THE NUTRITION SOCIETY TEXTBOOK SERIES

Clinical Nutrition

Second Edition

Edited by
Marinos Elia, Olle Ljungqvist, Rebecca J Stratton and Susan A Lanham-New

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Clinical Nutrition

The Nutrition Society Textbook Series

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Losing, gaining and making weight for athletes
Eating disorders and athletes
Bone health
Nutrition and the gastrointestinal tract for athletes
Immunity
Travel
Population groups: I
Population groups: II
Training and competition environments

Clinical Nutrition

Second Edition

Edited on behalf of The Nutrition Society by

Professor Marinos Elia
Institute of Human Nutrition
University of Southampton
UK

Professor Olle Ljungqvist
Department of Surgery
Örebro University Hospital and Karolinska Institutet
Sweden

Dr Rebecca J Stratton
Institute of Human Nutrition
University of Southampton
UK

Editor-in-Chief

Professor Susan A Lanham-New
Department of Nutritional Sciences
University of Surrey
UK

Foreword by Professor Dame Sally C. Davies

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Advancing Nutritional Science

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Editorial Offices
9600 Garsington Road, Oxford, OX4 2DQ, UK
The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK
2121 State Avenue, Ames, Iowa 50014-8300, USA

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Contributors

Dr Isabelle Aeberli
St John's Research Institute, India
ETH Zurich, Switzerland

Professor Simon P Allison
Formerly University of Nottingham
and Queen's Medical Centre
UK

Professor Bruce R Bistrian
Beth Israel Deaconess Medical Center
USA

Professor Federico Bozzetti
University of Milan
Italy

Dr Eduard Cabré
Hospital Universitari Germans Trias i Pujol
Spain

Dr Saveria Capria
La Sapienza University of Rome
Italy

Abeed H Chowdhury
Nottingham University Hospitals
Queen's Medical Centre, Nottingham
UK

Peter Collins
Queensland University of Technology
Australia

Professor John A Dodge
University of Swansea
UK

Professor Marinos Elia
University of Southampton
UK

Professor Filippo Rossi Fanelli
La Sapienza University of Rome
Italy

Professor Ken Fearon
University of Edinburgh
UK

Professor Gema Frühbeck
Clinica Universidad de Navarra-CIBERobn
Spain

Professor Miquel A Gassull
Hospital Universitari Germans Trias i Pujol
Spain

Dr Kate Gatenby
University of Leeds
UK

Professor Robert F Grimble
University of Southampton
UK

Professor Gianfranco Guarnieri
University of Trieste
Italy

Dr Anna Paola Iori
La Sapienza University of Rome
Italy

Cora F Jonkers-Schuitema
Academic Medical Centre, Amsterdam
The Netherlands

Professor Mark Kearney
University of Leeds
UK

Professor Anura V Kurpad
St John's Research Institute
India

Professor Olle Ljungqvist
Örebro University Hospital and Karolinska Institutet
Sweden

Professor Dileep N Lobo
Nottingham University Hospitals
Queen's Medical Centre, Nottingham
UK

Professor John MacFie
Scarborough Hospital
UK

Dr Paula McGurk
University Hospital Southampton
NHS Foundation Trust
UK

Dr Clare McNaught
Scarborough Hospital
UK

Professor Simon H Murch
Warwick Medical School, University of Warwick
UK

Associate Professor Maurizio Muscaritoli
La Sapienza University of Rome
Italy

Dr Nicholas I Paton
National University of Singapore
Singapore

Professor Mathias Plauth
Staedtisches Klinikum Dessau (Municipal Hospital Dessau)
Germany

Associate Professor Christine Rodda
Monash University
Australia

Dr Tatjana Schütz
Leipzig University Medical Centre
Germany

Professor Jean-Marc Schwarz
Touro University California
USA

Roberta Situlin
University of Trieste
Italy

Dr Rebecca J Stratton
University of Southampton
UK

Professor Luc Tappy
University of Lausanne
Switzerland

Dr Marian AE van Bokhorst-de van der Schueren
VU University Medical Centre
The Netherlands

Esther van den Hogen
Maastricht UMC
The Netherlands

Dr Stephen Wheatcroft
University of Leeds
UK

Dr Anthony F Williams
St George's, University of London
UK

Kate Williams
South London and Maudsley NHS Foundation Trust
UK

Dr Jean-Fabien Zazzo
Hôpital Antoine-Béclère (Assistance Publique-Hôpitaux de Paris)
France

Series Foreword

The Nutrition Society was established in 1941 as a result of a group of leading physiologists, biochemists and medical scientists recognising that the emerging discipline of nutrition would benefit from its own Learned Society. The Nutrition Society's mission was, and firmly remains, "*to advance the scientific study of nutrition and its application to the maintenance of human and animal health*". It is the largest Learned Society for Nutrition in Europe and has over 2,700 members worldwide. For more details about the Society and how to become a member, visit the website at www.nutritionsociety.org.

Throughout its history, a primary objective of the Society has been to encourage nutrition research and to disseminate the results of such research. This is reflected in the several scientific meetings with the Nutrition Society, often in collaboration with sister Learned Societies in Europe, Africa, Asia and the USA, organised each year.

The Society's first journal, *The Proceedings of the Nutrition Society* published in 1944, records the scientific presentations made to the Society. Shortly afterwards, in 1947, the *British Journal of Nutrition* was established to provide a medium for the publication of primary research on all aspects of human and animal nutrition by scientists from around the world. Recognising the needs of students and their teachers for authoritative reviews on topical issues in nutrition, the Society began publishing *Nutrition Research Reviews* in 1988. The journal *Public Health Nutrition*, the first international journal dedicated to this important and growing area, was subsequently launched in 1998. The Society is constantly evolving and has most recently launched the *Journal of Nutritional Science* in 2012. This is an international, peer-reviewed, online only, open access journal.

Just as in research, having the best possible tools is an enormous advantage in both teaching and learning. The Nutrition Society Textbook Series was established by Professor Michael Gibney (University College Dublin) in 1998. It is now under the direction of the second Editor-in-Chief, Professor Susan Lanham-New (University of Surrey), and continues to be an extraordinarily successful venture for the Society. This series of Human Nutrition textbooks is designed for use worldwide and this was achieved by translating the Series in multiple languages including Spanish, Greek, Portuguese and Indonesian. The sales of the textbook (>30,000 copies) are a tribute to the value placed on the textbooks both in the UK and worldwide as a core educational tool.

This Second Edition of *Clinical Nutrition* focuses on the metabolically compromised patient and provides a most thorough review of the importance of nutrition across the clinical spectrum. The textbook is aimed at those with an interest in nutrition in the clinical setting, including students, nutritionists, dietitians, medics, nursing staff or other allied health professionals.

In my capacity as the Chief Medical Officer (CMO) for England, and the UK Government's Principal Medical Adviser, the professional lead for all Directors of Public Health and Chief Scientific Adviser for the Department of Health, it gives me great pleasure to write the Foreword for the Second Edition of *Clinical Nutrition*. I have been actively involved in NHS Research and Development from its establishment and I understand how important clinical nutrition is to the patient and the medical team. This textbook brings together science and clinical practice and is a valuable resource to all those working in the field.

Professor Dame Sally C. Davies
Chief Medical Officer
Chief Scientific Adviser

Preface

The Nutrition Society's Textbook Series continues to go from strength to strength following its development over 10 years ago. The forward thinking focus that Professor Michael Gibney (University College Dublin) had at that time is to be especially noted. My task as the new Editor-in-Chief since 2009 is much easier than the visionary one that Professor Gibney had back in the late 1990s and it remains a tremendous honour for me to be following in his footsteps.

The first and second textbooks in the Series, *Introduction to Human Nutrition* (IHN) and *Nutrition and Metabolism* (N&M), are now out in Second Editions and sales continue apace. We are currently working on the Second Edition of the third textbook in the Series, *Public Health Nutrition* (PHN), and we are absolutely delighted now to present to the field of Nutritional Sciences, Elia *et al.*'s *Clinical Nutrition* Second Edition. This follows our publication last year of the fifth textbook in the Series, *Sport and Exercise Nutrition* First Edition (SEN1e). The sales of SEN1e have surpassed all expectations and we were most grateful to Dr Richard Budgett OBE, Chief Medical Officer for the London 2012 Olympic and Paralympic Games, for his enthusiasm, support and most generous Foreword.

Clinical Nutrition Second Edition (CN2e) is a great strength of the Textbook Series and the Nutrition Society is indebted to the Senior Editor, Professor Marinos Elia (University of Southampton), for his careful planning and editorial leadership of the book following the critical role he played with the development of the First Edition of *Clinical Nutrition*. Sincerest of thanks are also due to the Editors, Professor Olle Ljungqvist (Örebro University Hospital and Karolinska Institutet, Sweden) and Dr Rebecca Stratton (University of Southampton) for their immense work on this Second Edition.

This Second Edition is intended for those with an interest in nutrition in the clinical setting, whether they are dietitians or medics, nursing staff or other allied health professionals. The book starts by setting the scene in assessing nutritional status and discusses the clinical consequences and current management options with under-nutrition and over-nutrition, and eating disorders and metabolic disease. The subsequent later chapters deal with the different organ systems of the body, setting out the most up-to-date thinking on the role of nutrition, whether it involves nutritional support, nutritional education or a combination of both.

We are extremely honoured that the Foreword for the Second Edition has been written by Dame Sally Davies, Chief Medical Officer (CMO) for England, and the UK Government's Principal Medical Adviser. It gives us great confidence in this Textbook to have such a seal of approval from someone so eminent in the clinical field. Our sincerest of thanks indeed for Dame Sally's help and support.

The Society is most grateful to the textbook publishers Wiley-Blackwell for their continued help with the production of the textbook and in particular Nick Morgan, Sara Crowley-Vigneau and Marilyn Pierro, as well as Aravinthakumar Ranganathan, the project manager at SPi Publisher Services. In addition, many grateful thanks to Professor Lisa Roberts, Dean of the Faculty of Health and Medical Sciences, University of Surrey for her great encouragement of the Textbook Series production.

Finally, sincerest of thanks indeed to the Nutrition Society President, Professor Sean J.J. Strain (University of Ulster), for all his belief in the Textbook Series and to Professor David Bender, Honorary Publications Officer, for being such a great sounding board. The Series remains indebted to Sharon Hui (Assistant Editor, NS Textbook Series) and Jennifer Norton (NS Business Development Manager) for their huge contribution to the development of the Series and for making the textbooks such an enjoyable journey.

I do hope that you will find the textbook a great resource. Happy reading indeed!

With my warmest of wishes.

Professor Susan A. Lanham-New
Head, Department of Nutritional Sciences
Faculty of Health and Medical Sciences
University of Surrey
and Editor-in-Chief, Nutrition Society Textbook Series

The Nutrition Society Textbook Series Editorial Team

First Edition Acknowledgements

Editor-in-Chief
Michael J Gibney

Editors
Marinos Elia
Olle Ljungqvist
Julie Dowsett

Authors

Chapter 1: Principles of Clinical Nutrition
Marinos Elia

Chapter 2: Nutritional Assessment
Khursheed Jeejeebhoy
Mary Keith

Chapter 3: Overnutrition
Gema Frühbeck

Chapter 4: Undernutrition
Anura Kurpad

Chapter 5: Metabolic Disorders
Luc Tappy
Jean-Marc Schwarz

Chapter 6: Eating Disorders
Janet Treasure
Tara Murphy

Chapter 7: Adverse Reactions to Foods
Simon Murch

Chapter 8: Nutritional Support
Karin Barendregt
Peter Soeters

Chapter 9: Ethics and Nutrition
John Macfie

Chapter 10: The Gastrointestinal Tract
Miguel A Gassull
Eduard Cabré

Chapter 11: Nutrition in Liver Disease
Marietjie Herselman
Demetre Labadarios
Christo Van Rensburg
Aref Haffejee

Chapter 12: Nutrition and the Pancreas
Jean Fabien Zazzo

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Gianfranco Guarnieri
Roberta Situlin
Gabriele Toigo

Chapter 14: Nutritional and Metabolic Support in Hematologic Malignancies and Hematopoietic Stem Cell Transplantation
Maurizio Muscaritoli
Gabriella Grieco
Filippo Rossi Fanelli
Zaira Aversa

Chapter 15: The Lung
Annemie Schols
Emiel FM Wouters

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Bruce Bistrian
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Olle Ljungqvist
Kenneth Fearon
Roderick Little

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Nicholas Paton
Miguel A Gassull
Eduard Cabré

Chapter 21: Nutritional Support in Patients with Cancer
Federico Bozzetti

Chapter 22: Pediatric Nutrition
Anthony F Williams

Chapter 23: Cystic Fibrosis
Olive Tully
Julie Dowsett

Chapter 24: Water and Electrolytes
Meritxell Girvent
Guzman Franch
Antonio Stiges-Serra

Chapter 25: Illustrative Cases
Simon Allison

1
Principles of Clinical Nutrition: Contrasting the Practice of Nutrition in Health and Disease

Marinos Elia

Institute of Human Nutrition, University of Southampton, Southampton, UK

Key messages

- To understand how to best meet the nutritional needs of an individual, the distinction between physiology in health and pathophysiology in disease needs to be carefully considered.
- For some groups of patients, the requirements are higher than those in health, while for other groups of patients they are lower. If recommendations for healthy individuals are applied to patients with certain types of disease, they may produce harm.
- In health, only the oral route is used to provide nutrients to the body. In clinical practice, other routes can be used. The use of the intravenous route for feeding raises a number of new issues.
- Alterations in nutritional therapy during the course of an acute disease may occur because the underlying disease has produced new complications or because it has resolved. Similarly, in more chronic conditions there is a need to review the diet at regular intervals.

1.1 Introduction

Clinical nutrition focuses on the nutritional management of individual patients or groups of patients with established disease, in contrast to public health nutrition, which focuses on health promotion and disease prevention in the general population. The two disciplines overlap, however, especially in older people, who are often affected by a range of disabilities or diseases. Working together, instead of independently, the two disciplines are more likely to facilitate successful implementation of local, national, and international policies on nutrition. To understand the overlap between them, it is necessary to consider not only some of the principles of nutrition that apply to health, but also special issues that apply to the field of clinical nutrition. These include altered nutritional requirements associated with disease, disease severity and malnutrition, and nonphysiological routes of feeding using unusual feeds and feeding schedules. This introductory chapter provides a short overview of these issues, partly because they delineate qualitative or quantitative differences between health and disease, and partly because they form a thread that links subsequent sections of this book, which is divided into discrete chapters addressing specific conditions.

It is now possible to feed all types of patients over extended periods of time, including those who are unconscious, unable to eat or swallow, or have little or no functional gastrointestinal tract. It is possible to target specific patient groups with special formulations, and even to change the formulation in the same patient as nutritional demands alter during the course of an illness. Since some of these formulations may be beneficial to some patient groups and detrimental to other groups or to healthy subjects, the distinction

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between physiology in health and pathophysiology in disease needs to be considered carefully. It is hoped that some of the principles outlined here will help to establish a conceptual framework for considering some of the apparently diverse conditions discussed in this textbook.

1.2 The spectrum of nutritional problems

Clinical nutrition aims to treat and prevent suffering from malnutrition. However, there is no universally accepted definition for 'malnutrition' (literally, 'bad nutrition'). The following definition, which encompasses both under- and over-nutrition, is offered for the purposes of this chapter.

> Malnutrition is a state of nutrition in which a deficiency or excess (or imbalance) of energy, protein, and other nutrients causes measurable adverse effects on tissue/body function (shape, size, and composition) and clinical outcome.

In this chapter and elsewhere, however, the term 'malnutrition' is mainly used to refer to under- rather than over-nutrition.

Both under- and over-nutrition have adverse physiological and clinical effects. Those relating to under-nutrition (Table 1.1) are diverse, which explains why malnourished patients may present to a wide range of medical disciplines. Several manifestations may occur simultaneously in the same individual, although some predominate. They may be caused by multiple deficiencies. Specific nutrient deficiencies may also have diverse effects, affecting multiple systems, but it is not entirely clear why the same deficiency can present in a certain way in one subject and a different way in another. For example, it is not clear why some patients with deficiency of vitamin B_{12} present to the haematologist with megaloblastic anaemia, others to the neurologist with neuropathy and other neurological manifestations (e.g. subacute combined degeneration of the cord), and still others to the geriatrician with cognitive impairment or dementia.

The spectrum of presentations is more diverse than this would indicate because protein–energy malnutrition frequently coexists with various nutrient deficiencies. For example, patients with gastrointestinal problems are frequently underweight and at the same time exhibit magnesium, sodium, potassium, and zinc deficiencies, due to excessive losses of these nutrients in diarrhoea or other gastrointestinal effluents. There may also be problems with absorption; for example, patients with Crohn's disease affecting the terminal ileum, where vitamin B_{12} is absorbed, are at increased risk of developing B_{12} deficiency. Patients who have had surgical removal of their terminal ileum or stomach, which produces the

Table 1.1 Physical and psychosocial effects of under-nutrition.

Adverse effect	Consequence
Physical	
Impaired immune responses	Predisposes to infection
Reduced muscle strength and fatigue	Inactivity, inability to work effectively, and poor self-care. Abnormal muscle (or neuromuscular) function may also predispose to falls or other accidents
Reduced respiratory muscle strength	Poor cough pressure, predisposing to and delaying recovery from chest infection
Inactivity, especially in bed-bound patient	Predisposes to pressure, sores, and thromboembolism
Impaired thermoregulation	Hypothermia, especially in the elderly
Impaired wound-healing	Failure of fistulae to close, un-united fractures, increased risk of wound infection resulting in prolonged recovery from illness, increased length of hospital stay, and delayed return to work
Foetal and infant programming	Predisposes to common chronic diseases, such as cardiovascular disease, stroke, and diabetes in adult life
Growth failure	Stunting, delayed sexual development, and reduced muscle mass and strength
Psychosocial	
Impaired psychosocial function	Even when uncomplicated by disease, undernutrition causes apathy, depression, self-neglect, hypochondriasis, loss of libido, and deterioration in social interactions. It also affects personality and impairs mother–child bonding

intrinsic factor necessary for B_{12} absorption, fail to absorb vitamin B_{12}. Isolated nutrient deficiencies may also occur, for example iron deficiency due to heavy periods in otherwise healthy women.

Another complexity is the interaction between nutrients, which may occur at the level of absorption, metabolism within the body, or excretion. One nutrient may facilitate the absorption of another; for example, glucose enhances the absorption of sodium (on the glucose–sodium co-transporter). This is the main reason why oral rehydration solutions used to correct salt deficiency due to diarrhoea (or fluid losses due to other gastrointestinal diseases) contain both salt and glucose. In contrast, other nutrients compete with each other for absorption. For example, because of competition between zinc and copper for intestinal absorption, administration of copper may precipitate zinc deficiency, especially in those with borderline zinc status. Other nutrients interact with each other during tissue deposition. Accretion of lean tissue requires multiple nutrients, and lack of one of them, such as potassium or phosphate, can limit its deposition, even when adequate amounts of protein and energy are available (Figure 1.1). This emphasises the need to provide all necessary nutrients in appropriate amounts and proportions.

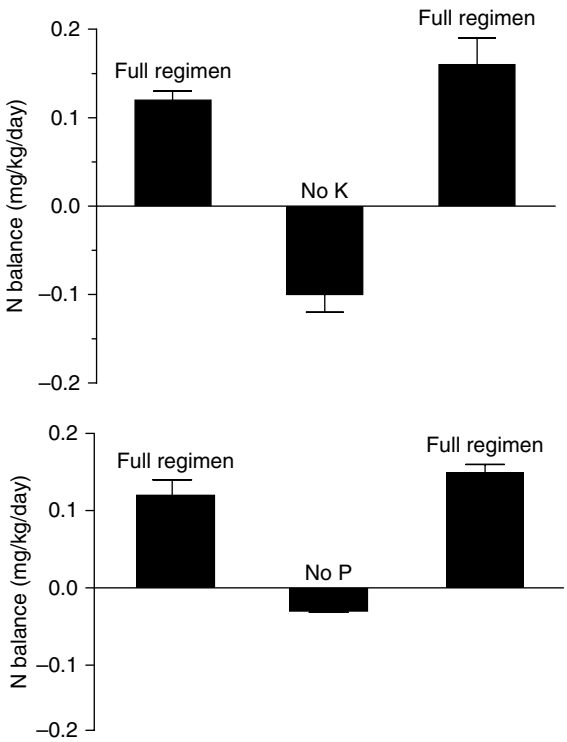

Figure 1.1 Effect of omitting potassium (K) and phosphate (P) from a parenteral nutrition regimen on the nitrogen (N) balance of depleted patients receiving hypercaloric feeding. Data from Rudman *et al*. (1975).

1.3 Nutritional requirements

Effect of disease and nutritional status

Fluid and electrolytes

The principles of nutrient requirements in healthy individuals are described in *Introduction to Human Nutrition* (Gibney *et al*., 2009), an earlier volume in this textbook series. The average nutrient intake refers to the average intake necessary to maintain nutrient balance. The reference nutrient intake (RNI) refers to the intake necessary to satisfy the requirements of 97.5% of the healthy population (+2 standard deviations from the average nutrient intake). In patients with a variety of diseases, the requirements are more variable (Figure 1.2): for some groups of patients, they are higher than for those in health, while for other groups they are lower. For example, in patients with gastrointestinal fluid losses, the requirement for sodium may be double the RNI, while in patients with severe renal or liver disease who retain salt and water, the requirements may be well below the average nutrient requirement for healthy subjects ingesting an oral diet. The requirements for potassium and phosphate may also be well below the RNI for patients with severe renal disease in whom there is failure of excretion. Therefore, if recommendations

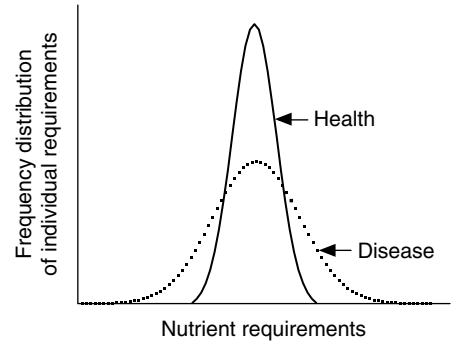

Figure 1.2 Frequency distribution of nutrient requirements in health and disease.

for healthy individuals are applied to patients with certain types of disease, they may produce harm. A general guide to the requirements for sodium and potassium in patients with gastrointestinal fluid loss (above those for maintenance) is provided in Table 1.2, which shows the electrolyte content of various fluids. A person with a loss of 1.5 litres of small-intestinal fluid may require ~150 mmol of sodium above maintenance (the RNI for sodium is 70 mmol/day according to UK reference standards), whereas loss of the same volume of nasogastrically aspirated fluid requires only ~90 mmol extra sodium. Note that the requirements for potassium in patients losing gastrointestinal fluids are generally much lower than those for sodium (Table 1.2).

Excessive salt and fluid administration can be just as detrimental as inadequate intake, causing fluid retention and heart failure in some individuals. Fluid retention is often detected clinically by noting pitting oedema at the ankles or over the sacrum, but oedema can also affect internal tissues and organs, causing a variety of problems. Some of these problems are shown in Table 1.3. A recent study has questioned the routine clinical practice of administering large amounts of fluid in the early postoperative period in an attempt to reduce the risk of hypotension. In a randomised controlled trial carried out in Denmark, routine fluid administration was compared with a fluid-restricted regimen that aimed to approximately maintain body weight. In those receiving routine fluid therapy, not only did body weight increase significantly more than in the fluid-restricted group, but it significantly increased a variety of complications, including tissue-healing and cardiopulmonary complications. It also increased mortality, but this did not reach statistical significance, possibly because only a small number of subjects died during the course of the study. Acute accidental and elective surgical trauma is associated with a tendency to retain salt and water, at least partly because of increased secretion of mineralocorticoids and antidiuretic hormone. Therefore, administration of excess salt and water as in protein–energy malnutrition may lead to fluid retention that would not occur in normal subjects.

Protein

Another difference between nutritional requirements in health and disease concerns body composition and nutrient balance. In healthy adults, nutritional intake aims to maintain body composition (lean body mass and fat mass) within a desirable range, but this may not be the case in subjects with disease-related malnutrition in whom there is a need to replete tissues so that body function can improve. The response of the body to nutritional support also varies between health and disease with or without malnutrition. Consider the effect of increasing protein intake in normal, depleted, and catabolic subjects (severe acute disease), all of whom are close to energy balance (Figure 1.3). In healthy subjects, nitrogen (N) (1 g N = 6.25 g protein) balance is achieved with an intake of 0.105 g N/kg/day (the RNI necessary to achieve balance in 97.5% of the population is ~0.13 g N/kg/day according to World Health Organization (WHO) reference data). Increasing the N intake above this amount leads to little or no further net protein deposition. Depleted subjects continue to deposit protein (positive N balance) when intake is increased above 0.1 (and above 0.13) g N/kg/day, while catabolic patients show

Table 1.2 Electrolyte contents of some body secretions (mmol/l).

Secretion/excretion	Na	K
Gastric	60	10
Pancreatic	140	5
Biliary	140	5
Small-intestinal	100	10
Diarrhoea	60[a]	20
Faeces	25	55
Sweat		
insensible	10	10
visible	60	10

[a] Variable (30–140 mmol/l)

Table 1.3 Some problems caused by oedema.

Site of oedema	Consequence
Liver	Abnormal liver-function tests
Gastrointestinal tract	Impaired gastric motility with subsequent delay in the time taken to tolerate oral food and recover from abdominal surgery; impaired absorption
Brain	Impaired consciousness in those with a head injury associated with some preexisting cerebral oedema
Wounds	Delayed healing

a negative N balance, with little improvement above an intake of ~0.25 g N/kg/day. With this in mind, protein requirements take into account the need to limit, but not necessarily abolish, N losses in catabolic patients, and the need to replete tissues in malnourished patients so that their function improves.

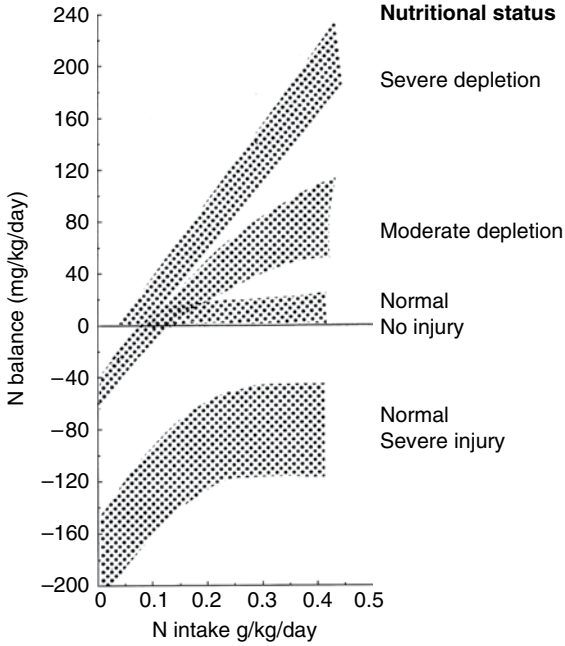

Figure 1.3 Effect of increasing protein (N) intake on N balance in depleted, healthy, and catabolic patients close to energy balance.

These criteria differ from those in healthy, well-functioning adults, who have no need to change their body composition. In contrast, in healthy children it is necessary to cater for growth and development, which is associated with deposition of tissue and a positive N balance. Similar considerations apply to calculating the requirements of other nutrients and of energy, but metabolism in health and disease differs in a number of ways, which affects concepts about requirements.

Energy

In healthy subjects the energy requirements necessary to maintain energy stores are often calculated as multiples of basal metabolic rate (BMR). However, in many acute diseases (Figure 1.4) and a number of chronic diseases BMR has been found to be increased, which led to the view that the energy requirements in such states were also usually increased. This conclusion failed to take into account the decrease in physical activity that occurs as a result of many diseases and disabilities. This decrease counteracts or more than counteracts the increase in BMR, so that total energy expenditure in most disease states (and hence the energy intake necessary to maintain balance) is actually close to normal, or even decreased. As previously noted, there is also the need to consider changes in energy stores. In obese individuals it is desirable to reduce the energy stores by providing hypocaloric feeding, and in depleted patients to increase energy stores by providing

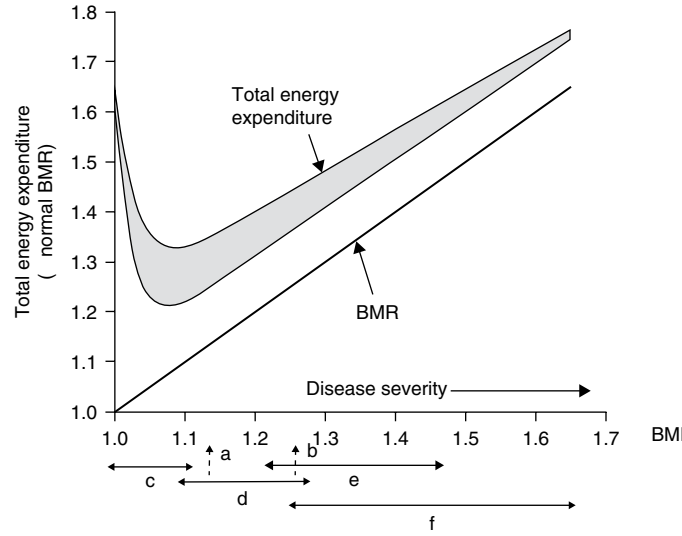

Figure 1.4 Effect of acute disease severity (expressed as multiples of normal BMR) on total energy expenditure (shaded area). The difference between total energy expenditure and BMR is due to physical activity (and some thermogenesis, which typically accounts for ~10% of energy intake). The increase in BMR is counteracted by a decrease in physical activity. (a) Infection, persistent fever (1 °C); (b) infection, persistent fever (2 °C); (c) burns 10% (first month), single fracture (first week), postoperative (first 4 days); (d) burns 10–25% (first month), multiple long-bone fractures (first week); (e) severe sepsis/multiple trauma (patient on respirator); (f) burns 25–95% (first month).

hypercaloric feeding. In both cases, it is usually better to do this during the recovery phase of illness rather than the acute and more unstable phase of illness (see later in this chapter).

In estimating the energy requirements of a hospitalised patient, it is worth considering the energy contribution from nondietary sources, such as intravenous dextrose 5% (~200 kcal/l), dialysate, and fat-based drugs such as propofol (~1.1 kcal/ml) and drugs that may need to be administered with saline.

Metabolic blocks and nutritional requirements

Inborn errors of metabolism

When there is a block in a metabolic pathway that involves conversion of substance A to B, there is an accumulation of substance A, which may be toxic (either directly or via its products), and a depletion in substance B, which needs to be either formed within the body by alternative pathways or provided by the diet. An alternative strategy is to replace the enzyme responsible for the block, for example by organ transplantation, although this has only been used for a few metabolic disorders. One of the best known examples of a metabolic block occurs in phenylketonurea (PKU), due to deficiency of the enzyme phenylalanine hydroxylase, the gene of which is located on chromosome 12 (12q). In the absence of phenylalanine hydroxylase, the gene of which normally converts the amino acid phenylalanine to tyrosine in the liver, there is an accumulation of phenylalanine and its metabolites, which causes brain damage, mental retardation, and epilepsy. Tyrosine, which is distal to the block, is provided by the diet so the treatment for PKU is to ingest a low-phenylalanine diet (some phenylalanine is required for protein synthesis) (see later in this chapter for the duration of treatment). The diet, which is not found in nature, is specifically manufactured to restrict the intake of phenylalanine. Other metabolic blocks may require exclusion of other individual nutrients, for example restriction of galactose and lactose in children with galactosemia. Some diets may exclude whole proteins, which can cause food allergy or sensitivity. In the case of coeliac disease, which is responsible for a small-bowel enteropathy with malabsorption, this means avoiding gluten, which is found in wheat and wheat products (see Chapter 8). However, the problem here is not due to a block in a metabolic pathway, but to an abnormal reaction to food, which appears to be acquired.

Acquired metabolic blocks

Not all metabolic blocks are inherited as inborn errors of metabolism. For example, deficiency of phenylalanine hydroxylase can occur as a result of cirrhosis. Since in healthy subjects tyrosine can be formed from phenylalanine, some feed manufacturers have added little or no tyrosine to parenteral nutrition regimens, especially since tyrosine has a low solubility. However, a few patients with severe liver disease lose the ability to synthesise sufficent tyrosine, with the result that it becomes rate-limiting to protein synthesis, even in the presence of all other necessary amino acids (i.e. the enzymatic deficiency is ultimately responsible for the metabolic block in protein synthesis, which can be reversed by administering tyrosine). Other examples of acquired metabolic blocks due to amino acids involve histidine in some patients with renal disease, and cystine in liver disease. It is therefore essential that these amino acids (described as conditionally essential) are provided in the diet (oral or intravenous) of such patients, even though they are not essential for healthy subjects.

Acquired metabolic blocks may involve other types of nutrients. An interesting example concerns vitamin D, which is hydroxylated in the liver to produce 25-hydroxy vitamin D and further hydroxylated in the kidney to produce the active metabolite 1,25-dihydroxy vitamin D (Figure 1.5). Some patients with chronic renal failure are unable to produce sufficient amounts of 1,25-dihydroxy vitamin D, due to loss of activity of the enzyme 1 alpha hydroxylase in the kidney. Such patients may suffer from metabolic bone disease, which is at least partly due to deficiency of 1,25-dihydroxy vitamin D. This metabolic block can be bypassed by providing either synthetic 1,25-dihydroxy vitamin D or synthetic 1-hydroxy vitamin D, which is converted to 1,25-dihydroxy vitamin D in the liver (Figure 1.5). Such therapy differs from that used in the treatment of PKU in at least two ways: it involves administration of substance distal to the block (cf. restriction of phenylalanine, which is proximal to the block) and it is not found in the normal diet in any significant amounts. It is an example of nutritional pharmacology involving administration of a bioactive substance.

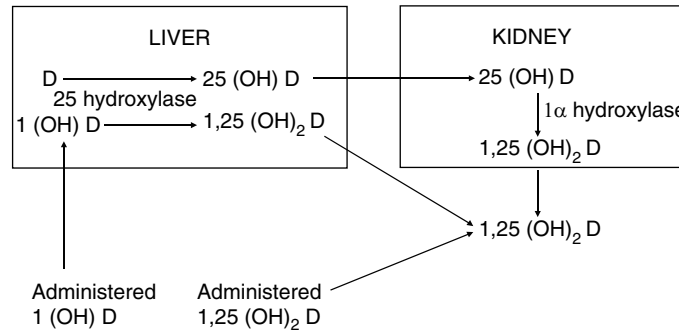

Figure 1.5 Metabolism of vitamin D in the liver and kidney. In renal failure, the formation of 1,25-dihydroxy vitamin D (1,25 $(OH)_2$ D) in the kidney may be inadequate, in which case 1,25-dihydroxy vitamin D or 1-hydroxy vitamin D (25 (OH) D) can be prescribed.

Table 1.4 Some examples of nutritional pharmacology.

Type I (prenutrients)	
Organic phosphates	The amount of calcium and phosphate that can be added to parenteral nutrition solutions is limited by the solubility of calcium phosphate, which can precipitate. Organic phosphates, such as glycerol-phosphate or glucose-phosphate, are soluble and do not precipitate in the presence of calcium. The organic phosphate is hydrolysed within the body to yield free phosphate
Dipeptides	Glutamine degrades during heat sterilisation and storage of parenteral amino acid solutions. It can be provided as a dipeptide (e.g. alanylglutamine), which is stable and can be stored for extended periods of time. Poorly soluble amino acids can be provided as soluble dipetides, such as glycyltyrosine or alanylcystine. The dipeptides are hydrolysed within the body to yield free amino acids
Type II (pharmacological doses)	
Glycerol	Free glycerol is used as an emulsifying agent in intravenous fat solutions
Medium-chain triglycerides	Medium-chain triglycerides (up to 50% of total lipid) may be better absorbed and tolerated than long-chain triglyceride. In intravenous use, these may avoid infusional hyperlipidaemia
Glutamine	Glutamine may be given in large amounts (12–30 g), with the aim of improving clinical outcome (e.g. in intensive care units)
Oligofructose	Bifidobacteria or oligofructose, which is a fermentable bifidogenic substrate, can be given orally with the aim of changing intestinal microflora and reducing the growth of potentially pathogenic organisms
Type III (bioactive substances)	
Erythropoietin	Increases utilisation of iron and Hb synthesis in anaemic patients with end-stage renal failure
1,25-dihydroxy and 1-hydroxy vitamin D	Used in renal failure when there is a block in 1α hydroxylation of 25-hydroxy vitamin D
Growth hormone	Aims to improve N balance

A variety of other bioactive substances have been used in clinical nutrition with the aim of improving outcome. Some products of metabolism require more than one class of substrate for their synthesis. For example, haemoglobin (Hb) comprises a variety of amino acids and iron, which forms part of the haem component. All the substrates may be available in adequate quantities, but a block in Hb synthesis can still occur as a result of a deficiency of erythropoietin, a bioactive substance produced by the kidney that stimulates Hb synthesis. Erythropoietin synthesis is upregulated during hypoxia, which explains the high Hb concentrations in people living at high altitudes. In contrast, lack of erythropoietin leads to anaemia. One of the features of end-stage renal failure is severe anaemia, which is at least partly due to the inability of the damaged kidney to produce enough erythropoietin. Traditionally, this anaemia was treated by repeated blood transfusions. Now that recombinant erythropoietin is available, it can be used to treat the anaemia and to eliminate or dramatically reduce the need for repeated blood transfusions, which carry the risk of transmitting infections, such as HIV and hepatitis, and which require admission of patients to special healthcare facilities. Importantly, injections of recombinant erythropoietin have also been shown to improve quality of life in patients with severe renal disease. Other examples of nutritional pharmacology, shown in Table 1.4, are divided into those involving administration of prenutrients, pharmacological

doses of normal nutrients, and bioactive substances (see Table 1.4 for the rationale for specific types of nutritional pharmacology).

The uncritical use of bioactive substances can produce unpredictable serious side effects, including death. An example involves injections of pharmacological doses of growth hormone (GH) in critically ill patients. It was thought that GH might be beneficial in limiting the marked N loss that frequently occurs in such patients (equivalent to overcoming a metabolic block in net protein synthesis). GH is known to stimulate protein synthesis, and had previously been shown to improve N balance in a wide range of clinical conditions. However, in a large multicentre trial involving patients admitted to intensive care units, pharmacological doses of GH doubled mortality compared with the placebo group (from about 20 to 40%), sending a signal to the scientific and clinical community about the dangers of such interventions, especially when the mechanisms of action have not been previously evaluated.

The mechanism(s) responsible for the increased mortality with GH is still uncertain, but several suggestions have been made. One is that large doses of GH have detrimental effects on immune cells, which play a key role in host defence in critical illness. Another concerns the fluid-retaining properties of GH (see earlier for the detrimental effects of fluid overload). Yet another concerns the protein-stimulating properties of GH, which were, paradoxically, the main reason for using GH in the first place. Since muscle is thought to be a major site of action of GH, it is possible that stimulation of protein synthesis here may limit the availability of amino acids, including glutamine, to other tissues. These amino acids would normally be used for synthesis of proteins, for example the acute-phase proteins in the liver, which participate in the response to infection and inflammation. They are also normally used as fuel for a variety of cells, including immune cells (some preferentially utilising glutamine as a fuel), which play an important role in combating infection.

It has also been suggested that some of the detrimental effects of GH are due to cardiac arrhythmias from high concentrations of non-esterified fatty acids produced by the lipolytic effect of GH. Another suggestion is that the mortality is partly due to disturbances in glucose homeostasis, since GH produces significantly higher circulating glucose concentrations than the placebo. Hyperglycaemia in critically ill patients can have a range of detrimental effects, including predisposition to catheter-related sepsis in those receiving intravenous nutrition.

Effect of the route of feeding on nutrient requirements

In health, only the oral route is used to provide nutrients to the body; in clinical practice, other routes (or a combination) can be used. Before discussing their effect on nutrient requirements, it is necessary to briefly consider the type of nutritional support and feeding route. In general, food is the first line of treatment, but if this is inadequate to meet the needs of patients, oral supplements may be used, followed by enteral tube feeding and then intravenous feeding (parenteral nutrition). However, this linear sequence is inadequate in a number of situations. The first-line treatment for someone who has acutely developed short bowel syndrome is parenteral nutrition, not oral nutrition, oral supplements, or even enteral tube feeding. Similarly, tube feeding may be the first-line treatment for a patient with a swallowing problem – not oral food or supplements, which can cause detrimental effects. In some situations (e.g. cerebral palsy), oral feeding is possible, but this can take several hours per day and so it may be more practical to tube feed. In essence, the simplest, most physiological, and safest route to provide a patient's nutritional requirements should be sought, while taking into account the practicalities of feeding. Occasional unusual and unsuspected routes deliver nutrients into the body (see below). The route of feeding can have major effects on nutrient requirements, particularly parenteral nutrition.

Parenteral nutrition

The use of the intravenous route for feeding raises a number of new issues, especially in relation to nutrients which are poorly absorbed by the gut. For some nutrients, such as sodium, potassium iodide, fluoride, and selenium, which are well absorbed, the intravenous requirements are similar to the oral requirements. For nutrients that are poorly absorbed, such as iron, calcium, and especially chromium and manganese, the intravenous requirements are considerably lower than the oral requirements, sometimes up to 10-fold lower (Figure 1.6). If the doses of some

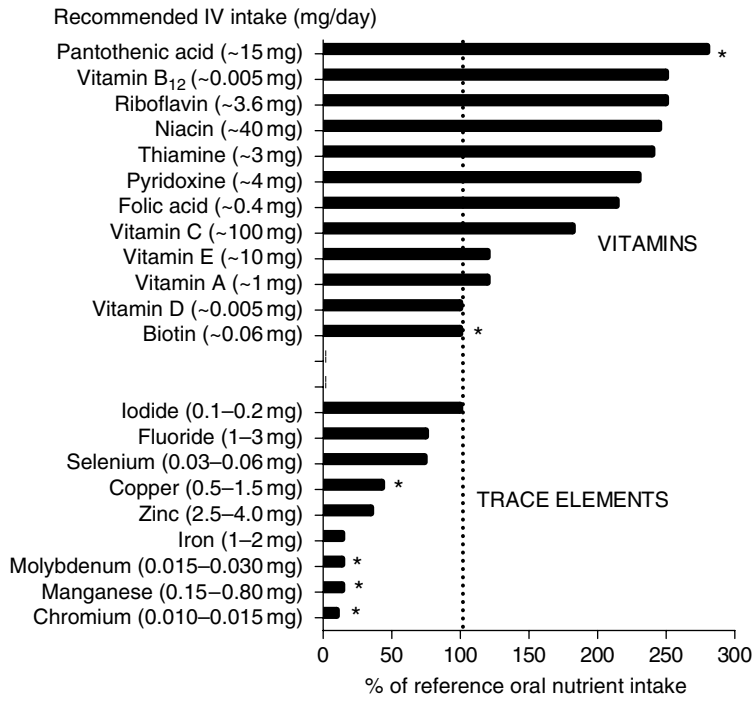

Figure 1.6 Recommended doses of vitamins and trace elements for intravenous (IV) nutrition expressed as a percentage of the recommended nutrient intake (UK values). Those marked with an asterisk indicate nutrients for which there was inadequate information to establish a reference nutrient intake (RNI). For these nutrients, the midpoint of the estimated average oral intake is used for comparative purposes.

of these trace elements or minerals recommended for oral nutrition were to be used intravenously over prolonged periods of time, they would probably produce toxic effects.

This consideration highlights the key role of the gut in regulating the amount of micronutrients absorbed in health. Sometimes the gut plays the only important role in controlling the status of nutrients within the body. For example, there is no effective physiological way of eliminating excess iron once it is within the body. In contrast to the recommended intakes of intravenous trace elements, those for intravenous vitamins are usually higher than the RNI for oral nutrition (Figure 1.6). There are several reasons why this is so. First, patients receiving parenteral (intravenous) nutrition usually have severe disease, which may increase the requirements for some vitamins. Second, patients are often affected by preexisting malnutrition and are in need of repletion. Third, the prescribed nutrients may not be delivered to the patient because they are lost during preparation or storage (e.g. vitamin C may be oxidised by oxygen present in the bag, a process catalysed by copper; vitamin A may be destroyed by sunlight; and some nutrients may be adsorbed on to the plastic bag containing the parenteral nutrition solution).

Gastric and jejunal feeding

Feed may be delivered directly into the stomach using a nasogastric tube, or a gastrostomy tube for long-term feeding in patients with swallowing difficulties. Jejunal feeding (e.g. jejunostomy or nasojejunal tube feeding) can be used in patients with poor gastric emptying, those at risk of regurgitation and aspiration pneumonia, and those with abnormal gastric anatomy and function. Nutrient requirements associated with these routes of feeding when the bowel is functioning normally are generally similar to those for oral feeding, although many patients on long-term tube feeding are physically inactive due to the underlying disease, and therefore their energy requirements may be less than in healthy subjects. An unusual complication of enteral tube feeding concerns the neurological control of eating. A few children who start tube feeding when young and continue receiving it for prolonged periods may 'forget' how to eat. They may have to relearn how to eat when tube feeding is terminated. In contrast, some patients with dementia appear to forget

how to eat, have difficulty in relearning, and thus need to start tube feeding.

Cutaneous (skin)

Essential fatty acid deficiency can be treated or prevented by topical skin application of corn oil or safflower oil, which allows sufficient uptake of essential fatty acids into the body. These observations are of more scientific/historical than practical clinical interest, since essential fatty acids can usually be delivered into the gut or directly into veins. Irradiation of the skin with ultraviolet light can also be used to prevent vitamin D deficiency in housebound patients not exposed to direct sunlight. Alternatively, vitamin D tablets can be prescribed, especially since the amount of vitamin in the normal diet is unlikely to be sufficient to meet the RNI (10 μg/day for subjects aged over 50 years, according to UK recommendations).

Subcutaneous

Subcutaneous infusions of saline/dextrose may be given to maintain comfort and hydration in some terminally ill patients requiring palliative care who cannot drink or eat and who have poor venous access.

Rectal

One of the physiological functions of the large bowel is to absorb salt and water, a property that can be utilised by a rectal infusion of saline in terminally ill patients who are unable to eat/drink and have poor venous access. In the past, rectal feeding was used to provide a range of other nutrients, including alcohol, which is relatively well absorbed from the large bowel. In 1881, American President James A. Garfield received rectal feeding, which included alcohol, during his terminal illness following a gunshot wound inflicted by an assassin.

Peritoneal

During peritoneal dialysis with solutions of hypertonic glucose, which can cross the peritoneal membrane, several hundred calories may enter the systemic circulation. This is a side effect of treatment that is often not appreciated.

It is useful to remember that tissues that are used to provide nutritional access to the body can also be sites of abnormal nutrient losses; for example, loss of protein, loss of trace elements from burned skin, loss of protein from the kidney of patients with nephrotic syndrome, and loss of a variety of nutrients from the gut in patients with inflammatory bowel disease or diarrhoea.

Effect of the phase of disease on nutritional requirements

One of the first steps in the management of patients with severe acute disease is to resuscitate them to establish adequate oxygenation and acid–base status, as well as cardiovascular and metabolic stability. This may involve correcting dehydration or overhydration, and treating any hypoglycaemia or hypothermia. Aggressive nutritional support before this stability is established can precipitate further problems with adverse clinical outcomes. For example, a common consequence of major abdominal surgery or systemic illness is ileus or slow gastric emptying. To facilitate oral feeding after surgery, several actions are useful. These include:

- Using appropriate analgaesia, including local anaesthetics given via a continuous epidural catheter during the first few days after surgery (this minimises the need for opiates, which have inhibitory effects on gastrointestinal motility).
- Avoiding overhydration, which predisposes to postoperative ileus.
- Ensuring that the patient is fully informed that they should eat.

For some patients, there are risks with giving normal food or oral nutrition shortly after surgery. Aggressive feeding by mouth or by a nasogastric tube may still lead to gastric pooling, predisposing to nausea, vomiting, regurgitation, or aspiration pneumonia. This is more likely to happen in patients who have swallowing problems or preexisting reflux problems (e.g. in association with a hiatus hernia), or who are nursed in a horizontal position.

Aggressive intravenous nutrition with copious amounts of glucose in the early phase of an acute illness, when there is insulin resistance, can result in hyperglycaemia, hyperosmolarity, and exacerbation of existing metabolic instability. During the early phase of a severe acute illness, it may therefore sometimes be necessary to start with hypocaloric nutrition and increase this over a period of time. This is to ensure metabolic stability and tolerance to nutrients, while maintaining adequate tissue function and limiting excess N loss.

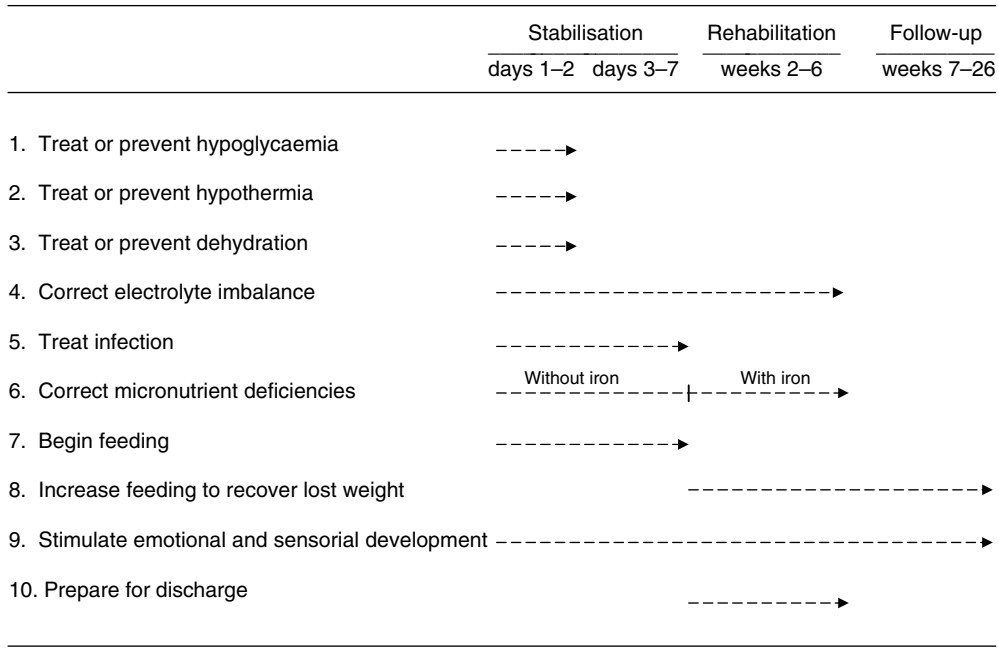

Figure 1.7 Time frame for the management of a child with severe malnutrition (the 10-step approach recommended by the WHO (2000)).

Tissue repletion is mainly recommended during the recovery phase of an acute illness. Similarly, in obese patients the focus on long-term weight loss usually occurs after the acute phase of illness.

The WHO has provided a 10-step guide to the nutritional management of malnourished children, which reemphasises the need to consider nutritional support according to the phase of disease. Again, this begins with the stabilisation phase, associated with resuscitation, which is followed by the rehabilitation phase, which can take several weeks, and finally the follow-up phase (Figure 1.7). It is notable that the guidelines suggest withholding iron supplementation during the early phase of illness. This is because of concern about the possible adverse effects of iron, which has prooxidant properties that facilitate formation of free radicals, which in turn produce cellular damage. The risk is considered to be greater during the early phase of disease, when oxidant stresses are high and antioxidant defences are frequently low as a result of preexisting malnutrition.

A particular complication of aggressive refeeding of malnourished individuals is the refeeding syndrome. Rapid refeeding of such individuals can precipitate respiratory, cardiovascular, and metabolic problems, which may result in sudden death. For example, sudden death was reported when victims of World War II concentration camps were rapidly refed, especially with high-carbohydrate diets. The metabolic abnormalities of the refeeding syndrome include low circulating concentrations of potassium, magnesium, and phosphate, which enter lean tissue cells during the process of repletion under the influence of insulin. The low circulating concentrations of these nutrients can precipitate cardiac arrhythmias and sudden death. Slow initial refeeding while monitoring the circulating concentration of these nutrients can reduce the risk of developing the refeeding syndrome. Precise feeding schedules vary from centre to centre, but they may begin with half or less than half of the requirements in severely depleted individuals.

Alterations in nutritional therapy during the course of an acute disease may occur because the underlying disease has produced new complications or because it has resolved. Similarly, in more chronic conditions there is a need to review the diet at regular intervals. A therapeutic diet lacking particular dietary components may no longer be needed if, for example, a specific food allergy or sensitivity has resolved. Another consideration is whether a vulnerable

developmental period has passed. It used to be thought that cerebral damage due to PKU did not occur after the early developmental period and that it would thus be possible to replace the phenylalanine-poor diet with a more normal diet during later childhood, despite persistence of the underlying metabolic abnormality. Children who reverted to a normal diet, especially during early childhood, were however found to be particularly vulnerable to regression of the developmental quotient (IQ) and development of other neurological symptoms. Children who stopped the phenylalanine-poor diet at or after the age of 15 were generally not affected in this way, but few long-term follow-up studies (e.g. 20–30 years) have examined effects on IQ. Many centres therefore recommend some restriction of phenylalanine throughout life.

Feeding schedules

In healthy people, food is normally ingested during a small number of meals, usually two to three per day, although additional snacks may also be taken. Most patients with disease follow similar patterns of eating, but some may require different feeding schedules. For example, children with certain forms of glycogen storage disease need to ingest small, frequent meals rich in carbohydrate to prevent hypoglycaemia. In patients receiving artificial nutritional support (enteral tube feeding or parenteral nutrition), less physiological feeding schedules may be employed, out of either necessity or convenience. Continuous feeding over prolonged periods of time, up to 24 hours per day, is simple and convenient to carers managing bed-bound patients, including those who are unconscious. Continuous feeding over prolonged periods may also be necessary when only slow rates of feeding are tolerated. For example, patients with certain intestinal problems, such as the short bowel syndrome, may be able to tolerate and absorb sufficient nutrients to meet their needs only if the gut is infused slowly with nutrients over a prolonged period of time during the day and the night. Such an enteral feeding schedule may avoid the need for parenteral nutrition, which is less physiological, more costly, and often associated with a greater number of serious complications.

Many patients on home parenteral nutrition and enteral tube feeding may be able to receive adequate amounts of feed during 12–16 hours per day. This means that they receive continuous pump-assisted infusion during the night (and part of the day), which is again unphysiological. During the day, such patients can disconnect themselves from the feeding equipment to undertake activities of normal daily living, including exercise. This practice can have both physical and psychological benefits. It is also associated with some disadvantages, however, including dependency on the feeding equipment and in some cases abnormal appetite sensations. Although lack of appetite is typical during acute illness, some patients with little or no inflammatory disease who are on long-term artificial nutrition may suffer from hunger and desire to eat, even when sufficient nutrients are delivered artificially by tube into the stomach or by catheter into a vein. These abnormal and sometimes distressing and persisting appetite sensations may be due to provision of liquid rather than solid food, to bypassing of part of the gut (gastric feeding) or the entire gut (parenteral nutrition), or to lack of or reduced gastric distension. They may also be the result of psychosocially conditioned responses, such as those stimulated by observing others eating. The physiological responses to normal food intake, which are associated with fluctuating hormonal and substrate responses, are either attenuated or absent when continuous feeding is provided. The clinical significance of these changes is unclear.

Structure and function

Several bodily functions are related to body composition, specifically the mass of tissue or tissue components. For example, the risk of fracture is greater in individuals with a low bone mineral mass (osteoporosis). Muscle strength is related to muscle mass, and body mass index (BMI = (weight in kg)/(height in m)^2) has been found to be a useful marker for a wide range of bodily functions and for wellbeing, including quality of life. Repletion of tissues is often associated with improvements in bodily functions, including muscle strength and fatigue, reproductive function, and psychological behavior. However, improvements in physiological function and clinical outcome can also occur in the presence of little or no change in gross body composition, and vice versa. Nutritional intervention during key phases of an illness can have an important effect on outcome. Examples include fluid balance (avoiding

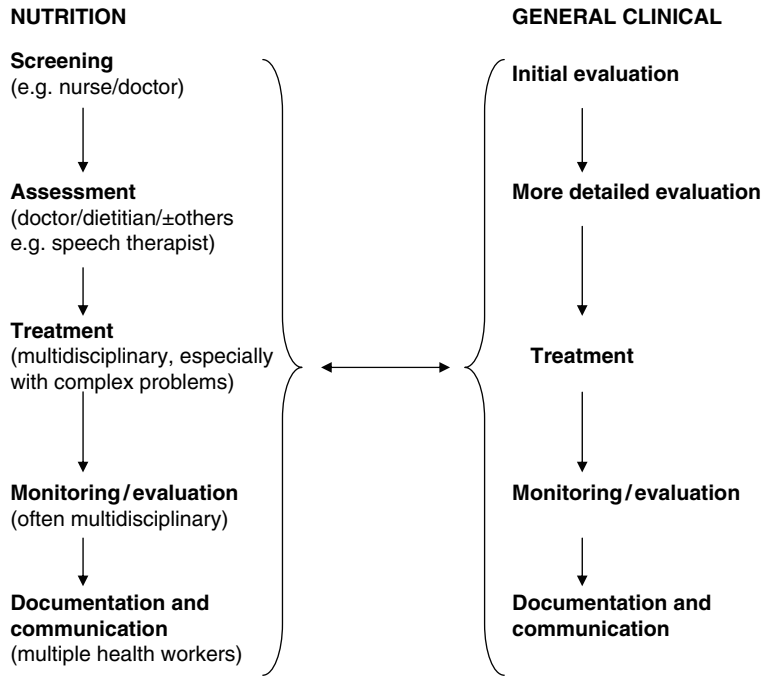

Figure 1.8 Similarities in nutritional and general clinical management pathways and the interaction between the two. Based on Elia (2003).

high fluid intake in the early postoperative period; see earlier in this chapter), oral nutritional supplementation in the perioperative period, and control of blood glucose concentration with insulin in critically ill patients (see earlier). The administration of GH to critically ill patients to improve N balance has been associated with detrimental effects, illustrating a dissociation between gross body composition and function.

1.4 Management pathways

Although resources vary in different countries, in different places in the same country, and at different times in the same place in the same country (e.g. during famines), there are common overarching management pathways. These begin with nutritional screening and assessment, which should be linked to care plans (Figure 1.8). The care plans may involve different healthcare settings (e.g. hospital, community care homes). Since the time spent in hospital may be short (<5% of the duration of an acute illness from onset to complete recovery), treatment initiated there may need to continue and be assessed in the community. It is disturbing that malnutrition is underrecognised and undertreated, and that there is frequent lack of continuity of care. The initial recognition of malnutrition or of risk of malnutrition is an essential first step in the management pathway and is discussed in the next chapter. Chapter 25 illustrates using case studies how the nutritional screening test becomes an integral part of management.

1.5 Concluding remarks

The science of clinical nutrition is rapidly expanding and includes an appreciation of medicine, pharmacology, and nursing disciplines. As you read this book, you will appreciate the link between nutritional needs and outcome, including quality of life, in a wide range of disease states. It is essential that clinicians provide education and nutrition support to patients, centred on the most up-to-date and sound evidence-based practices.

Whether physiological or nonphysiological interventions are used, the practice of clinical nutrition is guided by improvements in bodily functions and clinical outcomes, especially if these are also cost-effective.

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