# *Handbook of* TOTAL PARENTERAL NUTRITION

JOHN P. GRANT, M.D.

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# FOREWORD

During the past 15 years knowledge and experience in clinical nutrition have increased exponentially and in unprecedented fashion. This has largely been the result of the reproducible demonstration that sufficient nutrient substrates can be administered parenterally to support normal growth and development in neonates, infants, and children and to maintain or improve nutritional status and body composition in adults under a wide variety of clinical pathophysiologic conditions. Once the obvious relevance of maintaining optimal nutrition in critically ill patients had been appreciated by clinicians and scientists of many disciplines throughout the world, a great wave of activity in this vital area of clinical biochemistry followed. Concomitantly, there has been a virtual explosion in the availability of new techniques, solutions, infusion apparatus, and myriad related products for the safe and efficacious administration of total parenteral nutrition. In point of fact, it has been almost impossible to keep abreast of the many practical applications and clinically documented developments in this constantly changing area of endeavor, much less the plethora of basic advances being made daily in this seemingly limitless frontier. Accordingly, it has been frustrating at times for the novice to acquire the knowledge necessary to use total parenteral nutrition (TPN) with confidence and competence.

Dr. John P. Grant has undertaken the awesome task of attempting to summarize the current status of the art and science in this handbook. He has succeeded brilliantly in presenting not only a most equitable and comprehensive review of the literature but also valuable insight into his personal experiences and those of his team at Duke University Medical Center. Certainly a handbook of this nature is long overdue and will be an asset to the library of anyone with an interest in clinical nutrition.

This book, well written throughout its 11 chapters, covers the salient features of parenteral nutrition, beginning with an historical perspective and ending with discussions of the vitamin and trace element requirements and deficiencies related to total parenteral nutrition. Principles of patient selection, catheter insertion and long-term maintenance, preparation and administration of solutions, and recognition and management of all potential complications are presented successfully and succinctly. The text is complemented aptly by 24 tables, 83 figures, and almost 1000 refer-

ences. Those of us with an interest in total parenteral nutrition and those who will develop such an interest and who will acquire an expertise in total parenteral nutrition owe the author a great debt of gratitude for his efforts on our behalf.

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# PREFACE

Since introduction of techniques for intravenous nutrition in 1968 by Dudrick, Vars, and Rhoads, indications for its use and application to the hospitalized and home patient have greatly increased. With this growing experience, there has been a rapid accumulation of new metabolic and technical information, knowledge of which is now essential for the safe delivery of parenteral nutrition. In recognition of the growing need for highly specialized nutritional support, many medical centers have formed Nutritional Support Services consisting of physicians, nurses, pharmacists, dieticians, and physical therapists. Although specialized nutritional support teams are highly advantageous, especially in the larger medical centers, they are by no means necessary for safe and efficacious administration of parenteral nutrition. All that is required is a highly motivated, conscientious, and well-informed core of individuals, which may consist of only one physician and a nurse, pharmacist, dietician, or physical therapist.

It is the purpose of this monograph to summarize the many advances which have been made in intravenous nutrition over the past 10 years with emphasis on that new body of knowledge specifically related to safe and efficacious administration of intravenous support. The work is flavored in all sections by my experience in research and clinical application of total parenteral nutrition since 1969. To a great extent it reflects the experience at Duke University Medical Center since 1975, when a Nutritional Support Service was established. The initial impetus to undertake this monograph arose from constant questions concerning administration of parenteral nutrition from students, residents in training, practicing physicians, nurses, pharmacists, and dieticians. There was an apparent need for a reference source which presented a workable "cook book" approach to parenteral nutrition as well as a review of pertinent past and ongoing research material to answer specific questions and to guide further investigation for the nutritional enthusiast. This monograph is intended to begin to fulfill that need. It is hoped that the individual with little or no prior experience in total parenteral nutrition will gain a level of expertise that will permit him to identify patients requiring intensive nutritional support, initiate a support program, and avoid as much as possible technical, metabolic, and septic complications. It is hoped that individuals with a sound background in total parenteral nutrition will find in this work new "tricks of the trade" that I have found quite helpful in my practice. For these individuals an exhaustive list of

references with each chapter has been included for more in-depth review. The last two chapters concerning requirements for vitamin and trace element supplementation during total parenteral nutrition may offer further stimulus for thought to the trained parenteral nutritionist, as many more questions are raised in these chapters than are answered.

The monograph is organized in a progressive manner beginning with initial patient evaluation and continuing through catheter insertion, catheter maintenance, solution formulation, solution administration, and recognition and avoidance of various metabolic and technical complications. Chapters have been inserted on the history of parenteral nutrition, the organization of a nutritional support service, and basic human metabolism as related to parenteral nutrition and are recommended to the reader.

In a field that is changing rapidly, it is impossible to publish an entirely current monograph. However, an attempt has been made to reference all pertinent literature up to and including October, 1979. The reader must be cautioned that any drug products, recommended dosages, and therapeutic procedures mentioned within this manual are subject to change with time and he is advised to refer to continuing publications for new information as it becomes available.

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# *Chapter 1*

# HISTORY OF PARENTERAL NUTRITION

The beginnings of parenteral nutrition can be traced to the middle and latter parts of the seventeenth century when Sir Christopher Wren, Robert Boyle, Caspar Scotus, and Courten injected various substances intravenously into animals. Opium, wine, and oil were given and the researchers predicted that similar solutions could be safely injected into the bloodstream of man. It was not until 1831, however, that a substance was successfully infused into man. In that year a Scottish physician, Latta, injected a salt solution into patients stricken with cholera.[1] Claude Bernard demonstrated in 1843 that sugar solutions could be safely given to animals. Menzel and Perco, after extensive animal experiments, administered fat by subcutaneous injection to an emaciated patient suffering from Pott's disease in 1869.[2] Several attempts at intravenous infusion of fresh cow's milk into man for both intravascular volume expansion and nutritional support were reported by Thomas, Hodder, and Howe in 1878 with surprisingly good results.[3] Eighteen years later, in 1896, Biedl and Kraus successfully administered a glucose solution intravenously to man.[4]

As techniques of intravenous infusion were refined, interest in human metabolic processes and nutritional support grew rapidly. A new era of metabolic research began around the turn of this century with many researchers seeking the development of total intravenous nutritional support. The importance of protein administration for nitrogen balance, weight gain, and general well-being was demonstrated as early as 1852 by Bidder and Schmidt[5] and confirmed by Voit in 1866.[6] Intravenous administration of crude protein solutions, however, resulted in strong allergic reactions. Abderhalden and Rona[7] experimented with rectal instillation of protein in animals in 1904 and concluded that they had achieved nitrogen absorption and utilization. In 1906 they applied the same technique to a boy who could not eat and again claimed nitrogen equilibrium.[8] In 1913 Henriques and Anderson[9] hydrolyzed casein to form a non-allergenic, amino acid, di- and tripeptide solution and successfully infused the mixture intravenously to nourish a goat. Similar success was achieved in animals by Elman in 1937.[10] Two years later he and Weiner[11] infused a solution of 2 per cent casein hydrolysate and 8 per cent dextrose into a patient, with no adverse reactions. A variety of protein hydrolysates have since been studied, including hydrolysates of lactalbumin, bovine serum protein, human serum albumin, meat, fibrin, and casein. In 1940 Schohl and Blackfan[12] infused a mixture of synthetic crystalline amino acids into infants. Refinements in crystalline amino acid solutions have since increased their metabolic usefulness by supplying L-isomers[13] and defining more optimal ratios of essential to total amino acids.

Infused protein and amino acids are also utilized extensively for energy production when adequate caloric support is not given. Various substances, including fructose, sorbitol, xylitol, glycerol, and alcohol, have been administered as caloric sources

to decrease protein catabolism. Fat emulsions derived from castor oil and cotton seed oil appeared to be ideal solutions because of their high caloric value and low osmolarity; however, intravenous administration of these substances resulted in fever, low back pain, non-specific coagulation defects, liver infiltration by ceroid pigment, and jaundice.[14] Because of these untoward reactions, the Food and Drug Administration banned use of fat emulsions in the United States in 1964. Continuing investigations in Europe, however, led to a new fat emulsion derived from soybean oil. No significant side effects were observed, and the fat appeared to be readily utilized.[15] These findings, along with data from selected research centers in the United States,[16] led to the recent FDA approval for parenteral use of a soybean oil fat emulsion, Intralipid* and a safflower oil emulsion, Liposyn.†

None of the above caloric sources, however, has been found superior to the low-cost, abundant, and metabolically efficient substance dextrose. In 1944 Helfrick and Abelson[17] supported a five-month-old infant for five days by providing through an ankle vein a solution of 50 per cent glucose and 10 per cent casein hydrolysate alternated with a homogenized 10 per cent olive oil-lecithin emulsion. Although marked thrombophlebitis occurred, the infant's general nutritional status greatly improved. Dennis et al.[18, 19] met with variable success in attempting to maintain nutrition by administering 15 to 20 per cent dextrose with blood and blood products through peripheral central venous lines. In 1949 Meng and Early[20] and Rhode et al.[21] reported maintenance of normal nutrition in dogs with infusion of hypertonic dextrose and protein solutions through catheters placed in the central venous system. In 1960 Rhoads[22] experimented with large-volume infusions of 10 per cent dextrose and hydrolyzed proteins, maintaining fluid balance with generous use of diuretics.

The perfection of a technique for placement of intravenous catheters in the superior vena cava via the subclavian vein made possible administration of hypertonic dextrose and protein solutions over prolonged periods without phlebitis and thrombosis. In 1968 and 1969 Dudrick et al.[23, 24] demonstrated that solutions of 20 to 25 per cent dextrose and 4 per cent to 5 per cent amino acids could be administered through such catheters with minimal side effects. Daily caloric needs, essential nitrogenous building blocks, and necessary electrolytes, minerals, and vitamins could be provided easily. Their work renewed interest in the metabolic needs of seriously ill, catabolic patients and in the role of nutrition in their management. Ongoing studies continue to demonstrate the utility of parenteral nutrition in the treatment of a wide range of diseases.

Since 1970 numerous publications have reported research in human metabolism utilizing intravenous nutrition. Several books review this research for the interested reader.[25–30] In this monograph, emphasis will be placed on the techniques of providing parenteral nutrition to the adult patient. Patient selection, catheter placement and care, solution preparation and administration, and recognition and management of complications will be dealt with in detail. Introductory chapters on trace element and vitamin requirements and metabolism are included in recognition of the significant role they will certainly play in future research on nutritional support.

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# *Chapter 2*

# A TEAM APPROACH

Parenteral nutrition has become increasingly complex. To administer parenteral nutrition effectively and safely, it is necessary to possess a basic understanding of nutrition, biochemistry, physiology, bacteriology, epidemiology, pharmacology, and psychology. Although intravenous nutrition can be lifesaving in many situations, careless use, through inadequate understanding or poor supervision, can result in devastating complications, including septicemia, metabolic imbalances, and death. To maximize benefits and minimize complications, many medical centers have developed a team approach to parenteral nutrition. Solution preparation, catheter insertion, dressing care, and patient management are performed by well-trained individuals.

Duke University Medical Center has developed a Nutritional Support Service under the Department of Surgery, incorporating physicians, clinical pharmacists, a nurse-clinician, a dietician, members of the intravenous line team (I.V. team), physical therapists, and the nursing staffs of the various wards. Their individual responsibilities are outlined below.

***Physicians.*** The director of the Nutritional Support Service is a surgical staff physician. He is responsible for the development and implementation of guidelines for the use of metabolic and nutritional support techniques and procedures. His duties also include supervision of nutritional research. The director oversees the activity of the entire team and periodically reviews statistical data to assure optimal results. He is directly responsible for senior surgical residents, who rotate through the service for two-month periods. These residents consult on all potential candidates for nutritional support. When intravenous nutrition is indicated, they place a central line under controlled conditions and, with the pharmacist-clinician, review the metabolic data and write parenteral nutrition fluid orders. They make rounds daily on all patients and are available 24 hours a day for management of complications. Both the director and senior surgical resident conduct in-service training programs for the hospital nursing staff and are involved in the medical school education program.

An infectious disease physician is available upon request to review practices of the parenteral nutrition team. When an infectious complication is detected, he assists in the evaluation of possible etiology and offers suggestions for improvements in the protocol. His service is of particular value during parenteral nutrition for severely infected, septic patients.

***Clinical Pharmacists.*** Duke has established two positions for clinical pharmacists who devote full time to the parenteral nutrition team. They have a special interest in the clinical application of pharmacology and contribute necessary expertise in complex drug-nutrient interactions. They monitor patients closely, make rounds daily with the senior surgical resident, collect and record metabolic data, and assist in writing daily fluid orders. It is their responsibility to assure correct formulation of nutritional fluids under strictly controlled aseptic conditions and to monitor quality control data closely. They are also available to assist in the insertion of subclavian catheters and may evaluate candidates for parenteral nutrition.

***Nurse-Research Clinician.*** A registered nurse functions as a central figure in patient relations and in the conduct of clini-

cal research. The nurse, who makes daily rounds with the senior surgical resident and the pharmacist-clinician, interprets the team goals and activities for the patient and answers questions he may have. The nurse sees all patients returning for outpatient visits and assists in the care of patients on home parenteral nutrition. The nurse is also the liaison between the team and the nursing staff and is responsible for in-service education programs.

In addition to patient care responsibilities, the nurse-clinician maintains all permanent records, periodically reviews all aspects of the team's performance, and prepares a quarterly statistical report on technical and metabolic complications and therapeutic results. The nurse maintains a reference library on nutrition, which is open to medical students and the house staff. Finally, the nurse has specific duties in all research projects conducted by the Nutritional Support Service. These duties include seeing that research protocols are thoroughly understood and followed by personnel who care for study patients, collecting appropriate metabolic data, and assisting in data interpretation.

***Dietician.*** A dietician who is interested in active patient care and knowledgeable in special dietary formulas and tube feeding programs is essential to the parenteral nutrition team. All consultations for the team are first referred to the dietician, who performs an initial nutritional assessment that includes evaluations of visceral and somatic proteins, fat depots, dietary intake, and metabolic requirements. These assessments are then reviewed by the senior surgical resident, and a decision is made from the three alternatives available: pursuing further nutritional assessment, initiating oral or enteral nutritional support, or beginning parenteral nutrition. If oral or enteral nutritional support is indicated, the dietician assumes full responsibility for its delivery. Another responsibility of the dietician is the periodic nutritional assessment of every patient receiving nutritional support. This allows for continual monitoring of therapeutic results. The dietician is also helpful in weaning patients from parenteral nutrition when various malabsorption problems or food intolerances are present.

The dietician meets daily with the director of the Nutritional Support Service and makes rounds daily on all patients receiving oral or enteral nutritional support.

***IV Team.*** The hospital intravenous line team (IV team), composed of registered nurses, is charged with the responsibility of changing subclavian dressings on a regular basis. It is our policy to change dressings every Monday, Wednesday, and Friday, with daily checks and additional changes as needed. A strict protocol for changing dressings is followed, as discussed in Chapter 5. The IV team is also available to assist in catheter placement.

***Physical Therapist.*** While physical therapy has occasionally been employed as an adjunct to nutritional support, the role of mobilization and daily activity in the care of the malnourished patient is still poorly defined. There is evidence, however, that regular exercise benefits the malnourished patient by enhancing utilization of nutrients and promoting synthesis of lean body mass. Muscle work exerts an effect parallel to, but independent of, insulin in the transport of some sugars across the cell barrier.[1,2] Further, it has been shown that the rate of amino acid transport in skeletal muscle increases with muscle work and is related to protein synthesis during work-induced muscle hypertrophy.

Clinical studies of normal adult men immobilized in spica casts for six to seven weeks have shown increased nitrogen excretion and loss of muscles mass and strength in spite of a dietary intake that maintained nitrogen balance during control and recovery periods.[3] The nitrogen losses were reduced if the patient was placed in an oscillating bed during the study period.[4] Patients in oscillating beds demonstrated a more rapid recovery of metabolic and physiologic functions than the first group. Other studies have shown that a hypercaloric diet given to non-exercised patients may lead to increased fat deposition rather than increased lean body mass.

In addition to the metabolic benefits of exercise, there are general benefits for bedridden patients, particularly with respect to maintenance of the circulatory and respiratory systems. A daily routine of light exercise and mobilization can minimize com-

plications of orthostatic hypotension, thrombophlebitis, and pneumonia. There are also psychologic benefits in that exercise is one of the more easily understood aspects of nutritional support. Exercise gives the patient an opportunity to participate actively in his care and provides positive feedback as increases in strength allow more independence. The interest shown in improving the patient's strength and energy and the welcome change in environment if the patient can go to the physical therapy department instill a new attitude of hope, enthusiasm, and cooperation in the often depressed patient. This response may carry over into other areas of his treatment.

The physical therapist visits all patients prior to and during nutritional support. A dynamic skeletal muscle and respiratory muscle evaluation is performed (see Chapter 3 concerning nutritional evaluation) and an individualized exercise program is developed for each patient for maximal activity. The exercise program consists of daily light exercise and functional activities, especially ambulation. Also included are breathing exercises based on results of respiratory testing. The exercise program is performed for brief periods three or four times daily, with care being taken not to induce fatigue. Some patients become more motivated as their nutritional status improves and can be instructed in an independent exercise program that does not require daily visits from the physical therapist.

If personnel resources are limited and a physical therapist is not available to see every patient, the physical therapist should serve as a consultant in establishing an exercise program that can be administered by other hospital staff members. The investment of staff time and energy in implementing some type of exercise program for the malnourished patient enhances the overall rehabilitation effort and often results in the return of an independently functioning individual concurrent with nutritional recovery.

*Nursing Staff.* Nurses perform primary patient surveillance. It is their responsibility to monitor vital signs, keep accurate records of fluid balance, and assure constant infusion of the parenteral or enteral nutrition solution, maintaining sterility at all times. They must be familiar with early symptoms of possible complications so that the physician can be alerted. The importance of the nurse's role cannot be overemphasized. The nurse is the vital link between the nutrition team and the patient. Inadequate knowledge, lack of concern, or neglect on the nurse's part can result in serious complications regardless of the efforts of the remaining team members.

The team approach has become recognized as an indispensable part of medical care for many diseases. It has been used effectively in treating renal transplant patients, patients receiving chemotherapy for metastatic malignant diseases, patients needing open heart surgery, and children with various types of leukemia. Nutritional support requires a similar team approach. The team outlined above works well at Duke University Medical Center but is only one example for institutions considering establishment of similar teams. The team members may vary, but it is vital to have a small number of highly interested people involved in the administration of parenteral nutrition. Whether one utilizes technicians, nurses, pharmacists, or house staff physicians, the goal should be the same: maximal benefit from intravenous nutrition with minimal complications.

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# *Chapter 3*

# PATIENT SELECTION

The administration of parenteral nutrition should be considered whenever adequate nutrition cannot be maintained through the gastrointestinal tract. It should not be considered if the gastrointestinal tract is capable of absorbing nutrients taken orally or infused through a nasogastric tube except when the patient might benefit from bowel rest. In general, parenteral nutrition should not be initiated unless it is anticipated that intravenous support will be required for at least five days, although preliminary data indicate as little as 72 hours preoperatively may be beneficial for malnourished patients.[1] An exception to this restriction is in the treatment of malnourished or stressed patients for whom nutritional support is urgent but whose gastrointestinal function is questionable. With these and other selected patients it is advisable to begin parenteral and enteral nutritional support simultaneously. As soon as the enteral diet is tolerated at the necessary protein-calorie load, the patient should be weaned from the parenteral infusion. In many patients, combined therapy may be necessary for only a few days. In others it may be necessary for several days or weeks, during which time intestinal adaptation to the osmotic load and volume of the enteral diet may occur and the optimal dietary formula may be found without progressive nutritional depletion.

Concomitant infections elsewhere in the body, diabetes, and obesity are not in themselves contraindications to parenteral nutrition. It is recognized that these conditions increase the risk of septic complications during parenteral nutrition, but, with proper care, the incidence of infectious complications should be only 4 to 5 per cent or less, with little morbidity.[2] Patients with either localized infection or generalized septicemia demonstrate a marked hypermetabolic response as great as that seen with trauma or stress. Therefore, instead of being a contraindication to parenteral nutrition, infection is a relative indication.

Diabetic patients usually present no special problems with respect to glucose tolerance. Hyperglycemia can be easily controlled by addition of regular insulin (up to 350 units of insulin per 250 grams of glucose) to the parenteral nutrition solution (see Chapter 7 concerning insulin). Further, the improved glucose tolerance that may occur with administration of glucose[3, 4] and the increased insulin release due to amino acid infusion (leucine in particular) decrease exogenous insulin requirements.

Moderate to marked obesity does not lessen the need for parenteral nutrition. Fatty tissue is poorly mobilized because of the hyperinsulinemia associated with the insulin resistance of stress (insulin is a potent inhibitor of peripheral fat mobilization).[5, 6] Administration of 5 per cent dextrose solutions also stimulates insulin secretion, further inhibiting peripheral fat mobilization.[7, 8] Consequently, during starvation and stress obese patients have protein catabolism and nitrogen losses similar to those of thinner patients and require similar nutritional support.

A partial list of indications for parenteral nutrition is given in Table 3–1. Experi-

**Table 3–1 INDICATIONS FOR PARENTERAL NUTRITION**

1. Protein-calorie malnutrition
   - Anorexia nervosa
   - Chronic vomiting
   - Chronic diarrhea
   - Malabsorption syndromes
   - Prolonged ileus or gastrointestinal obstruction
2. Short bowel syndrome
3. Acute pancreatitis and pancreatic fistulas
4. Enterocutaneous fistulas
5. Inflammatory bowel disease
6. Malignant diseases
7. Renal failure
8. Hepatic failure
9. Hypercatabolic states
10. Burns
11. Trauma

mental and clinical data relating to parenteral nutrition in some of these disease states will be presented below.

## PROTEIN-CALORIE MALNUTRITION

Several studies of hospitalized patients have reported frequent occurrence of malnutrition, based on serum albumin concentrations, hypovitaminemia, and anthropometric measurements.[9–13] Bistrian et al.[11] reported as many as half of the patients evaluated in an urban municipal hospital showed signs of moderate or greater protein-calorie malnutrition. Patients not only exhibit pre-existing malnutrition but often become more malnourished during hospitalization. Attention is frequently focused on diagnosis and the institution of medical or surgical therapy, while the nutritional status of the patient is overlooked. A patient with an acute exacerbation of chronic ulcer disease, progressively severe gastric outlet obstruction, and a 15 to 20 per cent weight loss due to poor dietary intake may undergo an upper gastrointestinal x-ray examination, saline load test, gastric acid analysis, and gastroduodenoscopy. Performance of these tests may require four to seven days of restricted dietary intake. Three to five additional days of nasogastric suction may be recommended to reduce pyloric edema or to prepare the patient for surgery. Postoperatively, five to seven days or more of nasogastric suction may be required before the gastroenterostomy functions adequately. In all, two to three weeks of restricted dietary intake may follow preexisting malnutrition. A patient with partially obstructing colonic carcinoma and a recent weight loss of 10 to 20 per cent may undergo bowel preparation for a barium enema and proctoscopy or colonoscopy. In preparation for partial colectomy he may be placed on a clear-liquid diet and be given laxatives for three to five more days. Following surgery, an oral diet may not be resumed for five to seven days.

It is not uncommon to receive a consultation requesting nutritional support for a chronically ill, severely depleted patient, in whom all therapeutic modalities have failed. Often the patient's physician will say that little else can be done medically and will ask whether parenteral nutrition has anything to offer. The neglect of progressive nutritional depletion is unfortunate, especially since the correlation of starvation with morbidity and mortality has been long known.[14–17] Mild malnutrition is associated with an increased incidence of clean-wound infections[18, 19] and postoperative ileus. In addition, a progressive increase in respiratory infections and insufficiency is seen with malnutrition. This is due, in part, to deterioration of respiratory muscle function and also to depression of the immune defense system. Doekel et al.[20] have proposed another possible contributing factor. They found that a balanced diet restricted to 500 calories a day for ten days significantly reduced ventilatory responses to hypoxia in healthy volunteers. Such depressed responses, they proposed, could contribute to the hypoxia and respiratory failure often seen in patients with malnutrition. Moderate malnutrition further contributes to patient morbidity[21, 22] by markedly impairing collagen synthesis,[23, 24] adversely affecting wound healing,[25–27] and depressing the immune response, which leads to decreased infection resistance (see later parts of this section). With marked malnutrition (acute loss of 30 to 35 per cent body weight) complications become so severe that a 90 to 95 per cent mortality is not uncommon.