original level over 10–20 minutes. Patients with no change in their CVP are empty and require further fluid resuscitation. Patients with a large, sustained rise in CVP have high preload and an element of cardiac insufficiency or volume overload.

Alexis Frank Hartmann, 1898–1964, paediatrician, St Louis, MO, USA, described the solution; should not be confused with the name of Henri Albert Charles Antoine Hartmann, French surgeon, who described the operation that goes by his name.
Sidney Ringer, 1835–1910, Professor of Clinical Medicine, University College Hospital, London, UK.

CARDIAC OUTPUT

Cardiac output monitoring allows assessment of not only the cardiac output but also the systemic vascular resistance and, depending on the technique used, end diastolic volume (preload) and blood volume. Use of invasive cardiac monitoring with pulmonary artery catheters is becoming less frequent as new non-invasive monitoring techniques, such as Doppler ultrasound, pulse waveform analysis and indicator dilution methods, provide similar information without many of the drawbacks of more invasive techniques.

Measurement of cardiac output, systemic vascular resistance and preload can help distinguish the types of shock present (hypovolaemia, distributive, cardiogenic), especially when they coexist. The information provided guides fluid and vasopressor therapy by providing real-time monitoring of the cardiovascular response.

Measurement of cardiac output is desirable in patients who do not respond as expected to first-line therapy, or who have evidence of cardiogenic shock or myocardial dysfunction. Early consideration should be given to instituting cardiac output monitoring for patients who require vasopressor or inotropic support.

Systemic and organ perfusion

Ultimately, the goal of treatment is to restore cellular and organ perfusion. Ideally, therefore, monitoring of organ perfusion should guide the management of shock. The best measure of organ perfusion and the best monitor of the adequacy of shock therapy remains the urine output. However, this is an hourly measure and does not give a minute-to-minute view of the shocked state. The level of consciousness is an important marker of cerebral perfusion, but brain perfusion is maintained until the very late stages of shock, and hence is a poor marker of adequacy of resuscitation (*Table 2.3*).

Currently, the only clinical indicators of perfusion of the gastrointestinal tract and muscular beds are the global measures of lactic acidosis (lactate and base deficit) and the mixed venous oxygen saturation.

BASE DEFICIT AND LACTATE

Lactic acid is generated by cells undergoing anaerobic respiration. The degree of lactic acidosis, as measured by serum lactate level and/or the base deficit, is sensitive for both diagnosis of shock and monitoring the response to therapy. Patients with a base deficit over 6 mmol/L have a much higher morbidity and mortality than those with no metabolic acidosis. Furthermore, the length of time in shock with an increased base deficit is important, even if all other vital signs have returned to normal (see occult hypoperfusion below under **End points of resuscitation**).

These parameters are measured from arterial blood gas analyses, and therefore the frequency of measurements is limited and they do not provide minute-to-minute data on systemic perfusion or the response to therapy. Nevertheless, the base deficit and/or lactate should be measured routinely in these patients until they have returned to normal levels.

MIXED VENOUS OXYGEN SATURATION

The percentage saturation of oxygen returning to the heart from the body is a measure of the oxygen delivery and extraction by the tissues. Accurate measurement is via analysis of blood drawn from a long central line placed in the right atrium. Estimations can be made from blood drawn from lines in the superior vena cava, but these values will be slightly higher than those of a mixed venous sample (as there is relatively more oxygen extraction from the lower half of the body). Normal mixed venous oxygen saturation levels are 50–70%. Levels below 50% indicate inadequate oxygen delivery and increased oxygen extraction by the cells. This is consistent with hypovolaemic or cardiogenic shock.

High mixed venous saturations (>70%) are seen in sepsis and some other forms of distributive shock. In sepsis, there is disordered utilisation of oxygen at the cellular level, and arteriovenous shunting of blood at the microvascular level. Therefore, less oxygen is presented to the cells, and those cells cannot utilise what little oxygen is presented. Thus, venous blood has a higher oxygen concentration than normal.

TABLE 2.3 Monitors for organ/systemic perfusion.

	Clinical	Investigational
Systemic perfusion		Base deficit
		Lactate
		Mixed venous oxygen saturation
Organ perfusion		
Muscle	–	Near-infrared spectroscopy
		Tissue oxygen electrode
Gut	–	Sublingual capnometry
		Gut mucosal pH
		Laser Doppler flowmetry
Kidney	Urine output	–
Brain	Conscious level	Tissue oxygen electrode
		Near-infrared spectroscopy

Christian Johann Doppler, 1803–1853, Professor of Experimental Physics, Vienna, Austria, enunciated the Doppler principle in 1842.

Patients who are septic should therefore have mixed venous oxygen saturations above 70%; below this level, they are not only in septic shock but also in hypovolaemic or cardiogenic shock. Although the S_vO_2 level is in the 'normal' range, it is low for the septic state, and inadequate oxygen is being supplied to cells that cannot utilise oxygen appropriately. This must be corrected rapidly. Hypovolaemia should be corrected with fluid therapy, and low cardiac output due to myocardial depression or failure should be treated with inotropes (dobutamine), to achieve a mixed venous saturation greater than 70% (normal for the septic state).

New methods for monitoring regional tissue perfusion and oxygenation are becoming available, the most promising of which are muscle tissue oxygen probes, near-infrared spectroscopy and sublingual capnometry. While these techniques provide information regarding perfusion of specific tissue beds, it is as yet unclear whether there are significant advantages over existing measurements of global hypoperfusion (base deficit, lactate).

End points of resuscitation

It is much easier to know when to start resuscitation than when to stop. Traditionally, patients have been resuscitated until they have a normal pulse, blood pressure and urine output. However, these parameters are monitoring organ systems whose blood flow is preserved until the late stages of shock. A patient therefore may be resuscitated to restore central perfusion to the brain, lungs and kidneys and yet continue to underperfuse the gut and muscle beds. Thus, activation of inflammation and coagulation may be ongoing and lead to reperfusion injury when these organs are finally perfused, and ultimately multiple organ failure.

This state of normal vital signs and continued underperfusion is termed 'occult hypoperfusion'. With current monitoring techniques, it is manifested only by a persistent lactic acidosis and low mixed venous oxygen saturation. The time spent by patients in this hypoperfused state has a dramatic effect on outcome. Patients with occult hypoperfusion for more than 12 hours have two to three times the mortality of patients with a limited duration of shock.

Resuscitation algorithms directed at correcting global perfusion end points (base deficit, lactate, mixed venous oxygen saturation) rather than traditional end points have been shown to improve mortality and morbidity in high-risk surgical patients. However, it is clear that, despite aggressive regimes, some patients cannot be resuscitated to normal parameters within 12 hours by fluid resuscitation alone. More research is underway to identify the pathophysiology behind this and investigate new therapeutic options.

HAEMORRHAGE

Haemorrhage must be recognised and managed aggressively to reduce the severity and duration of shock and avoid death and/or multiple organ failure. Haemorrhage is treated by arresting the bleeding – not by fluid resuscitation or blood transfusion. Although necessary as supportive measures to maintain organ perfusion, attempting to resuscitate patients who have ongoing haemorrhage will lead to physiological exhaustion (coagulopathy, acidosis and hypothermia) and subsequently death.

Pathophysiology

Haemorrhage leads to a state of hypovolaemic shock. The combination of tissue trauma and hypovolaemic shock leads to the development of an endogenous coagulopathy called acute traumatic coagulopathy (ATC). Up to 25% of trauma patients develop ATC within minutes of injury and it is associated with a four-fold increase in mortality. It is likely that ATC exists whenever there is the combination of shock and tissue trauma (e.g. major surgery). ATC is a component of trauma-induced coagulopathy (TIC), which is ultimately multifactorial (**Figure 2.1**).

Ongoing bleeding with fluid and red blood cell resuscitation leads to a dilution of coagulation factors which worsens the coagulopathy. In addition, the acidosis induced by the hypoperfused state leads to decreased function of the coagulation proteases, resulting in coagulopathy and further haemorrhage. The reduced tissue perfusion includes reduced blood supply to muscle beds. Underperfused muscle is unable to generate heat and hypothermia ensues. Coagulation functions poorly at low temperatures and there is further haemorrhage, further hypoperfusion and worsening acidosis and hypothermia. These three factors result in a downward spiral leading to physiological exhaustion and death (**Figure 2.1**).

Medical therapy has a tendency to worsen this effect. Intravenous blood and fluids are cold and exacerbate hypothermia. Further heat is lost by opening body cavities during surgery. Surgery usually leads to further bleeding and many crystalloid fluids are themselves acidic (e.g. normal saline has a pH of 6.7). Every effort must therefore be made to rapidly identify and stop haemorrhage, and to avoid (preferably) or limit physiological exhaustion from coagulopathy, acidosis and hypothermia.

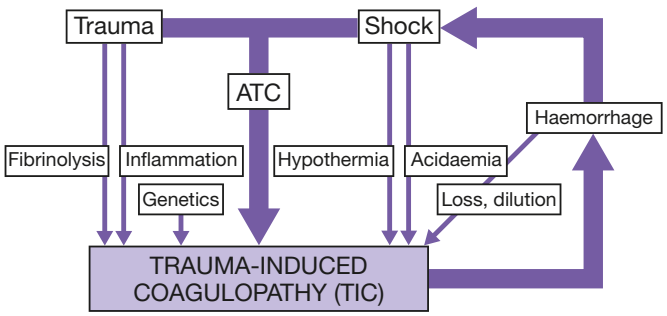

Figure 2.1 Trauma-induced coagulopathy.

Definitions

Revealed and concealed haemorrhage

Haemorrhage may be revealed or concealed. Revealed haemorrhage is obvious external haemorrhage, such as exsanguination from an open arterial wound or from massive haematemesis from a duodenal ulcer.

Concealed haemorrhage is contained within the body cavity and must be suspected, actively investigated and controlled. In

trauma, haemorrhage may be concealed within the chest, abdomen, pelvis, retroperitoneum or in the limbs with contained vascular injury or associated with long-bone fractures. Examples of non-traumatic concealed haemorrhage include occult gastrointestinal bleeding or ruptured aortic aneurysm.

Primary, reactionary and secondary haemorrhage

Primary haemorrhage is haemorrhage occurring immediately due to an injury (or surgery). Reactionary haemorrhage is delayed haemorrhage (within 24 hours) and is usually due to dislodgement of a clot by resuscitation, normalisation of blood pressure and vasodilatation. Reactionary haemorrhage may also be due to technical failure, such as slippage of a ligature.

Secondary haemorrhage is due to sloughing of the wall of a vessel. It usually occurs 7–14 days after injury and is precipitated by factors such as infection, pressure necrosis (such as from a drain) or malignancy.

Surgical and non-surgical haemorrhage

Surgical haemorrhage is due to a direct injury and is amenable to surgical control (or other techniques such as angioembolisation). Non-surgical haemorrhage is the general ooze from all raw surfaces due to coagulopathy and cannot be stopped by surgical means (except packing). Treatment requires correction of the coagulation abnormalities.

Degree and classification

The adult human has approximately 5 litres of blood (70 mL/kg children and adults, 80 mL/kg neonates). Estimation of the amount of blood that has been lost is difficult, inaccurate and usually underestimates the actual value.

External haemorrhage is obvious, but it may be difficult to estimate the actual volume lost. In the operating room, blood collected in suction apparatus can be measured and swabs soaked in blood weighed.

The haemoglobin level is a poor indicator of the degree of haemorrhage because it represents a concentration and not an absolute amount. In the early stages of rapid haemorrhage, the haemoglobin concentration is unchanged (as whole blood is lost). Later, as fluid shifts from the intracellular and interstitial spaces into the vascular compartment, the haemoglobin and haematocrit levels will fall.

The amount of haemorrhage can be classified into classes 1–4 based on the estimated blood loss required to produce certain physiological compensatory changes (*Table 2.4*). Although conceptually useful, there is variation across ages (the young compensate well, the old very poorly), variation among individuals (e.g. athletes versus the obese) and variation due to confounding factors (e.g. concomitant medications, pain).

Treatment should therefore be based upon the degree of hypovolaemic shock according to vital signs, preload assessment, base deficit and, most importantly, the dynamic response to fluid therapy. Patients who are 'non-responders' or 'transient responders' are still bleeding and must have the site of haemorrhage identified and controlled.

TABLE 2.4 Traditional classification of haemorrhagic shock.

	Class			
	1	2	3	4
Blood volume lost as percentage of total	<15%	15–30%	30–40%	>40%

Management

Identify haemorrhage

External haemorrhage may be obvious, but the diagnosis of concealed haemorrhage may be more difficult. Any shock should be assumed to be hypovolaemic until proven otherwise and, similarly, hypovolaemia should be assumed to be due to haemorrhage until this has been excluded.

Immediate resuscitative manoeuvres

Direct pressure should be placed over the site of external haemorrhage. Airway and breathing should be assessed and controlled as necessary. Large-bore intravenous access should be instituted and blood drawn for cross-matching (see **Cross-matching** below). Emergency blood should be requested if the degree of shock and ongoing haemorrhage warrants this.

Identify the site of haemorrhage

Once haemorrhage has been considered, the site of haemorrhage must be rapidly identified. Note this is not to identify the exact location definitively, but rather to define the next step in haemorrhage control (operation, angioembolisation, endoscopic control).

Clues may be in the history (previous episodes, known aneurysm, non-steroidal therapy for gastrointestinal [GI] bleeding) or examination (nature of blood – fresh, melaena; abdominal tenderness, etc.). For shocked trauma patients, the external signs of injury may suggest internal haemorrhage, but haemorrhage into a body cavity (thorax, abdomen) must be excluded with rapid investigations (chest and pelvis x-ray, abdominal ultrasound or diagnostic peritoneal aspiration).

Investigations for blood loss must be appropriate to the patient's physiological condition. Rapid bedside tests are more appropriate for profound shock and exsanguinating haemorrhage than investigations such as computed tomography (CT) which take time. Patients who are not actively bleeding can have a more methodical, definitive work-up.

Haemorrhage control

The bleeding, shocked patient must be moved rapidly to a place of haemorrhage control. This will usually be in the operating room but may be the angiography or endoscopy suite. These patients require surgical and anaesthetic support and full monitoring and equipment must be available.

Haemorrhage control must be achieved rapidly to prevent the patient entering the triad of coagulopathy–acidosis–hypothermia and physiological exhaustion. There should be no unnecessary investigations or procedures prior to haemorrhage

control to minimise the duration and severity of shock. This includes prolonged attempts to volume resuscitate the patient prior to surgery, which will result in further hypothermia and clotting factor dilution until the bleeding is stopped. Attention should be paid to correction of coagulopathy with blood component therapy to aid surgical haemorrhage control.

Surgical intervention may need to be limited to the minimum necessary to stop bleeding and control sepsis. More definitive repairs can be delayed until the patient is haemodynamically stable and physiologically capable of sustaining the procedure. This concept of tailoring the operation to match the patient's physiology and staged procedures to prevent physiological exhaustion is called 'damage control surgery' – a term borrowed from the military which ensures continued functioning of a damaged ship above conducting complete repairs which would prevent rapid return to battle.

Once haemorrhage is controlled, patients should be aggressively resuscitated, warmed and coagulopathy corrected. Attention should be paid to fluid responsiveness and the end points of resuscitation to ensure that patients are fully resuscitated and to reduce the incidence and severity of organ failure.

Summary box 2.4

Damage control surgery

- Arrest haemorrhage
- Control sepsis
- Protect from further injury
- Nothing else

Damage control resuscitation

These concepts have been combined into a new paradigm for the management of trauma patients with active haemorrhage called damage control resuscitation (DCR). The four central strategies of DCR are:

1 Anticipate and treat acute traumatic coagulopathy.
2 Permissive hypotension until haemorrhage control.
3 Limit crystalloid and colloid infusion to avoid dilutional coagulopathy.
4 Damage control surgery to control haemorrhage and preserve physiology.

Damage control resuscitation strategies have been shown to reduce mortality and morbidity in patients with exsanguinating trauma and may be applicable in other forms of acute haemorrhage.

TRANSFUSION

The transfusion of blood and blood products has become commonplace since the first successful transfusion in 1818. Although the incidence of severe transfusion reactions and infections is now very low, in recent years it has become apparent that there is an immunological price to be paid from the transfusion of heterologous blood, leading to increased morbidity and decreased survival in certain population groups (trauma, malignancy). Supplies are also limited, and therefore the use of blood and blood products must always be judicious and justifiable for clinical need (*Table 2.5*).

TABLE 2.5 History of blood transfusion.

1492	Pope Innocent VIII suffers a stroke and receives a blood transfusion from three 10-year-old boys (paid a ducat each). All three boys died, as did the pope later that year
1665	Richard Lower in Oxford conducts the first successful canine transfusions
1667	Jean-Baptiste Denis reports successful sheep–human transfusions
1678	Animal–human transfusions are banned in France because of the poor results
1818	James Blundell performs the first successful documented human transfusion in a woman suffering post-partum haemorrhage. She received blood from her husband and survived
1901	Karl Landsteiner discovers the ABO system
1914	The Belgian physician Albert Hustin performed the first non-direct transfusion, using sodium citrate as an anticoagulant
1926	The British Red Cross instituted the first blood transfusion service in the world
1939	The Rhesus system was identified and recognised as the major cause of transfusion reactions

Blood and blood products

Blood is collected from donors who have been previously screened before donating, to exclude any donor whose blood may have the potential to harm the patient, or to prevent possible harm that donating a unit of blood may have on the donor. In the UK, up to 450 mL of blood is drawn, a maximum of three times each year. Each unit is tested for evidence of hepatitis B, hepatitis C, HIV-1, HIV-2 and syphilis. Donations are leukodepleted as a precaution against variant Creutzfeldt–Jakob disease (this may also reduce the immunogenicity of the transfusion). The ABO and rhesus D blood groups are determined, as well as the presence of irregular red cell antibodies. The blood is then processed into subcomponents.

Whole blood

Whole blood is now rarely available in civilian practice because it has been seen as an inefficient use of the limited resource. However, whole blood transfusion has significant advantages over packed cells as it is coagulation factor rich and, if fresh, more metabolically active than stored blood.

Hans Gerhard Creutzfeldt, 1885–1946, neurologist, Kiel, Germany.
Alfons Maria Jakob, 1884–1931, neurologist, Hamburg, Germany.
Karl Landsteiner, 1868–1943, Professor of Pathological Anatomy, University of Vienna, Austria. In 1909 he classified the human blood groups into A, B, AB and O. For this he was awarded the Nobel Prize for Physiology or Medicine in 1930.

Packed red cells

Packed red blood cells are spun-down and concentrated packs of red blood cells. Each unit is approximately 330 mL and has a haematocrit of 50–70%. Packed cells are stored in a SAG-M solution (saline–adenine–glucose–mannitol) to increase shelf life to 5 weeks at 2–6°C. (Older storage regimes included storage in CPD: citrate–phosphate–dextrose solutions, which have a shelf life of 2–3 weeks.)

Fresh-frozen plasma

Fresh-frozen plasma (FFP) is rich in coagulation factors and is removed from fresh blood and stored at −40 to −50°C with a 2-year shelf life. It is the first-line therapy in the treatment of coagulopathic haemorrhage (see below under **Management of coagulopathy**). Rhesus D-positive FFP may be given to a rhesus D-negative woman although it is possible for seroconversion to occur with large volumes owing to the presence of red cell fragments, and Rh-D immunisation should be considered.

Cryoprecipitate

Cryoprecipitate is a supernatant precipitate of FFP and is rich in factor VIII and fibrinogen. It is stored at −30°C with a 2-year shelf life. It is given in low fibrinogen states or factor VIII deficiency.

Platelets

Platelets are supplied as a pooled platelet concentrate and contain about 250×10^9/L. Platelets are stored on a special agitator at 20–24°C and have a shelf life of only 5 days. Platelet transfusions are given to patients with thrombocytopenia or with platelet dysfunction who are bleeding or undergoing surgery.

Patients are increasingly presenting on antiplatelet therapy such as aspirin or clopidogrel for reduction of cardiovascular risk. Aspirin therapy rarely poses a problem but control of haemorrhage on the more potent platelet inhibitors can be extremely difficult. Patients on clopidogrel who are actively bleeding and undergoing major surgery may require almost continuous infusion of platelets during the course of the procedure. Arginine vasopressin or its analogues (DDAVP) have also been used in this patient group, although with limited success.

Prothrombin complex concentrates

Prothrombin complex concentrates (PCC) are highly purified concentrates prepared from pooled plasma. They contain factors II, IX and X. Factor VII may be included or produced separately. It is indicated for the emergency reversal of anticoagulant (warfarin) therapy in uncontrolled haemorrhage.

Autologous blood

It is possible for patients undergoing elective surgery to predonate their own blood up to 3 weeks before surgery for retransfusion during the operation. Similarly, during surgery blood can be collected in a cell-saver which washes and collects red blood cells which can then be returned to the patient.

Indications for blood transfusion

Blood transfusions should be avoided if possible, and many previous uses of blood and blood products are now no longer considered appropriate. The indications for blood transfusion are as follows:

- Acute blood loss, to replace circulating volume and maintain oxygen delivery;
- Perioperative anaemia, to ensure adequate oxygen delivery during the perioperative phase;
- Symptomatic chronic anaemia, without haemorrhage or impending surgery.

Transfusion trigger

Historically, patients were transfused to achieve a haemoglobin >10 g/dL. This has now been shown not only to be unnecessary but also to be associated with an increased morbidity and mortality compared with lower target values. A haemoglobin level of 6 g/dL is acceptable in patients who are not actively bleeding, not about to undergo major surgery and are not symptomatic. There is some controversy as to the optimal haemoglobin level in some patient groups, such as those with cardiovascular disease, sepsis and traumatic brain injury. Although, conceptually, a higher haemoglobin level improves oxygen delivery, there is little clinical evidence at this stage to support higher levels in these groups (*Table 2.6*).

TABLE 2.6 Perioperative red blood cell transfusion criteria.

Haemoglobin level (g/dL)	Indications
<6	Probably will benefit from transfusion
6–8	Transfusion unlikely to be of benefit in the absence of bleeding or impending surgery
>8	No indication for transfusion in the absence of other risk factors

Blood groups and cross-matching

Human red cells have on their cell surface many different antigens. Two groups of antigens are of major importance in surgical practice – the ABO and rhesus systems.

ABO system

These proteins are strongly antigenic and are associated with naturally occurring antibodies in the serum. The system consists of three allelic genes – A, B and O – which control synthesis of enzymes that add carbohydrate residues to cell surface glycoproteins. A and B genes add specific residues while the O gene is an amorph and does not transform the glycoprotein. The system allows for six possible genotypes although there are only four phenotypes. Naturally occurring antibodies are found in the serum of those lacking the corresponding antigen (*Table 2.7*).

Blood group O is the universal donor type as it contains no antigens to provoke a reaction. Conversely, group AB individuals are 'universal recipients' and can receive any ABO blood type because they have no circulating antibodies.

TABLE 2.7 ABO blood group system.

Phenotype	Genotype	Antigens	Antibodies	Frequency (%)
O	OO	O	Anti-A, anti-B	46
A	AA or AO	A	Anti-B	42
B	BB or BO	B	Anti-A	9
AB	AB	AB	None	3

Rhesus system

The rhesus D (Rh(D)) antigen is strongly antigenic and is present in approximately 85% of the population in the UK. Antibodies to the D antigen are not naturally present in the serum of the remaining 15% of individuals, but their formation may be stimulated by the transfusion of Rh-positive red cells, or acquired during delivery of a Rh(D)-positive baby.

Acquired antibodies are capable, during pregnancy, of crossing the placenta and, if present in a Rh(D)-negative mother, may cause severe haemolytic anaemia and even death (hydrops fetalis) in a Rh(D)-positive fetus *in utero*. The other minor blood group antigens may be associated with naturally occurring antibodies, or may stimulate the formation of antibodies on relatively rare occasions.

Transfusion reactions

If antibodies present in the recipient's serum are incompatible with the donor's cells, a transfusion reaction will result. This usually takes the form of an acute haemolytic reaction. Severe immune-related transfusion reactions due to ABO incompatibility result in potentially fatal complement-mediated intravascular haemolysis and multiple organ failure. Transfusion reactions from other antigen systems are usually milder and self-limiting.

Febrile transfusion reactions are non-haemolytic and are usually caused by a graft-versus-host response from leukocytes in transfused components. Such reactions are associated with fever, chills or rigors. The blood transfusion should be stopped immediately. This form of transfusion reaction is rare with leukodepleted blood.

Cross-matching

To prevent transfusion reactions, all transfusions are preceded by ABO and rhesus typing of both donor and recipient blood to ensure compatibility. The recipient's serum is then mixed with the donor's cells to confirm ABO compatibility and to test for rhesus and any other blood group antigen–antibody reaction.

Full cross-matching of blood may take up to 45 minutes in most laboratories. In more urgent situations, 'type specific' blood is provided which is only ABO/rhesus matched and can be issued within 10–15 minutes. Where blood must be given emergently, group O (universal donor) blood is given (O– to females, O+ to males).

When blood transfusion is prescribed and blood is administered, it is essential that the correct patient receives the correct transfusion. Two healthcare personnel should check the patient details against the prescription and the label of the donor blood. In addition, the donor blood serial number should also be checked against the issue slip for that patient. Provided these principles are strictly adhered to the number of severe and fatal ABO incompatibility reactions can be minimised.

Complications of blood transfusion

Complications from blood transfusion can be categorised as those arising from a single transfusion and those related to massive transfusion.

Complications from a single transfusion

Complications from a single transfusion include:

- incompatibility haemolytic transfusion reaction;
- febrile transfusion reaction;
- allergic reaction;
- infection:
  - bacterial infection (usually due to faulty storage);
  - hepatitis;
  - HIV;
  - malaria;
- air embolism;
- thrombophlebitis;
- transfusion-related acute lung injury (usually from FFP).

Complications from massive transfusion

Complications from massive transfusion include:

- coagulopathy;
- hypocalcaemia;
- hyperkalaemia;
- hypokalaemia;
- hypothermia.

In addition, patients who receive repeated transfusions over long periods of time (e.g. patients with thalassaemia) may develop iron overload. (Each transfused unit of red blood cells contains approximately 250 mg of elemental iron.)

Management of coagulopathy

Correction of coagulopathy is not necessary if there is no active bleeding and haemorrhage is not anticipated (not due for surgery). However, coagulopathy following or during massive transfusion should be anticipated and managed aggressively. Prevention of dilutional coagulopathy is central to the damage control resuscitation of patients who are actively bleeding.

This is the prime reason for delivering balanced transfusion regimes matching red blood cell packs with plasma and platelets. Based on moderate evidence, when red cells are transfused for active haemorrhage, it is best to match each red cell unit with one unit of FFP and one of platelets (1:1:1). This will reduce the incidence and severity of subsequent dilutional coagulopathy. Crystalloids and colloids should be avoided for the same reason.

The balanced transfusion approach cannot, however, correct coagulopathy. Therefore, coagulation should be monitored routinely, either with point-of-care testing (thromboelastometry) or with laboratory tests (fibrinogen, clotting times). Underlying coagulopathies should be treated in addition to the administration of 1:1:1 balanced transfusions.

There are pharmacological adjuncts to blood component therapy. The antifibrinolytic tranexamic acid is the most commonly administered. It is usually administered empirically to bleeding patients because effective point-of-care tests of fibrinolysis are not yet routinely available. There is little evidence to support the use of other coagulation factor concentrates at this time.

Blood substitutes

Blood substitutes are an attractive alternative to the costly process of donating, checking, storing and administering blood, especially given the immunogenic and potential infectious complications associated with transfusion.

There are several oxygen-carrying blood substitutes under investigation in experimental animal or early clinical trials. Blood substitutes are either biomimetic or abiotic. Biomimetic substitutes mimic the standard oxygen-carrying capacity of the blood and are haemoglobin based. Abiotic substitutes are synthetic oxygen carriers and are currently primarily perfluorocarbon based.

Haemoglobin is seen as the obvious candidate for developing an effective blood substitute. Various engineered molecules are under clinical trials, and are based on human, bovine or recombinant technologies. Second-generation perfluorocarbon emulsions are also showing potential in clinical trials.

FURTHER READING

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Chapter 3

Wounds, healing and tissue repair

Learning objectives

To understand:

- Normal healing and how it can be adversely affected
- How to manage wounds of different types, of different structures and at different sites
- Aspects of disordered healing that lead to chronic wounds
- The variety of scars and their treatment
- How to differentiate between acute and chronic wounds

INTRODUCTION

Wound healing is a mechanism whereby the body attempts to restore the integrity of the injured part. This falls far short of tissue regeneration by pluripotent cells, seen in some amphibians, and is often detrimental, as seen in the problems created by scarring, such as adhesions, keloids, contractures and cirrhosis of the liver. Several factors may influence healing. However, a clean incised wound in a healthy person where there is no skin loss will follow a set pattern as outlined below.

Summary box 3.1

Factors influencing healing of a wound

- Site of the wound
- Structures involved
- Mechanism of wounding
  - Incision
  - Crush
  - Crush avulsion
- Contamination (foreign bodies/bacteria)[a]
- Loss of tissue
- Other local factors
  - Vascular insufficiency (arterial or venous)
  - Previous radiation
  - Pressure
- Systemic factors
  - Malnutrition or vitamin and mineral deficiencies
  - Disease (e.g. diabetes mellitus)
  - Medications (e.g. steroids)
  - Immune deficiencies (e.g. chemotherapy, acquired immunodeficiency syndrome [AIDS])
  - Smoking

[a] In explosions, the contamination may consist of tissue such as bone from another individual.

NORMAL WOUND HEALING

This is variously described as taking place in three or four phases, the most commonly agreed being:

1 the inflammatory phase;
2 the proliferative phase;
3 the remodelling phase (maturing phase).

Occasionally, a haemostatic phase is referred to as occurring before the inflammatory phase, or a destructive phase following inflammation consisting of the cellular cleansing of the wound by macrophages (**Figure 3.1**).

The inflammatory phase begins immediately after wounding and lasts 2–3 days. Bleeding is followed by vasoconstriction and thrombus formation to limit blood loss. Platelets stick to the damaged endothelial lining of vessels, releasing adenosine diphosphate (ADP), which causes thrombocytic aggregates to fill the wound. When bleeding stops, the platelets then release several cytokines from their alpha granules. These are platelet-derived growth factor (PDGF), platelet factor IV and transforming growth factor beta (TGFβ). These attract inflammatory cells such as polymorphonuclear leukocytes (PMN) and macrophages. Platelets and the local injured tissue release vasoactive amines, such as histamine, serotonin and prostaglandins, which increase vascular permeability, thereby aiding infiltration of these inflammatory cells. Macrophages remove devitalised tissue and microorganisms while regulating fibroblast activity in the proliferative phase of healing. The initial framework for structural support of cells is provided by fibrin produced by fibrinogen. A more historical (Latin) description of this phase is described in four words: *rubor* (redness), *tumor* (swelling), *calor* (heat) and *dolor* (pain).

The proliferative phase lasts from the third day to the third week, consisting mainly of fibroblast activity with the production of collagen and ground substance (glycosaminogly-