GUIDELINES FOR THE SCIENTIFIC REVIEW OF ENTERAL FOOD PRODUCTS FOR SPECIAL MEDICAL PURPOSES

December 1990

Prepared for
CENTER FOR FOOD SAFETY AND APPLIED NUTRITION
FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
WASHINGTON, DC 20204

under
FDA Contract No. 223-88-2124
Task Order No. 6
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prepared by
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FOREWORD

The Life Sciences Research Office (LSRO), Federation of American Societies for Experimental Biology (FASEB), provides scientific assessments of topics in the biomedical sciences. Reports are based upon comprehensive literature reviews and the scientific opinions of knowledgeable investigators engaged in work in relevant areas of biology and medicine.

This report was developed for the Center for Food Safety and Applied Nutrition, Food and Drug Administration (FDA), in accordance with provisions of Task Order No. 6 of Contract No. 223-88-2124. The report was prepared and edited by John M. Talbot, M.D., Senior Medical Consultant, LSRO, FASEB, with the assistance of the LSRO staff, based on discussions of relevant issues in coordination with expert consultants who were selected for their scientific qualifications, experience, and judgment, with due consideration for scope and balance in appropriate professional disciplines. Names of the consultants and LSRO staff who participated in preparing this report are listed in Chapter VI.

The LSRO staff and consultants met in March and September, 1990 to obtain and review the background information, evaluate the state-of-the-art in appropriate uses of medical foods, and develop drafts of the report. A tentative draft was prepared for public review in June 1990. The consultants reviewed and evaluated comments from the public, and provided additional documentation and expert opinion for incorporation into the final report. The consultants and LSRO accept responsibility for the study conclusions and for the accuracy of the report. In addition, the conclusions and suggestions in regard to clinical management of patients are those of the consultants and LSRO, and should not be construed as the official position of the FASEB or the sponsoring Agency. Further, the listing of individuals in Chapter VI does not imply that each consultant specifically endorses all statements in the report.

The final report was reviewed and approved by the LSRO Advisory Committee (which consists of representatives of each constituent society of FASEB) under authority delegated by the Federation Board. Upon completion of these review procedures, the report was approved and transmitted to FDA by the Executive Director, FASEB.

While this is a report of the Federation of American Societies for Experimental Biology, it does not necessarily reflect the opinion of the individual members of these Societies.

[Signature]
Kenneth D. Fisher, Ph.D.
Director
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December 31, 1990

Date
EXECUTIVE SUMMARY

This report reviews available data on the scientific rationale for and clinical experience with medical foods given orally or by tube in four specified categories of diseases and disorders: end-stage renal disease; liver disease and hepatic coma; pulmonary diseases; and hypermetabolic states associated with injuries, major surgery, and sepsis. This review was conducted as a basis for the development of guidelines useful in scientific evaluation of enteral food products for specific medical purposes. The report also provides background information or evolution of definitions, regulation, and types of medical foods currently available.

Despite considerable effort during the past several decades, medical and regulatory authorities in this country and abroad have been unable to develop a universally acceptable definition of medical foods. Nevertheless, some definitions have evolved that are useful, including those of the FDA, the U.S. Congress (for orphan medical foods), and the Food and Agriculture Organization/World Health Organization's Codex Alimentarius Commission. Based on a relatively precise set of criteria, the consultants for this review have proposed a definition aimed at clearly separating medical foods from other foods for special dietary purposes.

In the United States, medical foods are regulated as foods. Consequently, they must meet the standards of Good Manufacturing Practice that are required for all foods. However, unlike drugs, premarket demonstration of whose efficacy and safety is required, makers of medical foods are not required to submit evidence of the suitability of their products before marketing.

The suitability of medical foods for their intended uses is an important issue that has not been resolved fully. It is closely tied to the goal of clinical nutrition support in general, which has been described as providing calories, macronutrients, and all essential micronutrients in a form that can be utilized by the patient to restore and maintain body cell mass. LSRO study consultants concurred with this concept that medical foods should provide an optimal profile of nutrients to meet the metabolic needs of patients. However, they concluded the goals of clinical nutrition (medical foods in particular), should include a favorable influence on clinical outcomes including improvement in disease manifestations, organ function, morbidity, and mortality.

The scientific rationale for using certain medical foods in the four categories of diseases and disorders reviewed in this study is appropriate in terms of basic principles of adequate nutrition as well as in the peculiar alterations in nutritional requirements associated with each disease. Accordingly, the formulas for enteral (as well as parenteral) nutrition products that are available do feature major alterations of dietary constituents compared with general purpose dietary products and ordinary foods. Thus, several commercially available products for the dietary management of certain types of diseases of the liver and kidney as well as hypermetabolic states associated with severe injury, sepsis, and major surgery, do meet the definition of medical foods proposed in this report. Expert opinion was divided on whether available high-fat, low-carbohydrate products meet the suggested criteria for medical foods. Some evidence suggests that patients with certain chronic lung diseases may benefit from high-fat, low-carbohydrate formulas and from branched-chain amino acid (BCAA)-enriched formulas to restore and maintain diaphragm muscle.

Several products containing supplements such as essential amino acids, BCAA, small peptides, medium-chain triglycerides (MCT), and oligosaccharides have been represented as being useful for the dietary management of the diseases and disorders addressed in this report. The number of reports of well-planned and well-executed clinical trials of these preparations is limited. To date, none has fully confirmed or refuted the putative advantages of these products over ordinary nutritionally adequate preparations. Trials of the clinical suitability of specially designed enteral formulas, such as BCAA-enriched products are continuing.
Similarly, some enteral nutrition products fortified with ingredients such as glutamine, arginine, and nucleotides have been developed recently. These products are designed to restore and maintain integrity of intestinal mucosal membranes and compromised immune systems. They have shown promise in the few clinical trials reported to date.

The record of the medical foods industry for producing products that are safe has been good, a result of such factors as careful planning of new formulations, adherence to the rules of good manufacturing practice, and, in some companies, voluntary premarket clinical testing. In general, the safety of enteral medical foods for their intended purposes involves factors such as purity and quality, shelf life, suitability for tube feeding, side effects, microbial contamination during use, nutritional adequacy, compatibility with other foods and with drugs, and procedures for safe use.

This report concludes with suggested guidelines for the design and evaluation of clinical trials of medical foods to determine the suitability for their intended purposes. Criteria for an adequate prospective, randomized, clinical trial are presented along with comments on other types of trials that may yield useful results. In addition, some of the limitations of clinical trials are described. A generic model of a methodology for evaluating clinical trials is described, along with a suggestion of its potential utility, when suitably modified, for assessing the quality of clinical trials of medical foods. This model includes the recommendation of the LSRO study consultants that any set of guidelines should incorporate premarketing assurance of the safety and suitability of enteral nutrition products. Further, the proposed guidelines also suggest that FDA should maintain a system for postmarketing surveillance of enteral nutrition products.
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I. INTRODUCTION

A. BACKGROUND

1. Definitions and terminology

   a. Foods for special dietary uses

   The definitions of foods for special dietary uses were developed prior to World War II and referred simply to foods that provided better nutrition than that supplied by the ordinary diet. Regulations on foods for special dietary uses were promulgated (Food and Drug Administration, 1941) and were incorporated in the Code of Federal Regulations in 1941. The definitions were further revised in the Code of Federal Regulations (originally 21 CFR 125.1, now 21 CFR 105.3) in 1973 and specified:

   "(a) The term 'special dietary use' as applied to food (including dietary supplements) used by man means a particular use for which an article purports or is represented to be used, including but not limited to the following:

   (1) Supplying a special dietary need that exists by reason of a physical, physiological, or other condition, including but not limited to the conditions of convalescence, pregnancy, lactation, infancy, allergic hypersensitivity to food, underweight, overweight, diabetes mellitus, or the need to control the intake of sodium. The use of an artificial sweetener in a food, except when specifically and solely used for achieving a physical characteristic in the food which cannot be achieved with sugar or other nutritive sweetener, shall be considered a use for regulation of the intake of calories and available carbohydrate, or for use in the diets of diabetics.

   (2) Supplying a vitamin, mineral, or other dietary property for use by man to supplement his diet by increasing the total dietary intake, except for foods for which nutrition labeling is used as required pursuant to § 1.17 of this chapter.

   (3) Supplying a special dietary need by reason of being a food for use as the sole item of the diet."

   Because of the passage of the Proxmire Amendment to the Federal Food, Drug, and Cosmetic Act of 1982, and the incorporation of provisions related to infant formulas, the revised Code of Federal Regulations (21 CFR 105.3) redefined special dietary uses as follows:

   "(a)(1) The term 'special dietary uses,' as applied to food for man, means particular (as distinguished from general) uses of food, as follows:

   (i) Uses for supplying particular dietary needs which exist by reason of a physical, physiological, pathological or other condition, including but not limited to the conditions of diseases, convalescence, pregnancy, lactation, allergic hypersensitivity to food, underweight, and overweight;

   (ii) Uses for supplying particular dietary needs which exist by reason of age, including but not limited to the ages of infancy and childhood;

   (iii) Uses for supplementing or fortifying the ordinary or usual diet with any vitamin, mineral, or other dietary property. Any such particular use of a food is a special dietary use, regardless of whether such food also purports to be or is represented for general use."
(2) The use of an artificial sweetener in a food, except when specifically and solely used for achieving a physical characteristic in the food that cannot be achieved with sugar or other nutritive sweetener, shall be considered a use for regulation of the intake of calories and available carbohydrate, or for use in the diets of diabetics and is therefore a special dietary use.

(b) [(Reserved)]

(e) For the purposes of the regulations in this part, the terms 'infant,' 'child,' and 'adult' mean persons not more than 12 months old, more than 12 months but less than 12 years old, and 12 years or more old, respectively."

b. Medical foods

The Food and Drug Administration (FDA) recognized the concept of medical foods as distinct from drugs in 1972 when it announced that Lofenalac® would be classed as a food for special dietary purposes rather than a drug (Food and Drug Administration, 1972). Shortly thereafter, FDA promulgated nutrition labeling regulations stating that foods represented for use solely under medical supervision to meet nutritional requirements in specific medical conditions must be so labeled (21 CFR 101.9 (h)(4)). Subsequently, FDA exempted amino acids used in special dietary foods from food additive regulations (21 CFR 172.320 (f)).

However, no further definition of "medical foods" was proposed by FDA. In 1977, a review of the topic by the Federation of American Societies for Experimental Biology led to the following proposed definition:

"Medical foods are foods that are specially formulated or prepared products consumed or administered enterally under direct or indirect medical supervision in the dietary management of individuals with specific diseases, disorders, or medical conditions in which the existence of associated special nutritional requirements is established by medical evaluation (Fisher et al., 1977)."

In 1982, an FDA task force defined medical foods as specially formulated or processed products represented for the dietary management of a specific disease, disorder, or medical condition, which products are consumed or administered enterally and are represented for use under the supervision of a physician (Food and Drug Administration, 1982). The task force also recommended that a policy to regulate medical foods primarily as foods be adopted.

Since then, periodic attempts to define medical foods have resulted in some improvements, but a clear definition satisfactory to all users such as manufacturers, clinicians, the scientific community, and federal agencies has not evolved nor has any definition been incorporated in the Code of Federal Regulations (Bass, 1989; Hattan and Mackey, 1989; Scarbrough, 1989).

In 1988, Congress amended the Orphan Drug Act to include medical foods (21 U.S. Code 360ee). The amendments included a definition of medical foods as:

"The term 'medical food' means a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements based on recognized scientific principles are established by medical evaluation" (U.S. Congress, 1988).

This definition was stated in the Orphan Drug Act as Amended to introduce the concept of orphan medical foods, which were defined subsequently in the 1988 Amendments as a subcategory of
medical foods that included products useful in the management of "any disease or condition that occurs so infrequently in the United States that there is no reasonable expectation that a medical food for such disease or condition will be developed without assistance" (21 U.S. Code 360ee).

This definition of medical foods has been incorporated into the Nutrition Labeling and Education Act of 1990 and is the current authoritative definition of medical foods (U.S. Congress, 1990). Thus, from a legal perspective foods for special dietary uses are a subcategory of foods, medical foods are a subcategory of foods for special dietary uses, and orphan medical foods are a special subset of medical foods.

Since 1980 the Codex Alimentarius Commission has sought to enhance international trade for special categories of foods (i.e., foods for special dietary uses, medical foods, and foods for special medical purposes) by developing consensus on definitions and standards (Cheney, 1989). Approximately 25 nations are participating in the development of an international Codex, "Standard for the Labeling of and Claims for Foods for Special Medical Purposes," through its subsidiary body the Codex Committee on Nutrition and Foods for Special Dietary Uses. To date, the process has advanced to step 5 (Joint FAO/WHO, 1989). The Codex Committee continues to refine definitions for these products, considers medical food products to be a special category of foods for special dietary uses for which specific claims are made, and recognizes that these products should be used under medical supervision. The Codex draft definition states:

"Foods for special medical purposes are a category of foods for special dietary uses which are specially processed or formulated for the dietary management of patients and may only be used under medical supervision. They are intended for the exclusive or partial feeding of patients with limited or impaired capacity to take, digest, absorb or metabolize ordinary foods or certain nutrients contained therein, or have other special medically determined nutrient requirements, the dietary management of whom cannot be achieved by the modification of the normal diet alone, by other foods for special dietary uses or by a combination of the two" (Joint FAO/WHO, 1989).

During further consideration of this definition, the Codex Committee agreed to modify the first sentence to delete the word only in regard to medical supervision. The current Codex draft standards for product labeling of medical foods suggest that label information for these products should include:

- The intended claim for the specific disease, disorder, or medical condition for which the product will be used.
- The statement "USE UNDER MEDICAL SUPERVISION."
- A description about product rationale.
- A description about the details of nutrient modification.
- A statement about intended use as a sole food source.

The Codex Committee draft for medical food product labeling currently recommends that manufacturers provide detailed information about product content. Specifically, the draft suggests that:

"Foods for special medical purposes in which the essential characteristic involves a modification of the content or the nature of proteins, fats or carbohydrates shall bear a complete quantitative declaration of the amino acid, fatty acid or carbohydrate profile, as applicable." and,

"A statement specifying the nutrient(s) reduced, deleted, increased or otherwise modified, relative to normal nutrient requirements and the reason why the nutrient(s) is (are) reduced, deleted, increased or otherwise modified" (Joint FAO/WHO, 1989).
In addition, the Codex draft recommends the incorporation of cautionary statements and warnings about health hazards, adverse effects, side effects, contraindications, and drug interactions (Cheney, 1989). After completion of the necessary additional steps, the Committee will submit a final draft standard for adoption, possibly by 1991.

The draft standards of the Codex Alimentarius Commission for labeling of and claims for foods for special medical purposes use terminology for medical foods that is more analogous to that incorporated in the Orphan Drug Act as Amended [(Section 5, (B)(2–3))] than previous definitions currently included in the Code of Federal Regulations. As noted by Scarbrough (1989), there are no regulations on medical foods per se in Section 105 of Chapter 21, Code of Federal Regulations.

c. FDA concepts of medical foods

The FDA has excluded from its working concept of medical foods parenteral nutrition formulations, single-nutrient products that may be used for therapeutic purposes such as zinc in treating acrodermatitis enteropathica, and traditional foods for special dietary uses such as products for weight loss (Scarborough, 1989). In order to aid in administering its Compliance Inspection Program for Medical Foods, the Agency has described the scope of its medical foods concept in terms of categories of products and minimum standards for designation as medical foods (Food and Drug Administration, 1989). The Compliance Program states:

"Medical Foods (MF) are distinguished from other foods for special dietary purposes or foods which make health claims (e.g., fiber in relation to cancer) by the requirement that they (MF) be used under medical supervision. In addition, single ingredient nutrient products that are promoted for the treatment of specific disease states will continue to be regulated under existing drug law (e.g., zinc sulfate for the treatment of acrodermatitis enteropathica), as will all injectable nutrient formulations. In general, in order to be considered a MF a product must, at a minimum, meet the following criteria:

- The product is a food for oral or tube feeding.
- The product is labeled for the dietary management of a medical disorder, disease, or condition.
- The product is labeled to be used under medical supervision."

The use of enteral medical food products is based on a need to provide energy and or specific nutrients because of an underlying medical condition. For example, nutritional management of the postsurgical patient generally requires calorically dense, nutritionally complete formulations that provide all nutrients in a single product. Products developed for inherited metabolic disorders must be free from certain nontolerated nutrients or must contain certain substances that have nutritional utility for a given disorder.

The FDA has classified medical foods into four categories based on the rationale for their use. These are:

(1) Nutritionally complete formulas: contain either polymeric macronutrients (ordinary proteins, fats, and carbohydrates) and micronutrients (vitamins and minerals) or defined formula products containing readily absorbable, oligomeric sources of macronutrients such as free amino acids, protein hydrolysates, oligopeptides, and selected carbohydrates such as glucose oligosaccharides. All nutrients must be provided in sufficient quantities to maintain the nutritional status of an individual receiving no other sources of nourishment.
(2) Nutritionally incomplete formulas: include individual "modular" type products that may be mixed with other products before use (e.g., protein, carbohydrate, or fat modulars).

(3) Formulas for metabolic (genetic) disorders: include special formulations for individuals who have diagnosed inborn errors of metabolism such as phenylketonuria, homocystinuria, and carnitine deficiency syndrome. Those formulas developed for use by infants with such disorders are regulated as exempt infant formulas (21 CFR 107.50).

(4) Oral rehydration products: contain primarily water and electrolytes to replace or maintain electrolyte balance as a result of dehydration.

These criteria and the classification were considered useful provisions in addressing the issues discussed in this report. In addition, the consultants noted that the term "enteral nutrition" pertains mainly to oral, oronasal, intragastric, and intrajejunal feeding by tube, but also includes regular oral intake of enteral nutrition products. The term "defined formula diet" is preferred over such terms as "elemental diet" and "chemically defined diet" although the latter terms are widely used in the literature. None of the "elemental diets" is elemental in a chemical sense, and few of the "chemically defined diets" are precisely analyzed for chemical composition and purity. In "defined formula diets," "defined" refers to ingredients prepared by designated commercial procedures that ensure their composition, although not always with chemical precision (Shils, 1988).

In summary, it should be evident, from this brief overview of terminology, that evolution of a precise definition of the term "medical food" has been difficult. As more information, data, and products have become available, the definition of medical food in terms of clinical and regulatory meaning has evolved continuously.

d. FASEB consultants' suggestions

The FASEB consultants consider it essential to improve the definition and criteria for medical foods. They suggest that to be considered a medical food, a product must be:

- Safe and suitable for its intended use.
- Intended for use as the exclusive or supplemental source of nutrition for patients with limited or impaired capacity to ingest, digest, absorb, or metabolize ordinary foodstuffs or certain nutrients contained therein, or have other special medically determined nutrient requirements, the dietary management of whom cannot be achieved by the modification of the normal diet alone, by other foods for special dietary uses, or by a combination of the two.
- Suitable for oral ingestion or enteral feeding by tube.
- Labeled for the nutritional management of a medical disease or disorder.
- Identified as requiring prescription by a physician.
- Have documented evidence supporting claims of maintenance or improvement of nutritional status of patients with a specific disease and or improvement of one or more specific nutrient-related disease manifestations, significantly more than that observed from use of commercially available, nutritionally complete formulas or their dietary equivalents composed of readily available foodstuffs. Nutritionally complete formulas are defined on page 4. "Significantly more than" relates to the results of well-designed clinical studies from which statistically valid conclusions may be drawn. "Readily available foodstuffs" are foods and food components readily available to the public without prescription.
Consequently, the following kinds of products do not qualify as medical foods: general purpose nutrition products, general purpose dietary supplements, and other foods for special dietary purposes that do not satisfy the foregoing criteria.

Thus, the definition of medical foods derived by the study consultants is as follows:

Medical foods are a category of foods for special dietary uses, processed or formulated for the management of patients, designed for use under continued medical supervision, and that demonstrate greater suitability for nutritional management of a specific disease than standard enteral formulas. They are intended for use as either the exclusive or supplemental source of nutrition for patients with limited or impaired capacity to ingest, digest, absorb, or metabolize ordinary foodstuffs or certain nutrients contained therein, or have other special medically determined nutrient requirements, the dietary management of whom cannot be achieved by the modification of the normal diet alone, by other foods for special dietary uses, or by a combination thereof.

**Labeling.** The consultants in this study concur in the five provisions on labeling suggested by the Codex Committee, namely:

- The intended claim for the specific disease, disorder, or medical condition for which the product will be used.
- The statement "USE UNDER MEDICAL SUPERVISION."
- A description about product rationale.
- A description about the details of nutrient modification.
- A statement about intended use as a sole food source.

The consultants also suggest that labeling of medical foods in which the essential characteristic involves a modification of the content or the nature of proteins, fats, or carbohydrates should indicate a complete quantitative declaration of the amino acid, fatty acid, or carbohydrate profile as applicable. Moreover, the product information should include a statement that specifies the nutrients that are reduced, deleted, increased, or otherwise modified, relative to normal requirements for that nutrient and the reason why the nutrients are reduced, deleted, increased, or otherwise modified.

Finally, the suggestions of the Codex Committee in regard to the incorporation of cautionary statements and warnings about health hazards, adverse effects, side effects, contraindications, and known drug interactions (Cheney, 1989) should be implemented where possible on labels and in product information.

2. **History**

The history of tube feeding by mouth, rectum, and ostomies in the upper gastrointestinal tract has been reviewed by Randall (1984a,b). Tube feeding via the orogastric route, often consisting of milk, eggs, meat extract, meat powders, wine, and brandy, was an accepted mode by the end of the 19th century. Scientific knowledge of the physiology and biochemistry of digestion and metabolism advanced markedly during the first half of the 20th century, enabling investigators to improve formulations for tube feeding including use of protein hydrolysates.

An important milestone was demonstration of practical intravenous alimentation for which the infusate was a mixture of casein hydrolysate and dextrose (Elman and Weiner, 1939 as reported by
Randall 1984a). Parenteral nutrition then became the primary mode of nutritional support in many medical centers (Randall, 1984a,b). Nevertheless, formulations, techniques, and apparatus for enteral nutrition continued to progress and included, for example, development of "elemental diets" containing crystalline amino acids (Greenstein et al., 1960).

Nutramigen® (Mead Johnson), introduced in 1942, was the first commercial defined formula diet developed for clinical use. Lofenalac® (Mead Johnson), designed for phenylketonuric patients, contained a low-phenylalanine protein hydrolysate and was the prototype of a series of special dietary formulas for children with inborn errors of amino acid metabolism (Shils, 1988). Winitz and associates conducted the first long-term human feeding studies of liquid diets whose exclusive nitrogen sources were L-isomers of essential amino acids (Winitz et al., 1970).

A series of reports of clinical investigations by Randall and associates beginning in 1959, in which the commercial formula Vivonex® (Eaton Laboratories) was used for dietary management of patients with nutritional problems, led to the conclusion that such formulas could be useful in patients with a variety of nutritional problems and that "tube feeding was a simpler, less expensive, and potentially less hazardous procedure than total parenteral nutrition (TPN)." This led to a proliferation of commercial formulas and the development of improved feeding tubes and associated equipment (Shils, 1988). This trend has continued; today, there is available a wide selection of enteral nutrition products. As the number of products and uses has grown, so has the complexity of formulations and regulations. In 1988, the Food and Drug Law Institute sponsored a symposium on medical foods, which has been published recently (Bass, 1989). This document should be consulted for additional information on the history of use and regulation of medical foods.

3. Assumptions

For purposes of this study, it is assumed that members of the medical and allied health professions who are familiar with the principles of clinical nutrition generally favor the concept of nutritional support for patients with diseases and injuries that, directly or indirectly, impair nutritional status. This is based on the concept that adequately nourished patients recover more rapidly with fewer complications than malnourished patients. The question of scientific documentation for this point of view is addressed in Section C of this chapter.

4. Clinical uses of representative products

Shils (1988) listed several types of clinical indications for which enteral nutrition support may be appropriate. Examples include:

- Persistent anorexia.
- Painful swallowing.
- Impaired swallowing with risk of aspiration.
- Coma.
- Malabsorption, with diarrhea, associated with oral intake of ordinary foods.
- Altered metabolic needs such as hypercatabolic states that cannot be satisfied by voluntary oral feeding.
- Persistent fistulas of the upper small bowel that can be bypassed by an enteral feeding tube.
As supplements to parenteral feeding.

Available products range from nutritionally complete, lactose-free feeding formulas containing intact proteins or oligomeric protein components to "disease-specific" products designed to (1) limit the amounts of offending ingredients in disorders of amino acid metabolism or (2) provide supplemental amounts of specially prescribed nutrients such as medium-chain triglycerides (MCT) and branched-chain amino acids (BCAA).

Suggested product categories vary by author. For example, Bell et al. (1989) list (1) standard formulas with intact macronutrients; (2) high-nitrogen, with intact macronutrients and >15% of total calories as protein; (3) predigested, elemental, with hydrolysed macronutrients; (4) concentrated, with intact macronutrients; (5) fiber-containing, blenderized, with natural food fiber or added soy polysaccharide; and (6) specialty products for liver, renal, and pulmonary disease.

5. Regulatory status

Foods that are marketed for use solely under medical supervision to meet nutritional requirements in specific medical conditions are exempt from provisions on nutrition labeling (21 CFR 101.9), but must be labeled in compliance with 21 CFR 105. The FDA has reaffirmed its intent to continue the exemption for medical foods in its recently published proposed rules on food labeling, mandatory status of nutrition labeling, and nutrient content revision (Food and Drug Administration, 1990). Section 105 of Title 21 of the Code of Federal Regulations addresses foods for special dietary uses that supply particular dietary needs that exist by reason of a physical, physiological, pathological, or other condition. There is nothing in section 105 about their use solely under medical supervision.

Most, if not all, medical foods marketed currently include labels or insert brochures that comply with the basic labeling requirements of the Federal Food, Drug, and Cosmetic Act and its implementing regulations.

These include statements of identity, ingredients, net quantity of package contents, and name and business address of the manufacturer, packer, or distributor (21 CFR 105) (Raubicheck, 1989). In addition, medical foods are marketed with a variety of nutritional claims (Hattan and Mackey, 1989).

The FDA Compliance Program Guidance Manual (Program 7321.002) (Food and Drug Administration, 1989) identifies the requirement that medical foods be used under medical supervision as the unique or critical difference setting medical foods apart from foods for special dietary purposes or foods that make health claims. The Compliance Program Guidance Manual also notes that medical foods are analogous to infant formulas (21 CFR 106); however, unlike infant formulas there are no registration requirements for manufacturers and or products.

However, medical foods are covered by regulations related to Good Manufacturing Practices (GMP) (Office of the Federal Register, 1990a,b). The major purposes of GMPs are to provide guidance on how to reduce unsanitary manufacturing practices, how to protect against food becoming contaminated, and to state explicit objective requirements that enable industry to know what FDA expects when an inspector visits the manufacturing plant (Food and Drug Administration, 1989). Additional purposes are to ensure against omission of a required ingredient and or to ensure that a finished product is neither too dilute nor too concentrated (Serafino, 1989). The guiding issues for GMPs are safety and suitability of use of foods including medical foods.

The regulations for low-acid, thermally processed foods (21 CFR 113) (Office of the Federal Register, 1990b) govern most packaging of medical foods. These regulations specify process requirements, deviation tolerances, and record-keeping requirements for human foods and should be applicable to medical foods (Serafino, 1989). According to Serafino, the interests of reputable manufacturers and
FDA in ensuring the quality and safety of medical foods are the same. He noted, "The practices of most manufacturers of ... medical foods probably exceed the quality prescriptions of the current regulations. For example, although it is not required, many manufacturers engage in clinical testing of their products to determine that they are safe and suitable for their intended purpose."

FDA directed a medical foods compliance inspection program to its field districts for fiscal year 1988. It has been revised for fiscal years 1989, 1990, and 1991 (Food and Drug Administration, 1989). According to Hatton and Mackey (1989), the program aims to ascertain the measures used by the medical foods industry to preclude microbial and environmental contamination and improper composition of formulations as well as to verify suitability of the therapeutic claims associated with these products.

Although FDA does not require premarketing approval of enteral nutrition products, the Agency maintains vigilance in terms of the safety and suitability of these products. FDA evaluates the results of clinical trials of such products when data are made available from the manufacturers. Moreover, if questions of safety and suitability arise, FDA may require submission of supporting data. FDA’s Office of Nutrition and Food Science believes that a standardized format for the review of medical foods is needed to ensure their safety and suitability (Hatton and Mackey, 1989). In addition, FDA’s Center for Food Safety and Applied Nutrition is considering the feasibility of establishing and maintaining a post–marketing surveillance program to monitor any adverse reactions associated with the use of medical foods (Hatton and Mackey, 1989).

B. OBJECTIVES AND SCOPE OF THE STUDY

The purposes of this scientific review are to:

- Obtain a state–of–the–art summary of the scientific rationale for certain types of medical foods.
- Develop guidelines for evaluating studies designed to substantiate the safety and suitability of medical foods for their intended purposes.

The categories of medical foods to be considered are those:

- Formulated for end–stage renal disease.
- Containing branched–chain amino acids for dietary management of hepatic disease.
- Formulated for pulmonary diseases.
- Used for the dietary management of trauma and other hypermetabolic conditions.

The scope of work includes:

- A summary of background information on medical foods used in the above–specified diseases and disorders such as composition, recommended uses, therapeutic claims, and ongoing clinical studies.
- Description and evaluation of the scientific rationale and principles for the use of medical foods in the specified diseases and disorders.
- Critical review of the scientific evidence to demonstrate safety and suitability of each type of medical food reviewed along with suggestions for future research.
• Development of guidelines that may be used for designing and evaluating procedures and protocols for clinical studies whose purpose is to support claims for clinical suitability and safety.

• Preparation of a scientific report for FDA embodying all of the foregoing.

C. GENERAL CONSIDERATIONS ON SUITABILITY OF ENTERAL NUTRITION PRODUCTS FOR THEIR INTENDED USES

Suitability of enteral products in management of diseases and disorders is based on knowledge and observations that such approaches are efficacious in avoiding or addressing the nutritional consequences of the disease or disorder. The principal disturbances of physiology, biochemistry, metabolism, and organ function and their nutritional significance for the four categories of clinical disorders addressed in this report are described in Chapter II A–D.

1. Objectives of clinical nutritional support

Expert opinion varies widely on whether nutritional support of the sick or injured makes a significant difference in clinical outcome. Several leading clinical nutritionists have emphasized the extreme difficulty in attempting to reach definitive conclusions about the efficacy of nutritional support in terms of improvement in morbidity and mortality and reduction in time of hospital stay. For example, Grant (1987) noted that "review of hundreds of publications on the effectiveness of nutritional support in clinical practice fails to show significant improvement in patient survival." However, he suggested that survival may not be the appropriate criterion for judging nutritional efficacy; rather, the true goal of clinical nutritional support should be to provide an optimum profile of nutrients to meet the metabolic needs of the patient so that malnutrition does not become a comorbidity or comortality factor in the disease process. Other important goals include:

• Do no harm.

• Improve nutrition assessment indices.

• Prevent single and multiple nutrient deficiencies.

• Promote organ integrity and function.

• Ameliorate clinical manifestations of the disease.

• Favorably influence the disease process.

• Positively influence morbidity and mortality (patient outcome).

The outcomes and end points that are appropriate for clinical trials of medical foods in the four designated groups of diseases and disorders were carefully considered. Documenting effects on morbidity and mortality, while ultimately most desirable, has usually proven to be impractical or unattainable. The etiology, severity, and stage of disease, individual resistance and stamina, intercurrent illness, and many other clinical parameters differ widely in patients requiring nutritional support. Clinical outcomes depend upon these variables, their management, and patient responses to all therapeutic measures employed. Hence, attempting to stratify these and other variables in controlled studies of nutritional support is usually impractical. These issues are discussed further in sections 2–a and 2–b of this chapter.
Practical end points that are more feasibly achieved are measurements that include:

- Improved nutrition assessment indices
- Corrected metabolic imbalances
- Restored organ and organ system function
- Alleviated clinical manifestations of disease

The consultants suggested that if investigators would design studies that use a reasonable outcome such as a change in clinical manifestations (which may or may not reflect any change in morbidity or mortality), more research could be accomplished with less commitment of time and resources than is possible with morbidity and mortality as the primary end points. Of course, if a marker of the disease that correlates with morbidity and mortality is available, so much the better. In Chapter 2, the clinical outcomes and end points for clinical trials considered useful and practical by the LSRO consultants are described for each disease category including variables for clinical outcome and those that should be clinically monitored.

Suitability of an enteral nutrition product may be judged in part in terms of its potential uses. Typically, possible uses are derived from medical understanding of the disease or disorder. Where needs are identified, individuals and groups such as clinicians, dietitians, and manufacturers develop products for clinical use. Commercially available products are labeled for uses suggested by the respective manufacturer. Suitability of products for such uses, and consequently commercial availability, are determined largely by the safety, nutritional adequacy, and consistency with the principles of good nutrition. Other aspects including the objectives of nutritional support and the cost of the product also affect suitability.

2. Evaluation of evidence for suitability

In Congressional briefings on the cost-effectiveness of nutritional support in January 1986 (American Dietetic Association, 1986), it was noted that "Thousands of supporting articles document that nutrition support is . . . a therapy that can save lives when properly delivered." Results of an unpublished study of 800 patients conducted by Arthur Andersen & Company for Ross Laboratories reported that poorly nourished patients had three times the number of major complications and were three times more likely to die. Malnourished patients cost hospitals more per patient than well-nourished patients. In considering the suitability of enteral (as well as parenteral) nutritional support, an important question is whether improving nutritional status translates into a better clinical outcome (Koretz, 1984a). A perspective on the usefulness of nutritional support for major surgery of the gastrointestinal tract may be gained by analysis of nutrition-associated complications (NAC) such as poor wound healing, infection, respiratory failure, fistula formation, and possibly phlebitis and pulmonary embolism. Reduction of NAC by either parenteral or enteral alimentation appears to be as much as 50% (Detsky et al., 1984; Randall and Caldwell, 1987).

Few reports were identified of clinical trials designed to determine the suitability of enteral nutrition products for patients with the diseases and disorders specified for this study (see Chapter II for discussion). The LSRO consultants generally favored inclusion of reports of parenteral alimentation where the nutritional objectives and related metabolic effects were basically similar to those associated with enteral nutrition. Moreover, to illustrate certain concepts and principles of clinical nutrition, reference is made in a few instances to studies involving diseases and disorders other than those specified for this study. Consequently, part of this section concerns reports of enteral nutrition; a second part, reports of parenteral nutrition; and a final part, end points for judging suitability of products.
a. **Enteral nutrition experience**

Giacchino et al. (1981) reported that patients undergoing emergency surgery for end-stage renal disease, who were nutritionally supported, showed improved survival compared with similar patients who were not nutritionally supported. Enteral nutrition was usually employed after initial support by parenteral alimentation. Patients with end-stage liver disease and encephalopathy who attained nitrogen balance via nutritional support had a significantly lower mortality rate.

Rombeau and associates (1988) note that "many studies have confirmed the association between malnutrition and adverse clinical outcome in surgical patients," and other studies have shown that nutritional support improved or normalized laboratory and anthropometric indices. Two controlled clinical trials of preoperative enteral nutrition in patients with benign or malignant abdominal disorders reviewed by these authors reported beneficial effects in terms of wound infections, anastomotic leakage, hepatic and renal failure, and length of hospitalization. However, it is extremely difficult to answer the critical basic question of whether nutritional support can improve clinical outcome as measured by decreased postoperative complications and shortened hospital stays (Rombeau et al., 1988).

In the malnourished patient a galaxy of clinical abnormalities such as cardiac, respiratory, and renal dysfunction, impaired immunocompetence, delayed wound healing, and muscle atrophy have been described (Doekel et al., 1976; Friedman and Cerra, 1984; Lowry, 1985; Mullen, 1981). These nutrition-related conditions are regarded by many authors as sufficient justification for nutritional intervention to prevent starvation effects. However, if these abnormalities of organ function are disease-related instead of resulting from malnutrition, our ability to manipulate them nutritionally is very limited.

The technology of clinical nutrition support aims to maintain adequate nutritional status and prevent or reverse protein-calorie malnutrition (Hunter, 1989); it also enables modification of diet to meet disease-specific nutritional requirements. Homsy and Blackburn (1983) considered that "the goal of nutritional support is to provide proteins, calories, electrolytes, vitamins, and all essential nutrients in a form that can be utilized by the patient to restore and maintain the body cell mass, particularly the visceral component."

Koretz (1986) reviewed a series of 20 prospective randomized controlled trials (PRCT) of enteral nutrition products used for nutritional support in a variety of illnesses including cancer, upper gastrointestinal cancer surgery, inflammatory bowel disease, acute renal failure (essential amino acids), hepatic encephalopathy (BCAA), asthma (one study), and head injuries (one study). There was evidence of some improvement in cases of acute renal failure and in hepatic encephalopathy, but most trials failed to show a beneficial clinical effect, a fact suggesting that the impact of the associated malnutrition in many of the patients was small. Most of the attempts to show that nutritional support benefited clinical outcome were unsuccessful. However, whether the associated malnutrition in these trials was disease-related or nutrition-related (and therefore amenable to nutritional intervention) is not clear. Data from large, prospective, randomized, controlled trials are needed to prove or disprove the possible merits of various proposed applications of nutrition support (Koretz, 1986).

In a previous study, Koretz and Meyer (1980) analyzed available laboratory and clinical data on the composition, nutritional adequacy, physiologic effects, clinical applications, and toxicities of several enteral products*. These products were lactose-free, contained no fiber, and provided either amino

* The enteral nutrition products used in the reviewed studies included four adult preparations (Standard Vivonex®, Vivonex HN®, Flexical®, and Vital®) and two infant formulas (Nutramigen® and Pregestimil®).
acids or hydrolysed proteins, vegetable fats and or MCT, and carbohydrates as glucose oligosaccharides or sucrose, dextrin, and polysaccharides. Koretz and Meyer (1980) concluded:

- Data are lacking to support the premise that defined formula diets are more readily absorbed than whole foods.
- Controlled trials had not been conducted to test efficacy in short bowel syndrome, enterocutaneous fistulas, inflammatory bowel disease, or acute pancreatitis.
- Hepatic encephalopathy, renal failure, phenylketonuria, and pancreatic exocrine insufficiency may benefit from use of specially formulated defined formula diets.
- Carefully designed physiologic and clinical experiments are needed to address questions of efficacy, cost–benefit, and safety.

Delmi et al. (1990) reported beneficial effects of a daily oral, nutritionally balanced diet supplement in a prospective, randomized trial of elderly patients with fractures of the femoral neck. Clinical outcome including rates of complications and mortality was significantly better in the supplemented group.

In a double-blind, placebo-controlled, randomized study of the effect of orally administered nutritional supplementation on anthropometric indices, pulmonary function, and immune status in malnourished patients with emphysema, Otte et al. (1989) found only weight gain but no change in other indices of well-being.

b. Parenteral nutrition

Mullen et al. (1980) showed that nutritionally supported (parenteral nutrition) patients who underwent major abdominal or thoracic surgery had half as many complications, less than half as many infections, and were one-fifth as likely to die as those given no pre- and postoperative nutritional support. Smale et al. (1981), after a retrospective analysis of 157 patients who had major cancer surgery, reported that preoperative parenteral nutrition significantly reduced operative morbidity and mortality.

Based on a meta-analysis of the pooled results of 11 clinical trials, Detsky et al. (1987) concluded that perioperative parenteral nutrition appeared to reduce mortality and the risk of complications of major surgery. However, the authors cautioned that the results of the meta-analysis were offset by poor quality of trial methodologies, inconsistencies in patient selection, and iatrogenic complications of intravenous alimentation.

Examples of other reports of favorable results of clinical nutritional support include: Adams et al., 1986 (enteral and parenteral); Deitel et al., 1978 (parenteral); Dempsey et al., 1988 (parenteral); Haffejee and Angorn 1979 (enteral); and Moore et al., 1989 (enteral and parenteral). Adverse effects of poor nutritional status in hospitalized patients have been reported by a number of authors including Bistrian et al., 1976; Buzby et al., 1980; Green et al., 1982; Haley et al., 1980; Laven et al., 1980; Scrimshaw et al., 1959; and Weinsier et al., 1979.

Koretz (1984b) noted that over 60 prospective, randomized, clinical trials (PRCT) examined the role of nutrition support in various diseases and disorders, and that in about 80% of the trials, clinical outcome did not differ between patients receiving nutritional support and those managed conventionally, although nutritional status improved. Moreover, the remaining 20% of the trials included some in which the nutritionally supported patients did poorly or in which the benefits of nutrition support were trivial or not cost effective.

The definition of clinically significant inpatient malnutrition has not been standardized to the satisfaction of many investigators (Silk, 1986a). An associated unresolved problem is whether malnutrition arises as a result of the underlying disease and may, therefore, not be amenable to
nutritional correction. Clinical investigators have attempted to divide malnourished patients into high- or low-risk groups; however, the question of whether nutritional support affects morbidity or mortality in the "at risk" malnourished group is largely unanswered because most clinical trials of nutritional support lacked proper experimental design and have included normally nourished as well as malnourished patients (Silk, 1986a).

In an investigation of the influence of nutritional status on morbidity and mortality of patients in a geriatric rehabilitation unit, Sullivan and coworkers (1990) attempted to control also for nonnutritional factors that could affect outcomes. They noted that the correlation between nutritional status and outcomes was significant even when age and selected nonnutritional variables were controlled for, a fact that lent support to the concept that nutritional status may be causally related to mortality in this population. Additional carefully designed clinical trials are needed to answer the question, "Is malnutrition clinically significant?"

The lack of confirmatory clinical outcome data was emphasized in an ASPEN presidential address by Rombeau (1989) who noted that only five of 12 PRCT of perioperative enteral nutrition support revealed substantive improvement in clinical outcome in surgical patients with a variety of illnesses. The self-evident, logical concept of nourishing patients who cannot eat will probably be unaccept-able in the future to hospital administrators and budget managers who may demand objective evidence to support the use of these expensive technologies (Rombeau, 1989).

In light of the currently available knowledge of the effects of nutritional support in seriously ill or injured patients, and the scarcity of convincing evidence that nutrition support makes a significant difference in clinical outcome in severe and advanced forms of the diseases and disorders addressed in this report, it seems prudent to adopt for the time being the view of Grant (1987) and others that the true goal of nutritional support should be to provide an optimum profile of nutrients to meet the metabolic needs of the patient. Whether such measures would ameliorate clinical manifestations of a disease and affect organ function and morbidity and mortality would then depend on the ability of the human organism (aided by disease-specific clinical measures such as surgery, drugs, antibiotics, radiation, and transplantation) to correct the offending metabolic derangements and restore injured tissues and organs to physiologic homeostasis. The use of nutrients in a truly disease-specific or organ dysfunction-specific mode is in its infancy.

3. Selection of enteral products

The most convenient guides for selection of medical foods are the handbooks of clinical nutrition and review articles and book chapters on the subject. Examples include the Dietitian's Handbook of Enteral and Parenteral Nutrition (Skipper, 1989); Handbook of Clinical Nutrition (Weinsier et al., 1989); selected chapters in Modern Nutrition in Health and Disease (Shils and Young, 1988); a book chapter on enteral nutrition (Alpers et al., 1988); selected chapters in Nutritional Support in Critical Care (Lang, 1987); The Physicians Desk Reference (1990); and reviews such as those of Heimburger and Weinsier (1985), Heymsfield et al. (1986), and Silk (1986b).

Many authors appear to regard cost among the most important of a long list of selection criteria. However, opinions vary regarding the relative importance of the criteria. Heimburger and Weinsier (1985) considered the major criteria for evaluating enteral nutrition products to be caloric density, protein content, route of administration (tube or oral or tube only), and cost. Their list of minor criteria included osmolality, complexity (polymeric or oligomeric), fat content, fat source (LCT or LCT+ MCT), residue, electrolyte and mineral content, form (ready-to-use or powder), and available clinical studies. Sources of protein (e.g., casein, egg, beef, amino acids), carbohydrates (e.g., corn starch, maltodextrin, vegetables, glucose oligosaccharides), vitamin content (provided that RDAs are met when 2000 kcal are delivered), and method of composition (compounded or blenderized) were regarded as inconsequential criteria.

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In contrast, a survey of a random sample of 200 registered dietitians from the Clinical Nutrition Management Dietetic Practice Group of the American Dietetic Association characterized the following criteria (among others) as more than moderately important: osmolality, lactose content, electrolyte content, protein source, fat source, and related clinical studies (Coffey and Carey, 1989). These authors noted that it is common practice in many hospitals surveyed to establish enteral nutrition formulas in which the selection criteria judged important by the hospital clinicians and dietitians may be used to provide optimum enteral nutrition service at the most economical cost.

Schwartz (1987) listed the following features of enteral solutions as clinically important: nutritional completeness, lactose content, osmolality, viscosity, caloric density, molecular form of substrates, and metabolic utilization.

4. Some specific ingredients

Certain nutrients that are believed to possess properties that may enhance nutritional support in various diseases and disorders are considered in Chapter II. Examples are the branched-chain amino acids, glutamine, and arginine. MCT oils and fructose are treated in the following paragraphs because of general applicability of some of their properties to the formulation and use of medical foods. Polyunsaturated fatty acids are also mentioned because of some concern over their possible untoward effects on immunocompetence.

Medium-chain triglycerides (MCT). These triglycerides (triacylglycerols) contain 6 to 10 carbon atoms and are available as supplements or as components of several commercial enteral products. Unlike long-chain triglycerides (LCT), which are hydrolyzed mainly in the intestinal lumen by pancreatic lipase to monoglycerides and free fatty acids (FFA), MCT are absorbed unchanged into the enterocytes where they are degraded to monoglycerides and FFA by an intracellular lipase. MCT offer theoretical advantages in patients with malabsorption problems from a variety of causes. MCT are more rapidly digested than LCT, relatively independent of pancreatic lipase and bile salts, more water-soluble than LCT, and thus more readily diffusible through cell membranes. They are metabolized and transported more rapidly than LCT and are not stored in fat depots (Linscheer and Vergroesen, 1986).

Fructose. Sometimes fructose is used as an energy source in parenteral solutions, and it may be used as a substitute for sucrose in various enteral nutrition products. Fructose is absorbed more slowly and less completely from the gastrointestinal tract than glucose and produces a less precipitous increase in blood glucose levels than glucose or sucrose (Kimura and Carr, 1976).

A 1976 review of the metabolic and health aspects of fructose used as a nutritive sweetener concluded that crystalline fructose had a long history of use in Europe without reports of adverse effects. However, medical opinion compiled in this study suggested there were no clinical advantages of substituting fructose for glucose either orally or parenterally in any disease state (Kimura and Carr, 1976).

More recent reports generally indicate metabolic advantages of moderate, physiologic amounts of dietary fructose as a substitute for glucose or sucrose (Crapo and Koltermin, 1984; Förster, 1987; Grigoresco et al., 1988; Reiser et al., 1989; Thorburn et al., 1990). However, there is controversy about the possible undesirable effects of dietary fructose on serum lipids and other metabolic processes such as nonenzymatic glycosylation of proteins (Bantle, 1989). Although fructose is less glucogenic than glucose or sucrose, it may be incompletely absorbed when consumed in excess of dietary glucose, leading indirectly to abdominal distension, cramps, and increased gastrointestinal motility. Moreover, it is more lipogenic and generally causes greater elevations in serum lipids than other carbohydrates (Hallfrisch, 1980). Persons at increased risk of hypertriglyceridemia resulting from consumption of fructose include postmenopausal women, hyperinsulinemic men, and patients.
with noninsulin-dependent diabetes (Reiser, 1987a). In addition dietary fructose has been associated with increases in blood pressure and blood levels of uric acid and lactic acid (Reiser, 1987b).

There are scattered reports of malabsorption of fructose and fructose-sorbitol combinations manifested by gastrointestinal distress including cases of diarrhea in children consuming apple juice (Kneepkens et al., 1989; Ravich et al., 1983; Truswell et al., 1988). Hereditary fructose intolerance (estimated incidence 1 in 21,000 persons) requires elimination or severe restriction of fructose sources in the diet and is potentially lethal when large amounts of fructose are mistakenly given intravenously (Keller, 1989; Wagner and Wolf, 1984).

The polyunsaturated fatty acids are mentioned here and in Chapter III because of concern about their possible adverse effects on immunocompetence and survival in certain settings (Gottschlich et al., 1990a; Kelley et al., 1990; Saito et al., 1985; Virella et al., 1990).

5. **Suitability in terms of nutritional objective**

If the nutritional objective is to provide an optimum profile of nutrients to meet the metabolic needs of the patient, the product information should provide quantitative data on available energy and macro- and micronutrient content and documentation of suitability for its intended uses in terms of metabolic effects and nutritional indices.

If the objective is to influence clinical outcome, the product information should include documentation of a significant effect on such end points as morbidity, mortality, symptoms, organ function, length of hospital stay, quality of life, and or observational data on these factors.

Assessment of the composition and purity of enteral nutrition products requires manufacturers' data on composition, and comparative analytic and plant inspection data from FDA's Compliance Program (Food and Drug Administration, 1989). Nutritional adequacy judgments may be based upon the RDAs (National Research Council, 1989) for macro- and micronutrients as may be modified to meet metabolic requirements of the disease or disorder for which the product is intended. Estimating the appropriateness of products intended for use in a given disease or disorder depends upon knowledge of and experience in clinical medicine and clinical nutrition and in technical guidance available in the clinical nutrition literature including such references as were previously mentioned.
II. MEDICAL FOODS FOR SPECIFIED DISEASES AND DISORDERS

The FDA has requested that this LSRO review include an assessment of the scientific rationale for the use of enteral nutrition products in the management of the four categories of diseases and disorders specified in the contract. Consequently, this chapter is divided into overviews of the diseases and disorders and the associated principles of nutritional management. It also includes consideration of the suitability of generic examples of enteral nutrition products for use in the diseases and disorders designated for this review.

Selection of representative supporting or nonsupporting data was attempted. The literature cited in this report is, in the expert opinion of the LSRO consultants, appropriate for illustrating clinical experience in enteral (and in some instances, parenteral) nutritional management of patients with the diseases addressed in this chapter. In general, attempts to apply standard research laboratory assessment criteria to the cited clinical trials were unrewarding because of numerous interacting variables many of which could not feasibly be controlled by the investigators. For example, to acquire a statistically meaningful number of patients that would permit desirable stratification by applicable clinical parameters and provide necessary dietary control groups would almost certainly require a major, multicenter approach that has typically been beyond the reach of clinical investigators. Consequently, many of the cited studies were conducted with protocols that, in some reports, fall short of generally accepted design criteria. Nevertheless, the studies cited are representative of what is available in the literature. Indeed, the studies cited are, for the most part, prospective, randomized, controlled trials. Despite design inadequacies, these are examples of studies that have contributed significantly to an understanding of the capabilities and limitations of enteral nutritional support of seriously ill patients. The studies cited in Chapter II were selected because they deal with enteral nutritional support of the diseases discussed, because they are representative, and because they approach the guidelines developed in the course of this review (see Chapter IV).

Unless otherwise noted, the criteria used by LSRO for judging suitability were whether the product provided the nutrients required, met the metabolic needs of the patient, and use of the product resulted in stabilization or improvement in one or more objective measures of nutritional status.

A. END-STAGE RENAL DISEASE

1. Overview

Chronic renal failure (CRF) from a variety of causes tends to progress to end-stage renal disease although at widely varying rates in individual subjects (Walser, 1990a). For purposes of this review, medical foods for chronic renal failure at all stages are considered; these stages of renal failure were described by Cotran et al. (1989):

- Diminished renal reserve -- glomerular filtration rate (GFR) approximately 50% of normal.
- Renal insufficiency -- GFR 20–50% of normal (azotemia, polyuria, and nocturia present; anemia and hypertension may occur).
- Renal failure -- GFR <20–25% of normal (edema, metabolic acidosis, hypocalcemia, and hyperphosphatemia are typical; anemia may occur, with neurologic, gastrointestinal, and cardiovascular complications).
- End-stage renal disease -- GFR <5% of normal; this is the terminal stage of uremia.
Azotemia and uremia are terms often used in writings on renal failure. In a strict sense, azotemia is a biochemical abnormality that refers to increased levels of blood urea nitrogen and creatinine, mainly related to decreased GFR. Uremia is a clinical syndrome that includes azotemia and a variety of clinical signs and symptoms and associated biochemical and metabolic abnormalities. The uremic syndrome often includes impaired metabolism of carbohydrates, fats, and proteins and defective utilization of energy (Brenner and Lazarus, 1987; Cotran et al., 1989).

Examples of manifestations of chronic renal failure are:

- Fluid, electrolyte, and acid–base balance disturbances.
- Abnormal calcium, phosphate, and bone metabolism.
- Failure of renal synthesis of 1,25-dihydroxyvitamin D₃.
- Cardiopulmonary abnormalities.
- Hematopoietic disturbances (anemia; sometimes a bleeding diathesis) (Cotran et al., 1989).

Details of the pathophysiology of chronic renal failure are available in standard texts such as Brenner and Rector (1990).

In contrast with the kidney's recuperative powers in many forms of acute renal infections and intoxications, the progressive loss of nephron mass leads, in most cases, to irreversible chronic renal failure. Eventually, the reduction in renal mass leads to functional alterations in most of the body's organ systems (Brenner and Lazarus, 1987; Kopple, 1988).

One manifestation of advanced renal insufficiency is malnutrition, unless it is properly treated. Among the causes of malnutrition in chronic renal failure are proteinuria, anorexia, inadequate dietary intake, superimposed catabolic illness, uremic toxicity, endocrine abnormalities, blood losses from frequent venipunctures (especially in children), occult gastrointestinal bleeding, and loss of blood, plasma proteins, and nutrients during dialysis. Malnutrition may contribute to various aspects of the uremic syndrome such as decreased resistance to infection, impaired wound healing, decreased strength and vigor, and poor rehabilitation and quality of life (Blumenkrantz et al., 1980).

The following pathophysiologic indicators are associated with chronic renal insufficiency:

- Reduced renal clearance of urea, creatinine, uric acid, guanidine, Ca, P, possibly Mg, trace elements, and certain vitamins such as vitamin A and some of the B vitamins.
- Impaired ability to regulate Na, K, acid–base, and water balance.
- Impaired renal synthesis of erythropoietin that results in anemia; impaired renal synthesis of 1,25-dihydroxyvitamin D₃ and subsequent decreased calcium absorption; and reduced glycine–serine conversion.
- Decreased degradation and elevated serum levels of peptide hormones such as insulin, glucagon, parathyroid hormone, growth hormone, gastrin, and prolactin.
- Reduced serum total protein, albumin, and transferrin in individuals who are protein–malnourished or who have marked proteinuria.
- Abnormally high serum levels of several nonessential amino acids, low concentrations of essential amino acids including valine, isoleucine, and leucine, and high glycine:valine and phenylalanine:tyrosine ratios (Fürst et al., 1978).
- Anorexia, especially in children.
Impaired growth in children (Ashworth, 1978; Betts and Magrath, 1974; Chan et al., 1990a,b; Holliday, 1972; Holliday and Chantler, 1978; Jones et al., 1982; Potter and Greifer, 1978).

2. Objectives and rationale for nutritional management

Three principal goals of dietary management in CRF are to slow the rate of progression to end-stage renal disease, maintain good nutrition, and prevent or minimize uremic toxicity (Kopple, 1988). In children, normalization of growth is an important objective (Ashworth, 1978; Betts and Magrath, 1974; Chan et al., 1990a,b; Holliday, 1972; Holliday and Chantler, 1978; Jones et al., 1982; Potter and Greifer, 1978). General guidance for nutritional management of predialysis CRF includes:

- Adjustment of protein intake to minimize the accumulation of nitrogenous wastes and potentially limit disease progression, while providing sufficient high-quality protein to maintain protein nutrition and prevent wasting of lean body mass.
- Adjustment of the intake and or intestinal absorption (e.g., by phosphate binders) of minerals, electrolytes, and buffers such as Na, K, Cl, P, Fe, and HCO₃⁻.
- Assurance of adequate energy intake.
- Avoidance of potentially harmful intakes of P, Mg, Al, vitamin A, vitamin D, or citrate.
- Replacement of deficient hormones including erythropoietin and calcitriol.

Optimal levels of these nutrients will vary depending on age, body weight, and severity of renal failure. For instance, although more studies are needed to determine exact vitamin requirements in various diseases, existing data for adult patients suggest that a relatively narrow range is suitable for several vitamins (Shils et al., 1985).

3. Literature review

Methods for estimating nitrogen intake from nitrogen output are critical in evaluating dietary compliance (Kopple, 1981, 1983; Maroni et al., 1985). Dietary protein adjustment to approximately 0.6 g/kg body weight may slow progression of chronic renal failure (Ihle et al., 1989; Maschio et al., 1982, 1983; Oldrizzi et al., 1989; Rosman et al., 1984). However, in a subsequent report, Rosman et al. (1989) noted that, after four years, most of the patients in whom progression had been slowed earlier (Rosman et al., 1984) had renal function similar to that of the control group.

More severe protein restriction plus ketoanalogues of essential amino acids may also slow progression (Barsotti et al., 1984; Fröhling et al., 1984; Mitch et al., 1984; Walser et al., 1987). In addition to their possible effects on progression, ketoacid supplements have been reported to have a number of metabolic and endocrine effects in patients with chronic renal failure. The most widely used preparations contain ketocids as calcium salts, with disproportionately large quantities of the branched-chain keto acids (BCKA). These preparations reduce serum phosphate and parathyroid hormone levels more than do supplements of essential amino acids (Schmicker et al., 1984). Hypercalcemia may occur occasionally (Jones et al., 1983). Lesser effects on phosphate are seen if a preparation containing BCKA in the Rose proportions is used (Meisinger, 1987). During long-term therapy with the most widely employed formulas, renal osteodystrophy improves (Lindenau et al., 1987).
A related observation is that calcium salts of ketoacids are effective intestinal phosphate binders (Schaeffer et al., 1989), although whether they are more effective in this respect than other highly ionized salts like calcium acetate (Mai et al., 1989) remains to be established. Support for this explanation of the improvement in divergent ion metabolism is provided by studies of ketoacid preparations containing basic amino salts of ketoacids instead of calcium salts. Serum phosphate remains constant (Mitch et al., 1984) or tends to rise (Walser et al., 1987) with these formulas when given after a period of supplementation with essential amino acids.

Improvement in protein nutrition in patients with chronic renal failure has also been reported. Schmicker et al. (1984) followed 93 patients for an average of eight months on either ketoacid or essential amino acid supplements to a low protein diet. N balance, measured every three months, was usually less negative in those on ketoacids than in those on amino acids. Kampf et al. (1980), in a crossover comparison of BCAA supplementation versus branched-chain ketoacid (BCKA) supplementation, observed better nutritional parameters on BCKA exclusively in patients with severe renal insufficiency. When Lemke et al. (1989) treated 96 children with a low protein diet supplemented by either amino acids or ketoacids, N balance was more positive with the ketoacid supplement. Jureidini et al. (1990) found growth of children with chronic renal failure receiving ketoacid supplements to be faster than on conventional therapy.

On the other hand, Burns et al. (1978) observed no difference in N balance between a BCKA-containing supplement and a BCAA-containing supplement given to patients with chronic renal failure who were consuming an average of 44 g/d of protein. Hecking et al. (1980) administered 0.55 g protein per kg to uremic patients. After three months, either ketoacids or placebo were added. There was no evidence of protein deficiency before or during the treatment periods; the ketoacids essentially had no effect on protein metabolism. Lee and Jackson (1981) found no difference in N balance between ketoacid supplements as compared with amino acid supplements to a 39 g protein diet. In all three of these studies, the BCAA content of the diet was probably sufficient to meet BCAA requirements.

When ketoacid supplements containing BCKA in no more than proportionate amounts are given to an extremely low protein diet (0.21 g/kg), loss of weight and of muscle mass may occur, even though serum albumin and transferrin levels remain constant (Lucas et al., 1986).

The effects of BCKA on protein metabolism have recently been reviewed (Walser, 1990b).

It has been reported that ketoacid supplements to restricted protein diets improved glucose tolerance and insulin sensitivity in patients with chronic renal failure (Aparicio et al., 1989; Gin et al., 1987; Mak et al., 1986), although the relative importance of protein restriction and ketoacid supplementation in these effects has not been established. Likewise, a variety of hormonal disturbances of chronic renal failure improve when protein restriction and ketoacid supplementation are instituted (Frohling et al., 1988).

In hemodialysis patients, similar beneficial effects on divergent ion metabolism are seen when calcium salts of ketoanalogues are given in conjunction with either a low protein (0.4 g/kg) or a normal protein (1 g/kg) diet (Knefati et al., 1989; Mahmoud et al., 1988). Levels of parathyroid hormone and phosphate also fall in patients on continuous ambulatory peritoneal dialysis who were given a calcium ketoacid supplement to a 1–1.4 g/kg protein diet (Lindenua et al., 1986).

With further reference to the possible advantages of dietary manipulation, recent work has suggested that dietary restriction of protein and phosphorus may decrease the rate of progression of chronic renal disease (Barsotti et al., 1984; Ihle et al., 1989; Klahr, 1989; Maschio et al., 1982, 1983; Oldrizzi et al., 1989; Walker et al., 1989). This has been most frequently observed in studies involving severe protein restriction plus supplements of keto analogues of essential amino acids. Protein restriction, with or without supplements of essential amino acids or their keto-analogues or with or without phosphorus restriction, was associated with stabilization in GFR in six studies (Schaap et al., 1987; Viberti and Bending, 1988; Viberti et al., 1988; Walser, 1989; Walser et al., 1987; Zeller et al., 1990).
In one study, a low-protein diet plus essential amino acids was not associated with change in rate of progression of CRF (Alvestrand et al., 1989). Another study reported no correlation between unrestricted protein intake and rate of decline of GFR in patients with diabetic nephropathy (Nyberg et al., 1987).

Ihle et al. (1989) cited five studies of dietary protein restriction in which alleviation of uremic symptoms and marked reduction in the rate of progression of renal disease were reported. Only one of the studies was a prospective, randomized, controlled trial (Rosman et al., 1984). Based on their own prospective, randomized study, Ihle et al. (1989) concluded that moderately severe protein restriction (0.4 g/kg per day) "with adequate caloric supplementation from carbohydrates and fats can delay the progression of intrinsic renal disease without leading to overt nutritional deficiencies." Some data corrections were published subsequently (Ihle et al., 1990a). However, this study has been criticized for alleged problems with design and methodology (Fischer, 1990; Rosman et al., 1990). Ihle et al. (1990b) responded to the criticism by claiming that their original conclusions were sound.

Diabetic patients given protein-restricted diets (0.67 g/kg per day) reportedly showed declines in the rate of progression of chronic renal failure and had no adverse effects on nutritional status (Walker et al., 1989). The low-protein diet provided 40 g protein/d, with 60% of energy from carbohydrate and up to 35% from fat. Similar results have been reported by others (Acchiardo et al., 1986).

Although the results of these and other investigations are encouraging, they have not unequivocally demonstrated that low-protein, low-phosphorus diets slow the rate of progression in chronic renal failure; adequate scientific support of these important observations remains to be established. In order to clarify and validate the effect of low-protein, low-phosphorus diets on progression of renal insufficiency and nutritional status, a major, multicenter program of prospective randomized trials is in progress (Klahr, 1989). Results of Phase II of the program, Modification of Diet in Renal Disease Study, showed no evidence of overt malnutrition in patients who complied with very low-protein diets (Klahr, 1989).

Representative studies performed with commercial medical foods.

• Fürst et al., 1978--These authors reviewed their studies of severely uremic patients treated with a low-protein diet (approximately 18 g/d) who remained in negative nitrogen balance until supplements of seven essential amino acids plus histidine (Aminess®) in amounts estimated at two to three times minimum requirements were administered either intravenously or orally. However, in long-term treatment of five patients with this regimen, only two patients remained in nitrogen equilibrium. Based on their studies of intracellular free amino acids in uremic patients, these investigators altered the proportions of essential amino acids in the low-protein formula. After long-term treatment of seven uremic patients with the new amino acid formula, average nitrogen balance was positive by approximately 0.6 g nitrogen per day (Fürst et al., 1980) as compared with only two of five patients maintained on the Aminess®-supplemented diet (Fürst et al., 1978).

• Attman et al., 1979--Patients with advanced renal failure were fed a diet containing 20 g protein per day supplemented with different amounts of a mixture of essential amino acids and histidine (Aminess®). Amounts of the supplements corresponded to 1.3 and 2.6 g nitrogen per day when administered intravenously and 1.3 g when given orally. Apparent nitrogen balance improved with all supplementation schedules; however, apparent nitrogen balance was reported as better when 1.3 g nitrogen was given orally rather than intravenously.

• Sofio et al., 1979--Twenty-four acute (ARF) and 31 chronic renal failure (CRF) patients received dietary nitrogen from a high-calorie, low-electrolyte essential amino acid (EAA) supplement (Amin-Aid®) as the sole source of nitrogen or as part of a low-protein diet for a mean of 12.9 and 22.5 treatment days, respectively. Measurements included N balance, daily
rate of rise (ROR) of blood urea nitrogen (BUN); and serum K, PO₄, and Mg. The authors excluded the effects of dialysis on the measured values and concluded that the EAA dietary supplement decreased the ROR of BUN, stabilized serum K and PO₄ in both treatment groups, and was associated with positive N balance or improved N balance in the CRF and ARF patients, respectively.

4. **General principles for nutritional management**

Enteral nutrition products designed for use in chronic renal failure are typically lower in protein and phosphorus in relation to total energy content than are common diets. They may contain essential as well as nonessential amino acids such as histidine and tyrosine, carbohydrates, fats, minerals, and vitamins. Sodium and potassium are highly restricted in these formulas. Examples of such products are given in Appendix A.

Formulas that provide for the following are considered generally acceptable for nutritional management of chronic renal failure in predialysis patients. Renal transplant patients are not considered here because of reasons already stated.

- Adjustment of amount of high-quality protein to sustain lean body mass but not overload the impaired kidney, e.g., 0.6 g/kg bw per day, but more in stressed patients.
- Regulate phosphorus intake to 600–700 mg per day.
- Adequate energy intake from carbohydrates and fats, for example, 35 kcal/kg per day in uncomplicated renal failure, but more in superimposed catabolic illness.
- Regulation of fluid intake and electrolyte balance.

These generalizations are just guidelines; each patient must be evaluated periodically and dietary modifications made as indicated. Typical enteral products that have been used include low-protein, low-phosphorus, high-energy defined formula diets and modulars to provide supplements of essential amino acids, vitamins, and minerals.

5. **Studies that need to be done in patients with chronic and acute renal failure**

a. **Predialysis**

- Randomized control trials of the effect of "disease-specific" medical foods on progression of CRF and maintenance of nutritional status.
- Additional clinical trials of the effects on progression of different mixtures of amino acids and the calcium salts and other salts of the keto acid analogues.
- The effect on progression of amino acid versus keto acid or hydroxyacid analogue supplementation of very-low protein diets.
- Clarification of the significant influence on product suitability of various ingredients that are present in some but not all medical foods, such as histidine and tryptophan. Which product is best for slowing progression?
- Investigation of the possible influence of formulas containing unusual lipids such as fish oils on progression.
Some existing medical foods alter blood lipid profiles in patients with CRF. Identify lipids for use in MFs that are good energy sources yet have minimal influence on blood lipid profiles because of the associated risk of cardiovascular events.

b. Dialysis patients

- The influence on frequency of dialysis of very low-protein diets enriched with nitrogen supplements such as BCAA or keto acid analogues of essential AA.

- Studies to determine whether medical foods exist or can be developed that would improve nutritional status in malnourished patients on dialysis.

- The nutritional needs of patients treated with maintenance hemodialysis may differ from those of patients treated with continuous ambulatory peritoneal dialysis, and both may differ from the needs of patients with renal transplants. Studies are needed to determine optimal dietary support for these patients.

- Studies to determine whether it may be feasible to substitute enteral for parenteral nutrition to correct severe catabolic responses to dialysis.

c. Acute renal failure

A majority of patients with acute renal failure must be nourished parenterally because they cannot eat. Studies are needed to determine whether any AA formulation initially given intravenously then continued enterally increases the probability of renal recovery and decreases mortality.

6. Conclusions

In conclusion, certain types of enteral nutrition products may be suitable in the dietary management of chronic renal failure:

- For patients with GFR 25–70 ml/min per 1.73m$^2$ and mild-to-moderate renal impairment, suitable products should provide approximately 0.6 – 0.7 g protein/kg per day of which at least 0.35 g/kg is of high biologic value, and should restrict phosphorus intake to 4.7 mg/kg per day.

- For patients with GFR <25 ml/min per 1.73m$^2$ and not on dialysis, low-protein products supplemented with essential amino acids should provide the equivalent of about 0.28 g protein/kg per day. If they become authorized for general clinical use, keto acid or hydroxyacid analogues of essential amino acids may offer advantages over standard amino acids in retarding progression of renal failure.

- For patients with GFR <5 ml/min per 1.73m$^2$, regular dialysis therapy is suggested combined with diets providing 1.0–1.2 g protein/kg per day, of which at least 50% should be of high biologic value.
B. HEPATIC DISEASES

1. Overview

Blendis and Jenkins (1988) noted that the prevalence of serious liver disease and associated mortality is increasing in Europe and North America. The principal causes are chronic alcoholism and viral hepatitis, with deaths mainly from hepatic failure or the more severe complications of cirrhosis such as portal hypertension with ascites, variceal bleeding, intercurrent infections, and hepatic coma. A damaged liver often retains remarkable recuperative power when the injurious agent is removed and adequate nutrition is provided; however, a seriously injured liver suffers impairment of many of its metabolic functions including derangements of nutritional equilibrium. Changes in metabolism of carbohydrate, fat, protein, vitamins, and minerals result from liver injury and from inadequate dietary intake caused by anorexia, nausea and vomiting, fat malabsorption, depressed protein synthesis, and protein–calorie malnutrition (PCM) (Blendis and Jenkins, 1988; Weinsier et al., 1989). Growth failure is a significant problem in children with hepatic disease (Kaufman et al., 1987).

The etiology of hepatic encephalopathy (HE) is probably multifactorial, but its precise pathogenesis is obscure. Zieve (1987) listed 28 metabolic abnormalities that occur in HE. Putative etiologic factors include elevated levels of ammonia, mercaptans, phenols, and short–chain fatty acids in the extracellular fluid and abnormal amino acid profiles, all caused by impaired hepatic function.

Predisposing and precipitating factors include:

- Portal–systemic shunts.
- Hypoxia.
- Electrolyte depletion including Na or K.
- Acid–base imbalances.
- Nitrogen overload.
- Gastrointestinal hemorrhage.
- Drugs such as sedatives, tranquilizers, and narcotics.
- Dehydration and hypovolemia.
- Trauma or surgery.
- Effects of excessive diuresis.
- Infections.
- Shock.
- Additional intercurrent disease.

Zieve (1987) attempted a synthesis of prevailing ideas and hypotheses to explain the etiology of HE including:

- Accumulation of hepatic failure toxins causes neuropathy.
- Excessive CNS accumulation of ammonia, formation and efflux of glutamine, and accumulation of aromatic amino acids.
- Reduced brain glutamate and aspartate.
- Increased serotonin from tryptophan and false neurotransmitters from tyrosine replace dopamine and norepinephrine.
- Synaptic membrane receptor binding is reduced for glutamate and aspartate and increased for GABA and glycine.
- Excess inhibitory neurotransmitter activity further depresses function in toxin–damaged brain neurons.
2. Objectives and rationale for nutritional management

The basic principles of nutritional support in liver diseases and coma are the maintenance of adequate nutrition; enhancement of liver regeneration; and prevention or amelioration of, or recovery from, hepatic encephalopathy (Fischer and Bower, 1981). Liver diseases may impair critical functions such as regulation and metabolism of exogenous and endogenous substrates, protein synthesis, storage and activation of vitamins, and detoxification and excretion of toxic substances. Derangements of these integrated and coordinated regulatory functions result in altered energy expenditure, impaired metabolism of carbohydrates (e.g., glucose intolerance), fats (e.g., abnormal lipoprotein synthesis), proteins (e.g., impaired protein synthesis by the hepatocytes), and vitamin and mineral deficiencies (Jacobs et al., 1984).

While overall metabolism is deranged in hepatic failure (Fischer and Bower, 1981), alterations in nitrogen metabolism appear to be one of the prominent biochemical changes in chronic hepatic failure (Hiyama and Fischer, 1988). Impaired protein metabolism in severe liver disease, especially as it involves conversion of ammonia to urea and deactivation of other neurotoxic metabolites, appears to increase the risk of hepatic encephalopathy. Consequently, a critical nutritional requirement is provision of sufficient protein to offset the accelerated catabolism in liver disease without inducing hepatic coma.

The principal objectives of nutritional management in hepatic disease are to achieve and maintain adequate nutrition, support liver function and hepatocyte regeneration, and prevent, ameliorate, or aid recovery from hepatic coma. Other aspects of dietary management involve fluid and sodium restriction for patients with ascites, correction of electrolyte imbalances and vitamin deficiencies, and provision of alternate nitrogen sources for patients who are unable to tolerate customary dietary proteins.

3. Literature review

Branched-chain amino acids. In most patients with decompensated cirrhosis and hepatic encephalopathy, circulating levels of the BCAA (valine, leucine, isoleucine) are usually decreased, and levels of the aromatic amino acids (AAA) (phenylalanine, tyrosine, tryptophan) and methionine are increased (Maddrey, 1985). This is the basis of one concept of the pathogenesis of hepatic encephalopathy, the false neurotransmitter hypothesis. Accordingly, investigators have studied the possible benefits of administering formulas enriched in BCAA and reduced in AAA to patients with hepatic encephalopathy.

Eriksson and Conn (1989) reviewed the published randomized clinical trials of the use of BCAA in the treatment or prevention of hepatic encephalopathy in cirrhotic patients. In a total of 18 studies, 13 involved acute, chronic, or subclinical hepatic encephalopathy, three concerned the effects of BCAA on nitrogen metabolism, and two applied to treatment of hepatic encephalopathy with branched-chain keto acids. Seven studies involving parenteral administration of BCAA in acute hepatic encephalopathy yielded data suggesting that BCAA therapy was as effective as, but not better than, conventional therapy with lactulose or neomycin.

Four studies examined the effects of orally administered BCAA in patients with chronic HE. Three of the four studies (Eriksson et al., 1982; McGhee et al., 1983; Schafer et al., 1981) were crossover studies whereby the BCAA-enriched diet was not clinically superior to the control diet; in the fourth study (Horst et al., 1984), the mean plasma BCAA/AAA ratio increased significantly. Horst et al. (1984) concluded that oral BCAA supplements appear to promote nitrogen balance to the same extent as that of an equal amount of dietary protein, without precipitation of HE as frequently. However, psychometric, electroencephalograms (EEGs), and biochemical results reflected no significant change in any of the four studies (Eriksson and Conn, 1989).
Two investigations that attempted to determine the effects of orally administered BCAA supplements on subclinical hepatic encephalopathy (latent HE manifested by EEG or psychometric abnormalities, without overt symptoms) did not show this approach was beneficial. Three studies that compared intravenous or oral administration of BCAA with "normal" dietary proteins or conventional amino acids in terms of effects on nitrogen metabolism did not show BCAA to be more effective. Finally, Eriksson and Conn (1989) analyzed the results of two studies of the effects of orally administered α ketoanalogues of BCAA on chronic hepatic encephalopathy. The results of one study suggest that ornithine salts of BCKA are superior to twice as much BCAA in improving encephalopathy, electroencephalograms, and nitrogen balance. The other study revealed no advantage of BCKA supplements when they were compared with placebo capsules in patients with chronic, recurrent hepatic encephalopathy who consumed a low-protein diet and were simultaneously treated with lactulose.

In a meta-analysis of nine reports of randomized clinical trials of parenterally administered BCAA in patients with chronic liver dysfunction and hepatic encephalopathy, Naylor et al. (1989) concluded that available data do not permit an unqualified conclusion in favor of using BCAA solutions and hypertonic glucose as a nutritional support regimen. While the aggregate results suggest that BCAA have a statistically significant and beneficial effect on recovery from hepatic encephalopathy, the effect on mortality is markedly discrepant across trials.

Kanematsu et al. (1988) studied the effects of intravenous infusions of BCAA on prevalence of hepatic encephalopathy in postoperative nonencephalitic cirrhotic patients and concluded that this procedure apparently had no preventive effects on risk of encephalopathy.

Reported results in terms of improving encephalopathy have been disparate and a majority of reports show little evidence to support the use of BCAA in the management of HE.

Jacobs et al. (1984) noted that, although no controlled studies had shown that use of BCAA affected the clinical outcome of patients with cirrhosis and HE, the use of formulas enriched in BCAA had two potential benefits: In combination with other amino acids and hypertonic glucose, BCAA may be used parenterally to prevent or ameliorate encephalopathy and provide nutrition. Oral formulations of BCAA may be beneficial for long-term nutritional support of some cirrhotic patients.

Representative studies performed with commercial medical foods (and parenteral formulas). Because few prospective randomized clinical trials of enteral formulas have been reported, trials of parenterally administered formulas are included with the following because of potential value in formulating and using enteral nutrition products:

- Smith et al., 1982—High-caloric-density, low-calcium, low- to moderate-protein diets were administered enterally to three and parenterally to seven undernourished cirrhotic, ascitic patients for periods of 10 to 60 days: nine subjects showed improved serum albumin levels, creatinine/height, and mid-arm muscle and fat.

- Calvey et al., 1985—Sixty-four patients with acute alcoholic hepatitis received a controlled diet either alone or supplemented with 2000 kcal and 10 g nitrogen, the latter consisting of either 20 g BCAA and 45 g conventional AA or 65 g of conventional protein. Administration was oral, by nasogastric tube, or parenteral. Nutritional and biochemical indices did not differ between supplemental and control groups, and BCAA had no consistent effect on encephalopathy.

- Rossi–Fanelli et al., 1982—Thirty-seven patients with acute hepatic encephalopathy received parenterally either hypertonic dextrose and lactulose or 57 g BCAA in an isocaloric amount of hypertonic dextrose. After two days of treatment, arousal occurred in 70% of patients treated with BCAA versus 49% of the controls, but the difference was statistically insignificant.
• Fiaccadori et al., 1984—Patients with hepatic encephalopathy were divided into three dietary groups: (1) control diet plus lactulose, (2) BCAA-enriched formula plus hypertonic dextrose, and (3) groups (1) and (2) combined. Arousal appeared significantly higher in the BCAA-treated groups. Mortality was zero in group (3), one in group (2), and five in group (1).

• Cerra et al., 1985—In a multicenter trial, 80 patients with hepatic encephalopathy received parenterally, for 4 to 14 days, a BCAA-enriched formula plus hypertonic dextrose (25 kcal/kg per day) or neomycin plus an isocaloric amount of hypertonic dextrose. Rate of arousal was more rapid and nitrogen balance improved in the BCAA-treated group, and the rate of survival was markedly improved in the BCAA-treated group.

• Wahren et al., 1983—In a multicenter trial 50 patients with hepatic cirrhosis and encephalopathy, previously treated conventionally, were parenterally administered BCAAs in 5% glucose or 5% glucose alone (placebo) for five days or until "wake up." No statistically significant differences in rate of arousal were observed; differences in mortality at five days of treatment were not statistically significant. Critics considered that the 70% leucine in the BCAA mixture caused a toxic imbalance of amino acids.

• Marchesini et al., 1990—In a prospective, randomized, multicenter, control trial, cirrhotic patients with chronic portal-systemic encephalopathy, whose treatment regimens included lactulose and a moderately protein-restricted diet, were studied to compare clinical and nutritional effects of dietary supplements of BCAA or casein. For three months, 30 patients (group I) received BCAA supplements (0.24 g/kg bw); 34 patients (group II) were given an equinutrient casein supplement. Group I patients showed improvement in the encephalopathy index and semiquantitative N balance as well as slight improvement in nutritional parameters and liver function tests. Group II patients who did not improve after three months received the BCAA supplements for an additional three months, during which they rapidly improved. The authors concluded that dietary supplementation of oral BCAA is superior to casein supplementation for providing adequate N and for improving the mental state of cirrhotic patients with chronic encephalopathy.

• Weber et al., 1990—In an investigation to determine whether an amino acid solution enriched with BCAA would alter protein catabolic rate and plasma ammonia in cirrhotic patients, Weber et al. (1990) compared the effects on protein turnover and blood ammonia levels of a leucine-enriched amino acid solution with those of a standard amino acid solution in nine stable cirrhotic patients. The BCAA-enriched solution contained 97% more leucine than the standard solution. In six patients, the solutions were administered intravenously for 12 hours daily in separate nine-day periods. In three patients, solutions were infused for 24 hours daily for three days, primarily to study leucine turnover. The BCAA-enriched solution lowered plasma ammonia levels, but did not alter protein synthesis when compared with the standard amino acid solution.

Cabre et al. (1990) reported preliminary results of a PRCT on the effects of total enteral nutrition (TEN) in severely malnourished cirrhotic patients. The TEN group received by continuous enteral infusion, a polymeric diet containing whole protein enriched with BCAA. The control group consumed a standard, low-sodium hospital diet. Serum albumin concentration and Child's score improved in the TEN group as compared with the controls. In-hospital mortality was 12% in the TEN group compared with 47% in the controls. Child's score was not defined, nor is a definition readily available.

Enteric administration of ornithine salts of BCKA was reported to be more effective than BCAA in improving encephalopathy (Herlong et al., 1980). No additional clinical studies on ornithine salts of BCKA in hepatic encephalopathy have been reported.
4. General principles for nutritional management

Based on a general review of the literature, the following recommendations can be made:

- Provide 0.5–0.7 g protein/kg bw per day (about 62–90% of RDA for children) (this maintains nitrogen balance in most patients with liver disease; however, some authorities suggest 1.0 to 1.5 g protein per kg bw per day).

- Supplemental insulin or oral hypoglycemic agents are rarely needed despite some disturbance of glucose tolerance.

- Low–fat diets are not necessary for most patients with liver disease.

- For severe steatorrhea (<10% of patients have steatorrhea), substitution of long–chain triglycerides by MCT may benefit the patient.

- Repletion of deficient vitamins (e.g., B–complex in encephalopathy; fat–soluble vitamins in biliary cirrhosis).

- Restriction of sodium and fluids for ascites and edema.

- Normalization of growth in children with hepatic disorders such as biliary atresia by meticulous attention to providing adequate energy, nitrogen, minerals, and vitamins (particularly fat–soluble) by modern methods of enteral alimentation when necessary (Kaufman et al., 1987).

Stable patients with chronic liver disease generally tolerate 1.0 to 1.5 g dietary protein/kg bw per day (Rombeau et al., 1988). However, in patients with advanced liver failure and impending encephalopathy, protein intake must be modified. Amino acids given parenterally are generally better tolerated than an equivalent amount of protein given enterally. A suggested approach is to limit dietary amino acid intake to 20 to 40 g per day, supplemented by parenterally administered amino acid or BCAA–enriched solution sufficient to normalize plasma amino acid concentrations (Rombeau et al., 1988). Conversion to enteral nutrition should be done as soon as tolerable to the patient. This is based in part on the concept that enteral nutrition helps to preserve the integrity of gut membranes, theoretically preventing bacterial translocation and multiple organ failure in the seriously ill patient (Shils, 1988).

Some patients with minor hepatic insufficiency who are anorexic may be nutritionally maintained by enteral administration of nutritionally adequate formulas that are modestly restricted in protein (e.g., 40 g/L), (Jacobs et al., 1984). Smith et al. (1982) successfully managed ascitic cirrhotic patients by using low–sodium, high–caloric–density, high– (70 g/L) or low–protein (40 g/L) enteral formulas. Nine of ten treated patients showed improvement in serum albumin and other nutrition indices, as well as weight gains following the "phase one" treatment period when ascitic fluid was mobilized and eliminated. Modification or supplementation of nutritionally adequate or incomplete commercial enteral formulas to satisfy metabolic requirements of individual patients is another approach to assure suitability (Martin, 1981). Fixed formula, nutritionally adequate, commercial enteral products are often suitable for patients with decompensated chronic cirrhosis. When adequate calories cannot be provided within the limits of required fluid restriction, high–caloric–density formulas may be used (Jacobs et al., 1984). These nutritionally adequate high–caloric density products are relatively low in sodium and water, contain whole protein of high biologic value, and carbohydrates as complex oligosaccharides, starches, and monosaccharides. Some formulas provide fat as readily absorbed MCT.

The principles of nutritional support embrace normalizing liver function, preventing muscle wasting and encephalopathy, correcting azotemia, and repleting deficiencies of vitamins, minerals, and trace elements. A key objective is to supply enough protein for nitrogen balance without inducing
encephalopathy (Blendis and Jenkins, 1988; Jacobs et al., 1984; Maddrey, 1985). When the patient has a history of protein intolerance or encephalopathy, protein should be restricted initially to 0.5–0.7 g/kg bw per day and incrementally increased to determine tolerance. As a rule, undue protein restriction is unwarranted in view of the availability of effective, nonnutritional, oral treatment (lactulose, neomycin). For example, the common practice of restricting protein intakes to 40 g/d or less may not meet requirements (Blendis and Jenkins, 1988).

Parenteral nutrition has taken precedence in acute, fulminant liver injury because patients are frequently too ill to be fed orally, and they often need specially modified formulas. However, modular medical nutritional products are available for enteral use. Patients with decompensated, chronic cirrhosis may require preparations that restrict fluid and sodium intake such as nutritionally adequate, easily digested, high-caloric-density formulas. Such products are available.

Formulas that provide for the following are considered generally acceptable for nutritional management of cirrhosis, chronic liver failure, and hepatic encephalopathy:

a. **Cirrhosis and hepatic insufficiency without encephalopathy**
   - Normal amount of energy but supplemented if patient is hypermetabolic or undernourished.
   - Normal amount of protein; minimum 0.5 to 0.7 g/kg bw per day in unstressed patients.
   - Low-fat diet for serious steatorrhea with LCT replaced by MCT.
   - Restricted sodium and fluid volume for ascitic patients.
   - RDA amounts of vitamins and minerals supplemented as indicated by laboratory tests.

b. **Cirrhosis and hepatic insufficiency with encephalopathy**
   - Protein restriction to 50 g/d initially; restriction to 10–20 g/d for limited number of days if severely protein-intolerant.
   - BCAA supplements or enteral formulas that contain an amino acid profile designed to normalize plasma amino acids may be beneficial and may allow recovery from encephalopathy and achievement of nitrogen balance, but need further statistical verification of patient outcome efficacy.

c. **Uncomplicated, acute hepatitis**
   - Energy intake to 30–35 kcal/kg bw per day.
   - Protein intake 1 g/kg bw per day.

5. **Studies that are needed on enteral nutrition in liver disease and hepatic encephalopathy**
   - Basic data on the energy and macro- and micronutrient requirements of representative strata of patients with cirrhosis, hepatic insufficiency, and hepatic encephalopathy.
• Investigations to determine whether changing the nutritional status of patients changes the clinical outcome in liver disease.

• Controlled studies comparing BCAA-supplemented formulas with standard products containing equivalent amounts of nitrogen and otherwise similar components to provide definitive information on whether there is a significant advantage for the BCAA-supplemented formulas. Such studies should be prospective, randomized, stratified, and carefully controlled, and, where possible, should include patients receiving standard therapy for HE as one of the control groups.

• Studies of the effects of nutritional support on clinical outcome in noncirrhotic liver diseases, such as severe, acute viral hepatitis and chronic hepatitis.

• Additional studies on the effects of medical foods on drug absorption, metabolism and clearance, interference with which can lead to major problems in ICU.

• Data are inadequate on the effects of drug administration on nutrient absorption and metabolism.

• Investigations of the effects on suitability of enteral formulas containing different types of fats, such as MCT and structured lipids, as well as various types of carbohydrates.

• Studies to differentiate malnutrition caused by inanition versus the disease cirrhosis itself and possible nutritional methods of prevention or amelioration.

• Data to differentiate the effects of medical foods when delivered as continuous or bolus infusions.

• Although not yet proved, formulas containing vegetable protein instead of animal protein may be beneficial (reviewed by Blendis and Jenkins, 1988).

• Whether BCAA dietary supplements may be advantageous compared with standard amino acid sources for hepatocyte regeneration and restoration of lean body mass.

**Suggested variables to consider in planning clinical trials include the following:**

The appropriateness of the following variables will depend in part on other factors such as nutritional status, duration and severity of illness, presence of intercurrent disease, and immunocompetence.

a. **Outcome variables**

• Acute and chronic mortality.

• Length of hospital stay.

• Readmission rate.

• Quality of life.

• Encephalopathy.

• Ascites in some settings.

• Infection rate.

• Variceal bleeding.
b. **Monitored variables**
   - Body composition changes.
   - Plasma amino acids.
   - Liver function tests (classic enzymes, proteins, in vivo drug detoxification).
   - Effects of deficiencies or excesses of nutrients and electrolytes.

c. **Medical foods—specific variables related to special ingredients**
   - Examples — glutamine and gut physiology; arginine and immunocompetence.

6. **Conclusions**

For a large proportion of patients with decompensated cirrhosis and encephalopathy, standard nutritionally adequate commercial enteral products alone or with the addition of modular nutrient sources are suitable. The use of BCAA supplements in protein-intolerant patients with severe, diffuse liver disease to improve nitrogen balance and prevent encephalopathy remains controversial. Low-sodium, high-caloric density, high- or moderate-protein nutrition products are useful in ascitic cirrhosis. Similarly, high-caloric density, high- or moderate-protein nutritionals may be used in uncomplicated active or chronic hepatitis. Because of the protein calorie malnutrition associated with liver disease, management of energy, protein, fluid, vitamin, and mineral intake must be individualized.

C. **PULMONARY DISEASES**

It is not the purpose of this study to reiterate a comprehensive inventory of pulmonary diseases which are amply described in standard texts. Instead, the main focus is on a selection of respiratory disorders that illustrate the scientific rationale for and principles of nutritional support in patients with chronic respiratory diseases.

Diseases and disorders of the respiratory system that are of interest in this review include chronic bronchitis, chronic emphysema, bronchiectasis, bronchopulmonary dysplasia (BPD), chronic obstructive pulmonary disease (COPD), cystic fibrosis, sleep apnea, and the adult respiratory distress syndrome (ARDS). Acute respiratory failure is a clinical emergency whose management does not require enteral nutritional support. In children, cardiac arrest is most frequently caused by acute respiratory failure. However, patients who survive acute respiratory failure may enter a somewhat prolonged convalescence during which special nutrition support may be beneficial. Atrophy of the respiratory muscles is often associated with malnutrition and hypermetabolic stress states.

1. **Overview**

**Central control of respiration.** The effects of impairment of ventilatory drive vary according to the degree and duration of dysfunction, with respiratory failure as the extreme end point. Patients with COPD, ARDS, and sleep apnea may be particularly sensitive to depression of central respiratory drive. Sleep apnea accompanies other diseases such as renal failure, cardiac failure, and COPD. It is an example of a reduced CNS stimulation of respiration and can be a problem in neonates as well as in children and adults.
On the other hand, patients with pulmonary disease often have excessive central ventilatory drive compared with the capacity of the respiratory muscles and lung to respond. Thus, increasing ventilatory drive is undesirable in pulmonary disease patients who have excessive ventilatory drive to start with.

**Respiratory muscles.** The CNS output translates into diaphragm function, a muscular system. When there is protein malnutrition, the respiratory muscles atrophy in parallel with other skeletal muscles, and, while not generally recognized, in preexisting emphysema the respiratory muscle atrophy probably exceeds that of the other skeletal muscles. The associated loss of strength and increased fatigability of the respiratory muscles impede respiratory efficiency and increase risk of respiratory failure.

**Lung.** Respiratory failure and COPD are serious disorders whose clinical management may benefit from nutritional support. COPD is characterized by obstruction of pulmonary air flow and respiratory insufficiency. Chronic bronchitis and pulmonary emphysema, two separate diseases, are prominent features of COPD. Respectively, they exhibit excess secretion of mucus in the bronchi and enlargement and degeneration of the air spaces distal to the terminal bronchioles (Mitchell and Petty, 1982). Patients with chronic bronchitis are often overweight and retain excessive amounts of CO₂. Emphysematous patients tend to be underweight and hypoxemic. Bronchiectasis and asthma may also be components of COPD (Openbrier et al., 1983). Manifestations may include respiratory muscle fatigue, hypoventilation, sleep apnea, carbon dioxide retention, and oxygen depletion. As a result of the associated constriction of the pulmonary arteries, hypoxemia can lead to pulmonary artery hypertension and episodes of cor pulmonale (dysfunction of the right side of the heart). Patients with COPD are at high risk of developing respiratory failure (Driver et al., 1982).

Bronchopulmonary dysplasia is a chronic, but potentially reversible, lung disease of prematurely born infants who required mechanical ventilation and increased inspired oxygen concentration in the first weeks of life. Initially, the lungs show atelectasis, edema, and hyaline membranes with persistent consolidation and development of cystic areas. Growth failure in infants with BPD is a major problem (Fitzhardinge et al., 1976; Markstad and Fitzhardinge 1981; Meisels et al., 1986; Ruiz et al., 1981; Vohr et al., 1982; Yu et al., 1988). The growth failure is secondary to an increased metabolic requirement (Kurzner et al., 1988; Yeh et al., 1989).

Malnutrition is a common, pervading factor in chronic debilitating diseases, sepsis, and severe injuries with protracted convalescence. The associated muscle wasting includes the muscles of respiration and may be a complicating factor in the clinical outcome because of its adverse effects on respiratory muscle function, energy expenditure in breathing, hypoxic ventilatory response, resistance to infection, and lung structure, biochemistry, and metabolism (Arora and Rochester, 1982; Askanazi et al., 1982; Deitel et al., 1983a,b; Doekel et al., 1976; Green et al., 1977; James, 1972; Law et al., 1973; Lewis et al., 1986; Raeburn, 1977). Growth failure is a significant problem in children with pulmonary diseases. Evidence from animal studies suggests that disturbances of the lung surfactant system may prove to be a significant contributor to respiratory dysfunction in malnourished subjects.

2. **Objectives and rationale for nutritional management**

There is ample evidence that poor nutritional status adversely affects the functions of the respiratory system and that malnutrition and weight loss are associated with increased risk of respiratory failure and a poor prognosis in patients with COPD (Askanazi et al., 1982; Openbrier et al., 1983; Rochester and Esau, 1984; Vandenbergh et al., 1967). However, no study shows that preventing weight loss in lung disease improves life expectancy (Vandenbergh et al., 1967), but many reports show that two to three weeks of refeeding improves muscle strength, endurance, and exercise tolerance. An exception with regard to nutrition and life expectancy may be in patients with cystic fibrosis, in which progressive pulmonary disease is the major cause of mortality (see Literature Review, p.33).
Avoidance of excess carbon dioxide production by limiting the proportion of dietary carbohydrates and matching total calories to meet the patient's energy needs is one objective of nutritional management. Another important objective is prevention or correction of muscle wasting (including the respiratory muscles) associated with malnutrition. In general, caloric expenditure in respiratory diseases is 20–30% above predicted values (Goldstein et al., 1987).

The objectives of nutritional support in patients with chronic respiratory diseases include:

- Provision of sufficient energy and protein to restore and maintain lean body mass.
- Avoidance of excess carbon dioxide production by limiting total energy and carbohydrate intakes and increasing the proportion of dietary fats when clinically relevant.
- Avoidance of stimulation of excess ventilatory drive by limiting dietary protein and total energy intake to estimated metabolic requirements.
- Maintenance of fluid and electrolyte balance.
- Provision of essential micronutrients including adequate phosphorus.
- Maximization of exercise tolerance in ambulatory patients.
- Normalization of growth in children.

3. Literature review

Many authors have noted that the work load resulting from high carbon dioxide production may cause respiratory distress in spontaneously breathing patients with compromised pulmonary function (Askanazi et al., 1981; Covelli et al., 1981; Gieseke et al., 1977; Saltzman and Salzano, 1971). Moreover, high-carbohydrate loads reportedly can precipitate respiratory failure (Askanazi et al., 1980, 1981; Covelli et al., 1981), and impair ability to wean patients from mechanical ventilation (Bartlett et al., 1984; Garfinkel et al., 1983). Thus, it is possible that specialized high-fat, low-carbohydrate enteral nutrition products for pulmonary patients who are unable to nourish themselves orally may be advantageous in certain circumstances (Al-Saady et al., 1989; Deitel et al., 1983).

Data from studies of cystic fibrosis in Boston and Toronto showed that male patients in the Toronto cohort weighed more than those in Boston. Median age of survival in Boston was 21 years; in Toronto, 30 years (Corey et al., 1988). Better nutrition in the Toronto patients was implicated as a favorable factor in clinical outcome.

Using lipids to reduce lung inflammation in chronic bronchitis, for example, is hypothetically appropriate based on emerging evidence from animal studies (Archer et al., 1989; Askanazi et al., 1987; Skeie et al., 1987, 1988). In contrast, most emphysematous patients have little residual lung inflammation but tend to be underweight or malnourished. They may benefit by refeeding and special nutritional support such as supplemental BCAA to improve diaphragm function (see Studies that are needed on enteral feeding of patients with pulmonary disease and disorders, p.36).

A number of investigators have reported the benefits of adequate nutritional support in weaning patients from mechanical ventilation or for maintenance of long-term, ventilator-dependent patients (Bassili and Deitel, 1981; Deitel et al., 1983a,b; Larca and Greenbaum, 1982; Leong et al., 1983).
Representative studies performed with commercial enteral products

- Al-Saady et al., 1989—In a prospective, double-blind trial, adult patients who required artificial ventilation for a variety of clinical disorders and who were receiving enteral nutrition, were fed either a high-fat, low-carbohydrate product (Pulmocare®) or a standard enteral formula (Ensure Plus®). In the high-fat group, PaCO₂ decreased 16% but increased 4% in the standard regimen group. Average time spent on the ventilator was 62 hours less in the high-fat than in the standard formula group.

- Angelillo et al., 1985—In a randomized, double-blind study of dietary effects on metabolic and ventilatory values, patients with COPD and hypercapnia were fed low-, moderate-, and high-carbohydrate diets for 15 days. Patients on the low-carbohydrate diet (28% carbohydrate calories and 55% fat calories) showed lower CO₂ production, respiratory quotient, and arterial PCO₂, as well as substantial improvement in forced vital capacity and forced expiratory volume.

- Goldstein et al., 1987—In a prospective, randomized study to explore the mechanisms of weight loss in chronic lung disease, Goldstein and colleagues fed 10 patients with COPD and weight loss for one week, a hypercaloric carbohydrate based (CB, 53% of calories) or a hypercaloric fat-based (FB, 55% of calories) diet either enterally or parenterally. The alternate diet was administered the second week. Measurements included resting energy expenditure (REE). Study results suggested that malnourished patients with COPD have elevated REE and enhanced thermic response to nutrients compared with the malnourished controls who had no lung disease. The authors concluded that increased diet-induced thermogenesis may contribute to weight loss in patients with COPD.

- Goldstein et al., 1989—In a prospective, randomized study of the effects of varying the non-protein calories during hypercaloric feeding and exercise, Goldstein and co-workers fed eight ambulatory, malnourished COPD patients with emphysema (EMPH) and eight ambulatory malnourished patients without lung disease (MALN) a carbohydrate-based (CB, 53% of calories) or a fat-based (FB, 55% of calories) diet for one week. The alternate diet was given the second week. Measurements made during exercise by supine bicycle ergometry at three different intensities indicated a 12–15% greater 0₂ consumption, a lower respiratory quotient, and a larger 0₂ debt in the EMPH group compared with the MALN group. Resting ventilation was higher with the CB than with the FB regimen. Ventilatory response was exaggerated in the EMPH group during the CB regimen.

4. General principles for nutritional management

Formulas that provide for the following factors are considered to be generally acceptable for nutritional management in some pulmonary diseases and disorders (Askanazi et al., 1982):

- In the absence of contraindications to relatively high protein intakes, sufficient energy and protein to restore (energy intake 1.4–1.6 times estimated expenditure plus 1.6–2.5 g protein/kg bw) and maintain (energy intake 1.0–1.2 times predicted plus 1.2–1.9 g protein/kg bw) lean body mass (Askanazi et al., 1982; Bell and Shronts, 1987; Rombeau et al., 1988; Schwartz, 1989; Wilson et al., 1985).

- For patients not on mechanical ventilation, limitation of CO₂ production by reducing proportion of carbohydrates and increasing fat.

- Facilitation of matching total energy and protein intake to metabolic needs to avoid stimulating excess ventilatory drive.
Facilitation of maintaining fluid and electrolyte balance.

Provision of essential nutrients including adequate phosphate.

Maximization of exercise tolerance in ambulatory patients.

It is suggested that up to 55% of total calories be from fats; however, the quantity and composition of the lipids should conform to each patient's needs. Typical diets are based on vegetable oils and are high in polyunsaturated fatty acids.

Because aggressive nutritional intervention can overload a compromised cardiopulmonary system in spontaneously breathing, malnourished patients with COPD, some authors recommend moderation in nutritional management (Askanazi et al., 1982; Heymsfield et al., 1984, 1986). Maintenance of lean body mass requires an energy intake of 1.0–1.2 times energy expenditure and 1.2–1.9 g protein/kg bw. To restore lean body mass, energy intake should be 1.4–1.6 times estimated energy expenditure and 1.6–2.5 g protein/kg bw (Wilson et al., 1985).

In general, hypercaloric diets are inappropriate for patients with chronic bronchitis, because most of them are overweight and such diets tend to defeat the objective of reducing blood PCO₂ tension. Some studies show that feeding a high-fat product in hypocaloric amounts (for example, isocalorically with a regular diet) results in reduced PCO₂ tension in chronic bronchitis (Angelillo et al., 1985). Conversely, emphysematous patients are usually underweight and should be fed accordingly.

Enteral nutrition is recommended for ventilator–dependent patients with functional gastrointestinal tracts (Bassili and Deitel, 1981). National estimates suggest that about 22% of patients who are on mechanical ventilation are tube–fed (Narem, 1990). Because aspiration of stomach contents may be life threatening in pulmonary disease, and because patients with compromised respiration do not tolerate customary volumes of food in the stomach, tube feedings should be delivered into the small bowel at rates set to prevent undesirable side effects.

Because CNS respiratory drive is insufficient in sleep apnea, a therapeutic objective is to increase drive. Nutrients that increase CNS control of respiration biologically are proteins and, more specifically, the BCAA. Although controlled clinical trials in support of this relationship have not been reported, clinical observations and the basic biology of CNS control of respiration suggest it is valid (see 5, Studies that are needed on enteral feeding of patients with pulmonary disease and disorders, p.36). Conversely, increasing ventilatory drive is undesirable in patients with pulmonary disease whose ventilatory drive is excessive to start with. In such cases, feeding a high–protein diet and amino acid supplements tends to increase dyspnea (Askanazi et al., 1982).

Although Wilson et al. (1985) agreed that the optimal proportions of protein, carbohydrate, and fat in diets for patients with chronic lung disease were not firmly established, a wide range of commercial enteric formulas were suitable, "provided there is adequate protein as the nitrogen source, triglycerides and carbohydrates as the energy sources, and sufficient electrolytes, trace elements, and vitamins to satisfy nutritional requirements." In their experience, patients with emphysema and severe air–flow obstruction showed no adverse effects from diets containing 50% carbohydrate.

Beyond the issue of how much carbohydrate and fat is considered ideal, hypercaloric carbohydrate feeding is clearly undesirable. Hence, 100% carbohydrate as calories is a different issue if you are giving 1 X resting energy expenditure (REE) compared with 3 X REE. CO₂ production can increase 75%, which creates problems for respiratory patients. Thus, with eucaloric feeding, there is little difference between carbohydrate vs. fat regimens, but with hypercaloric feeding, carbohydrate–based diets are undesirable (Bartlett et al., 1984; Garfinkel et al., 1983).
5. Studies that are needed on enteral feeding of patients with pulmonary diseases and disorders

In general, for clinical trials of enteral products, investigators should attempt to separate well-nourished patients from those who are malnourished and from patients with obstructive versus restrictive pulmonary disease in selecting their treatment groups.

- The effects of BCAA on ventilatory drive and diaphragm function.
- Compatibility of diet formulas for hypermetabolic stress with pulmonary disease patients in terms of amounts of protein.
- The influence of the amount and composition of dietary protein on the respiratory muscles.
- The influence of the amount of fat and distribution of Ω-3 and Ω-6 fats compared with linoleic acid alone on lung surfactant, lung parenchyma, and the air–gas interface.
- The influence of the amount and type of dietary fat on lung inflammation and excess mucus secretion. Diets relatively high in fat may be useful for management of lung inflammation with excess mucus secretion.
- The clinical significance of impairment of the lung surfactant system has not been thoroughly explored. However, it is highly responsive to nutrition because it disappears in starvation and reappears with refeeding. In trauma, one of the causes of lung dysfunction is impaired surfactant, and lipids allegedly assist in helping the lung regenerate surfactant (Aeberhard et al., 1986; Bahrami et al., 1987). Does surfactant reappear more rapidly with lipid feeding than with glucose? Additional research is needed to establish the clinical significance of derangements of lung surfactant in human diseases and to determine whether special dietary intervention may be appropriate.
- Certain biologic characteristics of the diaphragm suggest nutritional approaches that may be exploited in clinical settings. A high capacity of the diaphragm to oxidize BCAA has been demonstrated in rats (Goldberg and Odessy, 1972), but not yet in the human diaphragm (Skeie et al., 1990). The diaphragm also has high ability to oxidize ketones for energy. Although these properties would not necessarily affect diaphragm muscle strength, they would probably aid in responding to fatigue (Askanazi et al., 1982). These biologic relationships also warrant further investigation.
- Studies to determine whether prevention of malnutrition affects morbidity and mortality in chronic pulmonary diseases.

6. Conclusions

In summary, for a majority of patients with chronic lung disease, the key issue seems to be adequate nutritional support. Specially designed enteral formulas are not needed. In hypercarbic patients, carbohydrate–fat ratios may become an important issue. In general, hypercaloric diets should be avoided in this disease group.

Additional research including animal studies and clinical trials should be directed toward elucidating the effects of amino acids on ventilatory drive, amino acids and lipid sources on diaphragm function, and different lipid sources on the pulmonary parenchyma.
D. HYPERMETABOLIC STRESS STATES

1. Overview

Major surgery, severe trauma, burns, certain debilitating diseases such as inflammatory bowel disease and peritonitis, and sepsis are associated with a varying metabolic response that may lead to hypermetabolism and malnutrition (Cerra, 1987; Shronts and Fish, 1989). Injured tissue may elicit a metabolic stress response that, in severe tissue injury, progresses from local to systemic. The stress response is mediated by numerous factors including bioactive cytokines released in part from activated cells which can affect organ function, endocrine status, CNS activation, and autonomic tone (Cerra, 1987). Beisel (1984) provides a review of the metabolic effects of infection that are regulated by endogenous mediators, glucoregulatory, thyroid, pituitary, adrenocorticoid hormones, the central nervous system, acute-phase glycoproteins, and other factors.

A review by Goldstein and Elwyn (1989) states that the increased levels of catecholamines, cortisol, and glucagon are largely responsible for the metabolic changes which occur following metabolic stress. Baro- and pain receptors are involved in signaling the afferent nervous system. Following the "ebb phase" of the first 24-48 hours after injury, which includes circulatory insufficiency, the "flow phase" of hypermetabolism occurs, with an increase in energy expenditure, high nitrogen excretion, total body protein catabolism, but a net increase in hepatic protein synthesis (Cuthbertson, 1930, 1942; Kinney et al., 1970; Shronts and Fish, 1989; Wilmore, 1974). The accompanying endocrine changes mediate an increased substrate flow but poor utilization of substrates. Whether these metabolic responses are beneficial or detrimental has not been established.

Examples of the metabolic changes associated with the hypermetabolic stress response include (Bassili and Deitel, 1981; Dahn et al., 1979; Kinney et al., 1970; Long et al., 1979; Shronts and Fish, 1989; Souba and Wilmore, 1988; Wilmore, 1974):

- Major increase in energy needs.
- Increased serum levels of glucocorticoids, catecholamines, glucagon and growth hormone.
- Serum insulin low in ebb phase, normal or elevated in flow phase.
- High rate of muscle protein catabolism.
- Increased ureagenesis.
- Increased gluconeogenesis from amino acids derived from muscle protein, as well as other precursors.
- Negative nitrogen balance.
- Increased mobilization of fat stores.
- Absence of ketonemia.
- Increased insulin resistance.
- Glucose intolerance and hyperglycemia.
- Anorexia.
2. Objectives and rationale for nutritional management

Data on the biochemical and pathophysiologic aspects of hypermetabolic stress states are abundant, but there are considerably fewer data concerning possible beneficial effects of various enteral diets in these conditions.

The main objectives of nutritional support are to achieve nitrogen balance throughout the acute and recovery phases of stress so as to prevent or correct malnutrition and its associated adverse side effects. Most injured or septic patients need 1.2 to 1.5 times their calculated basal energy expenditure, but in extensive injuries such as burns involving >40% of body surface, caloric requirements range up to 200% of basal expenditure. However, injured or septic patients should not be given calories in excess of their needs (Weinsier et al., 1989). Provision of 14 to 20% of calories as protein can preserve nitrogen balance in burn patients (Dominioni et al., 1985).

The nutritional goals for supporting hypermetabolic, stressed patients are to provide all essential nutrients in a form that can be utilized by the patient (Homsy and Blackburn, 1983). Many factors, including body size, age, gender, and disease state, influence the need for and extent of nutritional support. Weight gain should not be a major priority in critically ill patients. Complications of nutrient delivery are minimized and nutrient metabolism is generally optimized if these patients receive only the amount of energy necessary for weight maintenance throughout a complex and complicated clinical course. This quantity of energy rarely exceeds 2500 kcal per day in critically ill patients.

Protein requirements for such patients are increased when compared with those of normal individuals. Critically ill patients may need 1.5 to 2.0 g protein per kg bw per day. The ratio between nitrogen and caloric intake is important for optimal nitrogen utilization. The current trend in nutritional care of the critically ill is to provide nitrogen-to-calorie ratios of 1:150 and 1:100. The nitrogen-to-calorie ratio is 1:150 for most formulas prepared for such patients. Contraindications to this increased quantity of protein are renal failure (BUN > 40 mg/dl) and hepatic encephalopathy.

The relative concentrations of carbohydrate and fat have not been well studied in critically ill clinical practice. Currently, clinicians provide the following concentrations: carbohydrate 70 to 80%, and fat 20 to 30% of nonprotein calories.

Defined formulas containing a proportion of nitrogen as BCAA reportedly are advantageous in severe, persistent hypermetabolic stress. Most studies of the use of BCAA in hypermetabolic stress have been in patients receiving parenteral nutrition. Parenteral studies are included here for two reasons: first, while not directly comparable to enteral studies, they nevertheless illustrate important concepts and principles of clinical nutrition involving medical foods, and second, the number of reports of enteral studies is very limited.

3. Literature review

Use of BCAA for nitrogen balance. Reports of three investigations of parenteral use of BCAA-enriched formulas in metabolically stressed patients noted improved nitrogen retention and hepatic protein synthesis and decreased protein degradation (Bower et al., 1986; Cerra et al., 1983, 1984). These were all PRCT that compared the influence of BCAA with standard nitrogen sources on nitrogen retention in hypermetabolic, stressed patients, with or without sepsis. Cerra et al. (1983) suggested 0.5 g BCAA/kg bw per day as the minimal effective dose, but preferred 0.8 g/kg bw per day for significant improvement in nitrogen retention. In addition to improved nitrogen retention, patients who received BCAA-enriched formula showed elevated lymphocyte counts, improved plasma transferrin levels, and in 60% of BCAA-treated patients, reversal of anergy to recall skin test antigens.
In reporting results of a workshop on BCAA in stress and injury, Brennan et al. (1986) concluded, in part, that while some positive results in nitrogen metabolism had been reported when BCAA-enriched solutions were given to severely ill patients, a major effect on clinical outcome had not been demonstrated.

Kuhl et al. (1990) provided parenteral nutrition support to 20 injured patients in a prospective, randomized study of the effects on visceral proteins of standard versus BCAA-enriched amino acid supplements in the infusate. Results in terms of the measured parameters showed no significant differences between the standard and the BCAA-enriched amino acids when used as part of the parenteral nutrition of these injured patients.

A study of enteral nutritional support of critically ill patients, employing BCAA-enriched formulas showed improvements in nitrogen retention, visceral protein mass, and survival indices such as serum transferrin and peripheral lymphocyte counts compared with a standard crystalline amino acid commercial formula (Cerra et al., 1985). However, another investigation of the effects of BCAA-enriched enteral nutritional support of severely stressed patients reported no advantages of a BCAA-enriched formula compared with a conventional egg protein formulation (Yu et al., 1988).

Over a study period of seven days, von Meyenfeldt et al. (1990) investigated the effects of BCAA-enriched TPN on N balance, 3-methylhistidine (3MHD) excretion, morbidity, and mortality in 131 septic, traumatized patients. Fifty-two patients (group I) received a standard TPN solution and 49 (group II) a BCAA-enriched solution. Total energy, nitrogen, and percent fat calories were equivalent in both groups. Group II patients received 0.56 g BCAA/kg bw; group I, 0.18 g BCAA/kg bw. There were no significant differences between the groups for N balance, 3MHD excretion, morbidity scores, and stress–related or sepsis–related mortality.

**Intact protein, small peptides, and free amino acids.** Enteral formulas may contain protein as intact protein, peptides, or free amino acids. Prior to absorption, intact protein must be hydrolyzed to peptides/free amino acids. Di- and tripeptides may be directly absorbed by the enterocyte. Larger peptides are hydrolyzed by brush border enzymes prior to absorption. Single amino acids are absorbed by several mechanisms. Small bowel perfusion studies of normal adult volunteers have demonstrated increased absorption of di- and tripeptides compared with single amino acids under certain situations (Matthews, 1977; Silk et al., 1980). However, Hegarty et al. (1982) concluded that the putative advantage of peptides transport over that of free amino acids is doubtful.

A recent study in normal adult volunteers showed that, in the presence of fat and carbohydrate, nitrogen uptake was greater from a free amino acid source than from a short-chain length casein hydrolysate (Raimundo et al., 1989). Significantly slower absorption has been reported for peptides of predominantly chain length 4–5 than for chain length 2–3 (Grimble et al., 1987). In summary, there is a lack of data from PRCTs on the suitability and effectiveness of enteral products containing different nitrogen sources such as intact protein, oligopeptides, protein hydrolysates, and free amino acids (Shils, 1988).

**Glutamine.** Investigators are seeking ways to intervene nutritionally in patients with failure of the intestinal barrier (Rolandelli et al., 1990). Glutamine, a neutral amino acid, is a major source of respiratory fuel for the intestine and has been shown, mainly in animal studies, to promote intestinal mucosal integrity (Grant and Snyder, 1988; Souba et al., 1985). It promoted healing of radiation-induced lesions of the small bowel (Klimberg et al., 1990), reduced bacterial translocation from the gut and loss of IgA–producing intestinal cells in experimental enteritis (Alverdy, 1990; Romeau, 1990), and prevented pancreatic atrophy and fatty liver during elemental feeding (Felton et al., 1990). When added to parenteral solutions used as the sole source of nourishment in rats, glutamine was associated with increased jejunal mucosal weight, DNA content, and villus height compared with controls receiving solutions not enriched with glutamine (Hwang et al., 1986; O'Dwyer et al., 1989). Similar results have been reported in animals fed enterally with glutamine–supplemented diets (Fox et al., 1988; Salloum et al., 1989).
A recent review of the biological and nutritional aspects of glutamine includes brief descriptions of its possible roles in the gastrointestinal tract, skeletal muscle, kidney, liver, and immunologic cells (Lacey and Wilmore, 1990).

Glutamine infusion reportedly restores the marked fall in muscle glutamine that is associated with injury and possibly improves protein balance (Brown et al., 1990; Hammarqvist et al., 1989; Stehle et al., 1989; Vinnars et al., 1990). Increases in the free glutamine N pool apparently account for a substantial part of changes in N balance. Furthermore, a considerable portion of the negative N balance associated with injury may result from changes in the glutamine pool (Askanazi et al., 1980; Wernerman et al., 1990).

In an editorial review Walser (1991) addressed the relationship between changes in tissue glutamine concentrations and nitrogen balance. For example, with no accompanying changes in protein or amino acid stores, a 50% decrease in the free glutamine body pool represents a negative N balance of 6 g in a 70 kg subject. However, correction of a 50% depletion of the glutamine pool, with no change in protein stores, would amount to a positive N balance of 6 g.

In view of the foregoing as well as other available evidence, it is likely that a substantial portion of the negative N balance of trauma (or associated sepsis) and the positive N balance from infusion of glutamine represents nonprotein N balance. Correction may be made by use of the formula: change in glutamine pool = change in glutamine concentration expressed as a percent of normal glutamine concentration, times 170 mg N, times body weight (kg). The value 170 mg/kg may need some modification as more data become available on the response of visceral glutamine levels to injury (Walser, 1991).

Arginine is considered a nonessential amino acid in human beings because the urea cycle provides maintenance levels of arginine. However, in the traumatized, stressed patient, endogenous synthesis of arginine may be insufficient for optimal tissue repair and positive nitrogen balance.

Peripheral blood mononuclear cells of healthy human volunteers who consumed daily dietary supplements of 30 g arginine hydrochloride for 7 days showed significant increases in mitogenic blastogenesis. Arginine supplementation increased the average response to concanavalin A by 297% and 375% and to phytohemagglutinin by 246% and 259% respectively in autologous and AB serum (Barbul et al., 1981). In a prospective, randomized trial, cancer patients were fed enteral formula supplemented with L-arginine or L-glycine for 7 days postoperatively to investigate effects on immune function and nitrogen balance (Daly et al., 1988). Supplemental arginine enhanced the T-lymphocyte response to concanavalin A and phytohemagglutinin (PHA) and increased mean CD4 phenotype (% T-cells) compared with values for the glycine-supplemented control group. Positive mean nitrogen balance occurred between postoperative days 5 and 7 only in the arginine group. Similar results were reported for in vitro immune responses and nitrogen balance in postsurgical cancer patients who were tube-fed a new enteral formula containing added arginine, RNA, structured lipids and menhaden oil compared with control patients given a standard enteral formula (Lieberman et al., 1990). In animal studies, dietary supplements of arginine and glycine were associated with a 60–70% increase in post-injury nitrogen retention (Sitren and Fisher, 1977) and improved indices of immune system function (Barbul et al., 1983; Saito et al., 1987).

A PRCT was conducted on the effects on immunocompetence of a specially designed, nutritionally complete enteral nutrition product in malnourished, hypermetabolic surgical patients in intensive care (Cerra et al., 1990). Eleven patients received the experimental formula, which contained added RNA, fish oils, arginine, minimum linoleic acid and increased zinc, vitamins A, E, and C, folate, riboflavin, niacin, and thiamin. Nine control patients received a standard, nutritionally complete commercial enteral formula. Compared with controls, patients who received the experimental product showed improved proliferative responses of peripheral blood lymphocytes following in vitro stimulation with concanavalin A, phytohemagglutinin, and tetanus antigen.
Validation of the clinical suitability of enteral diets enriched with arginine and other putative immune-stimulating substances in hypermetabolic stressed patients is needed. Kulkarni et al. (1986) reported that mice fed a nucleotide-free diet demonstrated suppressed cellular immunity and decreased resistance to bacteriologic challenge compared with mice fed diets supplemented with RNA or uracil. Using a different approach, Koruda et al. (1990) studied the effects of short-chain fatty acids (SCFA) on the mucosa of the small bowel in rats. Intravenous as well as intracolonic infusions of SCFAs (acetate, propionate, and butyrate) were effective in inhibiting small bowel mucosal atrophy commonly observed in animals maintained solely with TPN. Some experimental evidence suggests that ω-3 and ω-6 fatty acids such as linolenic and linoleic acids may impair certain aspects of immunocompetence (Alexander et al., 1986; Gottschlich et al., 1990a; Kelley et al., 1990; Saito et al., 1985; Virella et al., 1990). In a standardized burned guinea pig model, enteral diets containing 10% of energy as fish oil (18% eicosapentaenoic acid) (EPA) resulted in better cell-mediated immune responses, and opsonic indices and lower serum C3 levels than diets containing safflower oil (74% linoleic acid) or diets containing pure linoleic acid.

In healthy human volunteers, a diet containing α-linolenic acid (C18:3n-3) as flax seed oil significantly depressed the proliferation of lymphocytes cultured with PHA. It also suppressed proliferation of lymphocytes cultured with concanavalin A, and the degree of induration in response to intradermal injection of antigens, but these results were not statistically significant (Kelley et al., 1990). A human volunteer who ingested 1.4 g/d of EPA in the form of a fish oil extract demonstrated depression of all parameters of humoral immunity after three weeks of fish oil supplementation, while parameters of neutrophil function were obviously depressed after six weeks of supplementation (Virella et al., 1990). Six weeks after fish oil supplementation was stopped, serum IgG levels were normal, but serum IgM remained below pretrial levels.

Mucosal barrier. With further reference to the gut mucosal barrier, components of the nonspecific layer of the barrier include mucus, pancreatic enzymes, and gastric acid; the specific immunologic layer contains gut-associated lymphoid tissue, IgA, and IgM. The gut mucosal barrier helps to contain within the gut lumen, bacteria, endotoxins, and antigenic macromolecules (Rolandelli et al., 1990). Each component of the barrier is believed to act separately to prevent antigenic invasion of the gut mucosa, induction of local inflammation, and translocation of gut bacteria to the portal or lymphatic circulation (Gottschlich et al., 1990a).

In animal studies, absence of food and intestinal fuels in the gut, as well as experimental introduction of toxins, has led to atrophy and disruption of the gut immune barrier (Deitch et al., 1987), resulting in conditions that favor translocation of gut bacteria and endotoxins to the portal and lymphatic circulations (Alverdy et al., 1985, 1988; Berg, 1981, 1983; Maejima et al., 1984; Morehouse et al., 1986; Steffen et al., 1988). Observations in human patients suggesting that a similar chain of events may occur when the gut mucosal barrier is impaired include patients with multiple organ failure syndrome (Marshall et al., 1988), cancer patients treated with chemotherapy (Bodey, 1981), and burn patients (Jarrett et al., 1978). Moore et al. (1989) reported reduced septic morbidity in abdominal trauma patients fed enterally with a commercial medical food compared with a similar group of trauma patients fed parenterally. Although available human data are insufficient to establish whether the atrophic changes in the gut that are associated with lack of enteral nutrition lead to clinically significant translocation of gut bacteria, endotoxins, and antigenic macromolecules, these considerations seem to justify the use of at least partial enteral nutrition as one means of maintaining the gut mucosa or reducing such complications.

Representative studies performed with commercial medical foods.

- Cerra et al., 1989—In a study designed to evaluate the effects of three commercial enteral products, hypermetabolic surgical patients were fed via nasogastric tube, formulas with three different nonprotein calorie:nitrogen (NPC:N) ratios: 97:1, 125:1, or 149:1. Patients who received the low NPC/N formula showed greater N retention, increased levels of plasma transferrin, and a lower respiratory quotient compared with those receiving the higher NPC/N formulas.
• Moore et al., 1989—The nutritional and clinical effects of total enteral nutrition (TEN) were compared with those of TPN in 59 postsurgical patients with major abdominal trauma. In this PRCT, 29 patients were given a commercial defined formula diet by TEN; 30 patients received a nutritionally equivalent TPN solution prepared with commercially available dietary components. Early TEN was well tolerated in these severely injured patients. Restoration of visceral proteins was better in the TEN group. The infection rate was 17% in the TEN group compared with 37% in the TPN patients; the frequency of major septic morbidity was 3% in the TEN group compared with 20% in the TPN group.

• Alexander and Gottschlich, 1990—In a prospective clinical study of burn patients, nutritional and clinical effects of a new enteral formula (Shriners' burn diet) were compared with those of standard enteral products. The new burn diet contained 20% of energy from whey protein, 2% from arginine, 0.5% from cysteine, and 0.5% from histidine. Fifteen percent of nonprotein calories was from lipids consisting of 50% fish oil and 50% safflower oil. Patients given the burn diet had fewer wound infections, shortened hospital stay, and reduced mortality compared with those given standard enteral formulas.

• Dominioni et al., 1985—In a burned guinea pig model, the effects of different levels of protein intake in enteral feedings with a caloric content equal to or in excess of the measured energy requirement were investigated. Formulas were prepared with commercially available dietary food modules. Formulas with 20–30% of calories as protein yielded the best metabolic and nutritional results.

• Gottschlich et al., 1990b—In a prospective clinical study of burn patients, metabolic and clinical effects of a new modular tube feeding recipe (MTF) were compared with those of two modified enteral formulas that are frequently used for burn patients. The new MTF is a high-protein, low-fat formula restricted in linoleic acid and enriched with ω-3 fatty acids, arginine, cysteine, histidine, vitamin A, zinc, and ascorbic acid. Patients given the MTF had fewer wound infections and shortened hospital stays compared with those given the modified commercial formulas.

Critics of this paper noted that an uneven distribution among the three test groups of cases complicated by smoke inhalation probably accounted for some of the differences in clinical outcome; in addition, they noted that the new enteral formula should not be compared with the two commercial products used because these were modified by supplementation with protein, vitamins, zinc, and in one, dilution (Borlase et al., 1990; Heimburger and Akrabawi, 1990). In response, Gottschlich and her colleagues acknowledged the difficulties of controlling for all variables in clinical trials, explained why the two commercial products were modified, and maintained that the new tube feeding formula designed for burn patients supported a better outcome in terms of wound infections and length of hospital stay (Gottschlich et al., 1990c; Gottschlich and Warden, 1990).

The investigations of Cerra et al. (1990), Daly et al. (1988), and Lieberman et al. (1990), cited on page 40, are also appropriate for this list of representative studies performed with commercial medical foods.

4. General principles for nutritional management

Formulas and principles that provide for the following factors are considered to be generally acceptable for nutritional management in hypermetabolic stress states:

• Total energy intake adjusted to stress level.

• Protein intake 50%, 100%, and 150% above basal RDA amounts, depending on stress level.
Carbohydrate 70 to 80% of calories.

Fat 20 to 30% of nonprotein calories including at least 1 to 2% essential fatty acids, depending on clinical status of the patient.

Vitamins and minerals equal to RDAs; supplements as indicated by clinical biochemistry.

The use of di- and tripeptides, BCAA supplements, and putative immune-stimulating ingredients is essentially experimental (see Studies that are needed on enteral feeding of hypermetabolic patients, p.43)

Carbohydrate overloading should be avoided because of the insulin resistance and glucose intolerance; thus, the carbohydrate proportion of nonprotein calories should be limited initially to 60% to 70% (Long et al., 1977) and adjusted according to the tolerance of individual patients. However, some clinical studies have demonstrated the suitability of early postoperative feeding with enteral formulas containing >70% carbohydrates (Moore and Jones, 1986; Moore et al., 1989). Fat constitutes the remaining 30 to 40% of nonprotein calories, and between 1 and 2% of total calories should be from essential fatty acids. MCT may be beneficial as part of the lipid component of enteral formulas for patients with impaired fat digestion or absorption (Linscheer and Vergroesen, 1988). For enteral formulas, the Recommended Dietary Allowances (RDAs) for vitamins and minerals may be used as a guide (National Research Council, 1989). However, as can be determined by clinical laboratory monitoring, supplements of minerals and vitamins may be indicated such as ascorbic acid, thiamin, niacin, zinc, potassium, phosphorus, and magnesium (Bernard et al., 1986; Hallbook and Helelin, 1977; Irwin et al., 1978; Shronts and Fish, 1989; van Rij et al., 1981).

Enteral feeding is generally preferable to parenteral alimentation in hypermetabolic stressed patients provided that their gastrointestinal tracts are functional and can be used safely (Alverdy et al., 1985; Cerra et al., 1985, 1988; Shronts et al., 1987).

Grote et al. (1987) compared the results of parenteral and enteral nutritional support in severely injured patients and concluded that, in general, they were nutritionally equivalent. The enteral product used was a defined formula liquid diet containing hydrolyzed casein, safflower seed oil, and maltodextrin. Energy and nitrogen balances were zero or positive by day three and thereafter.

5. Studies that are needed on enteral feeding of hypermetabolic patients

In studies of hypermetabolic stressed patients, investigators should attempt to separate septic from nonseptic patients to form study groups because of the marked differences in clinical outcome. There should be:

- More prospective randomized clinical trials of BCAA-enriched formulas to clarify the alleged advantages of BCAA.

- Preclinical and clinical trials of formula design to sort out the effects of such variables as: peptides versus whole proteins; arginine versus no arginine; glutamine versus no glutamine; nucleotides versus no nucleotides; increased versus decreased percentage of fat; fat containing $\Omega-6$ versus no $\Omega-6$ fatty acids; n-3 fats versus no n-3 fats. For example, data showing possible beneficial effects of supplemental glutamine on the starved, atrophic, but intact intestinal mucosa most commonly seen in ICU patients are not available.

- Preclinical and clinical studies to determine whether maintaining the gut mucosal barrier has clinical significance; if it has, then what is the best method of preserving it?
• More studies on tolerance to enteral feeding in critically ill, stressed patients including such parameters as intestinal transit time, diarrhea, abdominal distress, and malabsorption.

• Studies of the nature and biologic mechanisms of impaired immunocompetence including monitoring such potential markers as cytokine production, growth factor production, in vitro lymphocyte proliferation, antigen processing assay of macrophages, and nosocomial infection counts.

• Research on drug-nutrient interactions and the compatibility of drugs with enteral formulas.

• More studies of N:calorie ratios.

6. Conclusions

Rational principles and diets have been identified for nutritional management of hypermetabolically stressed patients, and their acceptability has been partially validated in randomized clinical trials. Enteral use of selected medical foods has improved certain nutritional and metabolic indices, but a significant favorable effect on clinical outcome has not been reported in most cases or was not a part of the investigative protocol. Important aspects of the pathophysiology of hypermetabolic stress states remain to be elucidated before substantial additional refinement of enteral formulas can be achieved.

Numerous commercially available enteral nutrition products including nutritionally adequate formulas with intact macronutrients or modified macronutrients such as hydrolyzed proteins, medium-chain triglycerides, and substituted carbohydrates are available and are generally suitable for use in mildly hypermetabolic patients. In addition, some enteral products are available that are designed to meet the nutritional needs of more severe hypermetabolic stress, such as those with relatively low NPC/N ratios, and those enriched in BCAA or modified amino acids and other modified macronutrients. While some of these have been shown to be suitable in a limited number of clinical trials, manufacturers of medical foods who claim superiority for their products should be required to submit scientific evidence that documents such claims.

Although the impact of nutritional support on posttraumatic morbidity and mortality has not been studied extensively in prospective randomized trials, the above-cited studies, among others, suggest that nutritional support in hypermetabolic states does, indeed, improve several nutritional indices such as the rate of total body and hepatic protein synthesis and plasma levels of visceral proteins. However, effects on body composition are less clear, and the suitability of specially designed, disease-specific formulas awaits confirmation in controlled clinical trials.
III. SAFETY OF ENTERAL NUTRITION PRODUCTS

In the past decade, manufacturers of medical foods have had minimal safety and contamination problems. Historically, issues related to safety of enteral formulations were focused on suitability for use with medical conditions, and efficient and safe delivery to the gastrointestinal tract rather than safety in terms of composition of products. As pointed out by Randall (1984a,b), early formulations administered orally were in fact mixtures of foods and food ingredients such as milk, raw eggs, and lactose or glucose. During the decades following World War II, clinical investigators made significant progress in developing safe and efficacious methods of administering hyperalimentation by various routes.

The composition of enteral products was also studied. For example, Barron (1959) explored the use of processed natural foods and other materials that were blended and filtered or processed as emulsions. Many investigators developed products that contained casein hydrolysates, amino acid mixtures, glucose and other simple sugars, dextrins, and other protein and carbohydrate sources (Randall, 1984a,b). In almost all of the studies reported, the components of enteral products were substances recognized as sources of energy or nitrogen; that is, foods or substances that were Generally Recognized As Safe (GRAS) for use in clinical nutrition. Historically, clinical trials were primarily focused on safe and suitable delivery of nutrients and nutritional adequacy of the formulations in patients with diseases or disorders of interest to the investigator. Safety of the formulation per se was not a primary concern.

Patients who receive these products are likely to be seriously, if not critically, ill. Often they may have impaired immune status, which increases their vulnerability to infection. Safe use and safety of products as consumed are important considerations. Enteral formulas support the growth of a wide variety of microorganisms (Anderson et al., 1984; Anderton, 1985; Bastow et al., 1982; Crocker et al., 1986). While contamination may occur during reconstitution (if applicable), decanting, and administration of the formula, as well as during its manufacture and packaging, it is important that the original product be of the highest quality in order to lessen the chance of bacterial proliferation during formula delivery.

Clinically serious infections have occurred in patients receiving enteral nutrition, particularly in connection with formulas prepared in diet kitchens from commercial components that were considered microbiologically safe prior to use (Casewell et al., 1981; de Vries et al., 1982). Baldwin et al. (1983) described three patients who experienced a septic syndrome associated with continuously infused enteral nutrition solutions via needle catheter jejunosomies. The syndrome consisted of nausea, vomiting, diarrhea, fever, leukocytosis, hypotension, and tachycardia. The authors considered that these episodes resulted from contamination of the enteral solutions (an elemental diet in two cases, an oligomeric formula in one) despite considerable care in their preparation and delivery.

Issues of safety include the composition and labeling of products, their quality including microbiologic safety and shelf life, their safe delivery to the patient, and related matters such as compatibility of medical foods with the wide variety of drugs needed by seriously ill patients and possible adverse effects of unusual amounts or combinations of nutrients in developmental enteral and parenteral products.

It is suggested that to assure the manufacture of safe medical foods, discussions among interested parties be scheduled. They should include a review of required good manufacturing practices to assure that existing requirements applying to all foods are sufficient to guarantee safety in the manufacture of medical foods. For example, consideration should be given to requiring that medical foods be commercially sterile. In addition, the question should be addressed whether labeling or package inserts should include information regarding duration of time that the product is
considered to be safe and appropriate for use after opening, reconstitution (if applicable), and hanging. Such guidelines would be helpful in determining how frequently to prepare formula, how to store it, when to discard it, and what volume to hang at one time. Appropriate handling reduces the likelihood of bacterial proliferation in the formula.

For nutritionally adequate, widely available, general purpose liquid or powder formulas suitable for tube feeding (Appendix B), safety and suitability are generally not at issue provided that: (a) all essential macro- and micronutrients are supplied in amounts at least equal to the RDAs; (b) all ingredients are GRAS or approved food additives; (c) known incompatibility with simultaneously administered drugs is listed on labels or in package inserts, and (d) the product meets the standards of good manufacturing practice and is microbiologically safe.

Defined formula diets and diet modules containing increased, decreased, modified, or substituted macro- and micronutrients should be consistent with (b), (c), and (d) above. In addition, their labels and package inserts should indicate whether the product is nutritionally complete or lacks essential macro- and micronutrients that require supplementation.

A key question of safety is whether signs of malnutrition occur less frequently when a product is used as directed than occur in control groups on ordinary diets. Another is whether use of the product has demonstrated any untoward side effects or toxicities. For critically ill, stressed patients, because of growing evidence of adverse effects of Ω-6 fatty acids on immunocompetence, it may be advisable to formulate medical foods so that sources of linoleic acid are limited to amounts needed to prevent essential fatty acid deficiency. Further research is needed on relationships between polyunsaturated fatty acids and immunocompetence in seriously ill, stressed patients.

The following are some factors that should be considered in evaluating product safety:

<table>
<thead>
<tr>
<th>1. Composition and purity</th>
<th>3. Side effects, toxicity, drug compatibility, patient acceptance</th>
</tr>
</thead>
<tbody>
<tr>
<td>• GRAS food ingredients or approved food additives</td>
<td>• Side effects (e.g., diarrhea, allergy)</td>
</tr>
<tr>
<td>• Package contents match label statement (FDA Compliance Program)</td>
<td>• Manufacturer-supplied laboratory and clinical trial safety data</td>
</tr>
<tr>
<td>• Balanced amounts of macro- and micronutrients</td>
<td>• Safety data from independent laboratory and clinical trials</td>
</tr>
<tr>
<td>• Manufactured in government-inspected facilities in accordance with GMP</td>
<td>• Drug incompatibility</td>
</tr>
<tr>
<td></td>
<td>• Effect of organoleptic properties on patient compliance for oral use</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Nutritional adequacy</th>
<th>4. Precautions for use</th>
</tr>
</thead>
<tbody>
<tr>
<td>• For short-term use</td>
<td>• Prescriber and consumer warnings (nutrient imbalance, excess fluid in some formulas, extra vitamin supplements in some disorders, dose adjustment for children and elderly, clinical monitoring)</td>
</tr>
<tr>
<td>• For long-term use</td>
<td></td>
</tr>
<tr>
<td>• Supplements needed</td>
<td></td>
</tr>
<tr>
<td>• Disease-specific supplements</td>
<td></td>
</tr>
<tr>
<td>• Nutrient stability</td>
<td></td>
</tr>
</tbody>
</table>

Safe use of enteral nutrition products involves clinical judgment on whether the patient's gastrointestinal tract can tolerate tube feedings, and skills relating to choice of delivery system, tube placement, product selection, rate of delivery, and systematic patient monitoring. Prevention of aspiration of liquid formula requires precautions, particularly in pulmonary disease patients. The physical consistency of enteral products is another factor that influences safety of use because of mechanical
difficulty in administering viscous formulas through small bore tubes; moreover, the ability to get the tube into the small bowel in terms of operator skill and tube design is a major safety factor.

Another issue related to safety is the compatibility of medical foods with the drugs needed for pharmacologic therapy. Because bolus administration of medications to patients with nasogastric tubes sometimes results in gastrointestinal intolerance, an alternate method of adding medications to the feeding formula was suggested (Niemec et al., 1983). In a study to assess the compatibility of medications with Ensure®, Ensure Plus®, and Osmolite® over a 12-hour infusion time, concentrations of digoxin and furosemide were essentially unchanged (Holtz et al., 1987). Addition of theophylline increased osmolality of all three products, and concentrations of phenytoin and methyldopa were altered significantly. Compatibility should be considered whenever it is planned to administer drugs along with enteral feedings. Other sources of information related to this topic include Baptista, 1983; Burns et al., 1988; and McKenzie, 1989. Cutie et al. (1983) recommended that medications not be mixed with formula but, when possible, that they be given as a bolus by tube or orally.

An even more important issue regarding compatibility is whether drugs added to enteral formulas retain their bioavailability and therapeutic efficacy. At present, information regarding this question is scanty; much research would be needed before routine co-administration of enteral formulas and most drugs could be recommended.

Some commentary and procedural guidance on interactions of medications and enteral formulas were received from the Enteral Nutrition Council, an association of manufacturers and marketers of enteral nutrition formulas in the United States. This material is presented in Appendix D.
IV. GUIDELINES

Under current regulations, review and approval of enteral nutrition products, except for compliance with good manufacturing practices, is not required. However, food manufacturers frequently request advice from FDA scientists on the acceptability of proposed products for their intended uses and on how such products should be tested for safety and suitability. As the numbers of medical foods increase and their composition becomes more sophisticated, the need for guidelines for evaluating and monitoring the research methods as well as validating the results of clinical trials of medical foods becomes more evident. Development of guidelines for evaluating the safety and suitability of medical foods for their intended purposes involves selection, suitability, and safety of enteral nutrition products (see Chapter I), the design of clinical trials, and methods for evaluation of clinical trials.

A. GUIDELINES FOR DESIGNING CLINICAL TRIALS OF MEDICAL FOODS

Examples of sources of expert guidance on this subject include reports, monographs, and texts such as: Arkin and Wachtel (1990), Chalmers et al. (1981), DeAngelis (1990), DerSimonian et al. (1982), the Enteral Nutrition Council (1990), Evans and Pollock (1985), Feinstein (1983a,b,c,d), Friedman et al. (1985), L’Abbe (1987), Meinert (1986), Moeteller et al. (1980), Peto et al. (1976, 1977), Sacks and Chalmers (1985), and the report of the Committee on Nutrition Task Force on Clinical Evaluation of Products for Metabolic Disorders (American Academy of Pediatrics, 1987).

Preclinical testing may be useful, but is limited by the availability of appropriate animal models of human disease and by the nutritional requirements of experimental animals that differ markedly from human requirements. However, animal testing may provide limited assessment of nutrient bioavailability, protein quality, metabolism, and availability of minerals.

Specific test protocols should be decided on a case-by-case basis because routine application of a predetermined set of tests would fail to include appropriate testing for some formulas and would produce unnecessary evaluations of others. Studies should be designed to measure relevant parameters in subjects for whom the product is represented such as the changes that the experimental food can induce in accepted nutritional assessment parameters (e.g., nitrogen balance and blood levels of urea, electrolytes, proteins, minerals, fatty acids, metabolic intermediates); metabolic and functional effects, and effects on clinical outcome. For example, a nutritional product for use in renal failure should minimize uremia, promote protein nutriture, and maximize energy delivery. Therefore, in assessing product performance, it would be appropriate to monitor nutritional parameters that relate to these stated goals, that is, uremia (BUN), protein status (serum albumin), electrolyte status (Na, K), major mineral status (CA, P) and weight maintenance (energy).

The consultants for this LSRO review suggested the following as appropriate types of end points for designing clinical trials: nutritional, metabolic, functional, and morbidity and mortality. Despite the difficulties of accurately relating the effects of nutritional support to morbidity and mortality as described on p.10, these end points should be part of the protocol whenever the investigator considers them feasible. An example of a functional end point is the ability of a patient with COPD to be weaned from mechanical respiration. Functional end points also include amelioration of the signs and symptoms of the disease.

The standard of excellence for clinical investigations is the prospective, randomized, blinded, controlled clinical trial (PRCT). Problems such as a limited population of subjects can be addressed by multicenter trials. Also, in trials of medical foods, it may sometimes be impractical to have a double-blinded study, but this does not preclude the possibility of using partial blinding methods.
Alternatives such as prospective longitudinal cohort studies, case-control studies, and crossover investigations can yield useful data with careful design and meticulous execution. Special precautions are needed in crossover trials to avoid or minimize carry-over effects.

The following requirements and principles apply to the design of protocols for PRCTs and other kinds of clinical investigations:

- State the study objective and precise test hypotheses.
- Provide an overview of the disease or disorder for which the medical food is intended.
- State the scientific rationale for nutritional intervention including "disease-specific" ingredients.
- Provide an external advisory group (Data Monitoring and Safety Committee) responsible to the investigator and the sponsor, whose primary role is to review adherence to the protocol and examine the data periodically for problems of safety.
- Specify the test procedures, case report forms, data acquisition, management, and analysis.
- Specify major study end points along with their associated laboratory and clinical tests and test schedules.
- Specify statistical characteristics of the study design (significance level desired; specification of minimum values for significant differences between the treatment and control groups; desired statistical power), as well as statistical methods to be used.
- Use rigorous criteria for selection of study subjects and control groups from as homogeneous a pool as possible, with inclusion of all eligible subjects so as to assure a representative sample of the available patient population.
- Sample size is the minimum number of test subjects and controls deemed to be necessary in order for the trial to test adequately the null hypothesis of no effect.
- List possible confounding factors and variables to be determined at baseline.
- Randomize assignment to test and control groups by an appropriate method.
- Subjects, controls, and investigators should be double blinded where possible, otherwise partially blinded.
- Carefully choose the control diets to resemble the test diet in all but the significant reductions or increases in macro- or micronutrients and additions of the putative "disease-specific" ingredients.
- Label the enteral nutrition products used in the study so as to assure their proper identification without interfering with blinding of the study.
- Specify guidance on safe use of the enteral product.
- Specify known product-drug incompatibilities.
- Specify procedures for detecting and measuring adverse effects of the test regimen.
- Format the protocol to comply with the written procedures of the study.
• Document Institutional Review Board approval, informed consent of study participants, and case report forms.

• Consider an outside, independent advisory group for review of study protocol, data monitoring, study progress, safety of study subjects, and scientific advice.

• In multicenter trials, all investigators must use the test product uniformly.

• Specify responsibility for summarizing results of the trial and preparing papers for publication.

The foregoing list of components of a PRCT may not be complete. Further details on each factor listed and additional components are available in Friedman et al. (1985) and Peto et al. (1976, 1977).

Some models for designing protocols for PRCT can be found in American Academy of Pediatrics, 1987; Friedman et al., 1985; Meinert, 1986; and Peto et al., 1976, 1977. An example of a well-planned and executed, prospective, multicenter, cross-over type clinical trial is that reported by Conn et al. (1977).

Data analysis.

• Analysis should be in accordance with the randomized assignment, that is, the intent to treat, because "A policy of withdrawal from analysis because of subject noncompliance can lead to bias." (Friedman et al., 1985).

• The best and most up-to-date statistical procedures should be used including adjustment for covariates.

• Investigators should be concerned with subgroup analysis when suggested by the data.

• Investigators should avoid making major findings from results with secondary or softer variables when there is a negative result that uses the prespecified major end points.

Additional comment from the medical foods industry.

High quality study results can only be obtained from well-designed, carefully planned and monitored, and meticulously executed research by appropriately qualified investigators. The documentation of clinical performance in support of product representations must be scientifically sound. The evidence should directly support the product representations and or indirectly support the underlying principles involved in the management of the disease or condition for which the product is designed. While it is not necessary to validate the use of every product in all clinical situations in which it might be useful, major new indications should be supported by direct clinical evidence (Enteral Nutrition Council, 1990).

Monitors for the sponsor. The task of study monitor is important to the success of clinical research. Monitors coordinate the effort on behalf of the sponsor, assuring the study protocol is followed and that the documentation is complete. Monitors are responsible for investigator site visits, first assuring that the investigator and facilities are adequate. They also play a key role in preparing the investigators and their staffs for the execution of the study, reviewing the protocol and procedures with the personnel involved, answering questions and making periodic visits to check on progress and assure compliance with the study protocol. Monitors have the responsibility to confirm the validity of the data contained in the case report forms (CRF) comparing data with the source document information. The monitor also assures an adequate supply of clinical product is available and that unused clinical supplies are properly disposed of at the end of the study. The monitor reviews study progress to assure that any unexpected findings are promptly reported to the sponsor, including the prompt follow-up on any adverse experiences recorded by the investigator (Enteral Nutrition Council, 1990).
Data management. The data management function encompasses the handling, manipulation and storage of data from the time the completed CRF are returned to the sponsor until the data are discarded. Data may be stored in electronic files or kept on the CRF. Generally the original documents are also retained and are eventually transferred to microfilm for limited access archival storage. Statistical analysis programs are validated and an appropriate trail is maintained to document manipulation of the data. Data analysis follows the statistical analysis program outlined in the study protocol. Where deviation is necessary, a written explanation is provided.

The final analysis of the clinical data provides the basis for the development of a final study report or manuscript for submission to a journal for publication. Both draft reports and manuscripts are subjected to scientific review by the sponsor. The approval process for publication is described as part of the original contractual agreement between investigators and sponsor.

Summary of quality control and study monitoring procedures. Quality control aspects of clinical investigations that involve enteral formulas are not dissimilar to those applicable to other products. The key requirements are:

- Scientifically sound study design.
- Written protocol, informed consent and case report forms.
- Written operating procedures.
- Documentation of study activity.
- Study monitoring.

Limitations and shortcomings of clinical studies. Procedures for evaluating nutritional adequacy do have certain limitations and shortcomings and in many instances can be applied inappropriately. Several comments regarding the latter point follow.

- The evaluation of gastrointestinal tolerance of a formulation involves assessment of many characteristics, such as cramping, nausea, bloating, stool volume, weight, and consistency. Only two of the parameters (stool volume and weight) can be measured objectively. The others may be of interest but are unreliable end points.

- Metabolic balance studies are notoriously difficult and potentially misleading because this type of study requires a relatively steady state. All but the most gross nutritional deficits in a formulation are likely to go undetected in a short-term metabolic balance study. Nitrogen balance tends to be positive when quantities in excess of nitrogen requirements are given. Errors in estimation of the balance of any nutrient tend to be positive because stool collection losses accentuate the difference in intake and output. Some nutrients cannot be studied reliably by this technique. In sick people under stress or taking medications, the subtle changes that may be related to nutrition products may be obscured.

- The metabolic balance study is traditionally carried out in normal volunteers. If the experimental product is designed for use in a patient population that requires nutrients that fall outside normal safe and adequate nutrient ranges (e.g., low electrolytes for renal patients or deficient phenylalanine for phenylketonuric subjects), normal subjects cannot be subjected to the potential deficiencies inherent in the experimental product; it can only be studied in the appropriate patients.
Studies of the pathophysiology of disease states and potential effects on physiologic parameters of nutritional formulations are subject to these same limitations. They may be used appropriately only when control periods and concurrent control subjects can be employed. These appear to be the most useful types of studies to demonstrate clinical suitability but are highly vulnerable to misinterpretation. The relatively weak effects of nutrients are easily obscured by the powerful effects of drugs and other treatments. This is a particularly difficult issue to control in research protocol design and one that deserves the careful attention of the nutrition researcher (Enteral Nutrition Council, 1990).

B. GUIDELINES FOR EVALUATING THE RESULTS OF CLINICAL TRIALS OF MEDICAL FOODS

The criteria listed in IV-A above may be used as a partial checklist for evaluating the soundness and completeness of the protocol. Chalmers et al. (1981) analyzed the quality of >260 clinical trial reports by a system they devised to weigh and assign values to components of a trial, which led to a numerical index of quality. The authors listed basic descriptive material, study protocol, data analyses, and data useful for combining results of several trials as necessary for assessing the quality of the results.

Chalmers and his colleagues have continued to refine their methodology for evaluating clinical trials. Appendix C describes their current sets of criteria for such assessments. Other reviews suggest additional or different attributes that would aid in evaluating clinical trials; for example, DerSimonian et al., 1982; Evans and Pollock, 1985; Mahon and Daniel, 1964; Mosteller et al., 1980; Peto et al., 1976, 1977.

It is suggested that a system of scoring clinical trials such as that described in Appendix C, modified to include elements recommended by other analysts and exclude elements that are inappropriate to the study of medical foods, could serve as a set of guidelines for the evaluation of clinical trials of medical foods.
V. LITERATURE CITED


Chalmers, T.C. 1990. Personal communication, April 24, with J. Talbot, Federation of American Societies for Experimental Biology, Bethesda, MD.


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<table>
<thead>
<tr>
<th>PRODUCT NAME</th>
<th>SUGGESTED USE</th>
<th>MANUFACTURER CITES CLINICAL STUDIES</th>
<th>GENERIC DESCRIPTION</th>
</tr>
</thead>
</table>
| Alimentum     | Cow's milk colitis 
Infant formula, also used in young children | Yes                                | Nutritionally adequate formula that includes casein hydrolysate.                    |
| Amin-Aid      | Acute or chronic renal failure                     | Yes                                | Nutritionally incomplete powder dietary supplement containing essential nutrients in readily digestible form with minimal electrolytes plus histidine. |
| (flavored)    |                                                    |                                     |                                                                                      |
| Hepatic-Aid II| Chronic liver disease                              | Yes                                | Nutritionally incomplete powder diet with essential nutrients in a readily digestible form, high in branched-chain amino acids, low in aromatic amino acids and methionine; contains arginine. |
| (flavored)    |                                                    |                                     |                                                                                      |
| Impact        | Nutrition support for the immune system under metabolic stress. Such conditions may include trauma, burns, sepsis, and other hyper-metabolic states. | Yes                                | Nutritionally adequate, ready-to-use liquid diet that is lactose- and gluten-free; low in cholesterol, sodium, and potassium; and supplemented with arginine, RNA, fish oils, and structured lipids. |
| Nutramigen    | Cow's milk colitis 
Infant formula, also used in young children | Yes                                | Nutritionally adequate, formula that includes casein hydrolysate.                    |
<table>
<thead>
<tr>
<th>PRODUCT NAME</th>
<th>SUGGESTED USE</th>
<th>MANUFACTURER CITES CLINICAL STUDIES</th>
<th>GENERIC DESCRIPTION</th>
</tr>
</thead>
</table>
| Pregestimil  | Cow's milk colitis  
Infant formula, also used in young children | Yes | Nutritionally adequate formula that includes casein hydrolysate. |
| Stresstein   | Nutrition support for the hypermetabolic patient. | Yes | Nutritionally adequate diet powder, high in protein and branched-chain amino acids. |
| Traum-Aid HBC Diet (flavored) | For hypercatabolic patients. | Yes | Nutritionally adequate, low residue powder diet containing readily digestible essential nutrients; high in branched-chain amino acids. |
| Travasorb Hepatic Diet (flavored) | Liver failure; liver disease that may be intolerant to dietary protein; hypermetabolic state. | Yes | Nutritionally adequate powder diet high in branched-chain amino acids, low in aromatic and ammonogenic amino acids; with added nonprotein calories. |
| Travasorb Renal Diet (flavored) | Acute or chronic renal failure; hypermetabolic state occurring with renal disease. | Yes | Nutritionally incomplete powder diet that is low in protein (contains essential and nonessential crystalline L-amino acids), high calorie, electrolyte-, lactose-, and fat soluble vitamin-free. |
| Vivonex T.E.N. | Conditions of metabolic stress including postoperative, trauma, and sepsis; malabsorptive states such as Crohn's disease and other indications listed by the manufacturer. | Yes | Nutritionally adequate defined formula, powder diet composed of essential nutrients in simple, readily absorbable form and low in fat. 100% free amino acid protein source, high in BCAA, glutamine and arginine. |
Appendix A. Continued.

1 Product name and suggested use are identified from manufacturers' product labeling or information catalogs or listings in available literature.

2 Manufacturer has made reference to, or supplied citation and/or clinical literature about published studies in peer reviewed publication and scientific studies cited in the package insert or other physician information materials.

3 Information available from Ross Laboratories, Columbus, OH.

4 Information available from Kendall McGau Laboratories of Puerto Rico, Inc., Sabana Grande, PR.

5 Information available from Sandoz Nutrition, Minneapolis, MN.

6 Information available from Mead Johnson Nutritionals, a Bristol-Myers Company, Evansville, IN.

7 Information available from Travenol Laboratories, Inc., a division of Clintec Nutrition Company and an affiliate of Baxter Healthcare Corporation, Deerfield, IL.

8 Information available from Norwich Eaton Pharmaceuticals, Inc., a division of The Procter & Gamble Co., Norwich, NY.
### Appendix B. Selected Medical Foods and Other Products that may be Used for Tube or Oral Feeding.

<table>
<thead>
<tr>
<th>PRODUCT NAME</th>
<th>SUGGESTED USE</th>
<th>GENERIC DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attain² (flavored)</td>
<td>General nutrition support</td>
<td>Nutritionally adequate, isotonic, low-residue, and lactose-free diet.</td>
</tr>
<tr>
<td>Attain L.S.² (flavored)</td>
<td>Renal and hepatic disorders requiring sodium restriction and other conditions listed by the manufacturer.</td>
<td>Nutritionally adequate, low-sodium, low-residue, and lactose-free diet.</td>
</tr>
<tr>
<td>Biocare Drink Mix²</td>
<td>General nutrition support.</td>
<td>Nutritional powder diet.</td>
</tr>
<tr>
<td>Carnation Instant Breakfast⁴ (flavored)</td>
<td>General nutrition support.</td>
<td>Nutritionally adequate powder diet when mixed with milk.</td>
</tr>
<tr>
<td>Casec⁵</td>
<td>Protein support as may be required for hepatic disorders and hypermetabolic states (burns). Clinical studies cited.</td>
<td>Nutritionally incomplete protein powder supplement low in sodium and fat.</td>
</tr>
<tr>
<td>Citrotein⁶</td>
<td>General nutrition support.</td>
<td>Nutritional supplement powder providing high quality egg protein and added vitamins and minerals.</td>
</tr>
<tr>
<td>Compleat⁶</td>
<td>General nutrition support.</td>
<td>Nutritionally adequate, ready-to-use liquid diet formulated from natural foods including meat, vegetables, milk, and fruit.</td>
</tr>
</tbody>
</table>

*Many of these products are marketed as medical foods or foods for special dietary purposes; some are dietary supplements and some are nutritionally adequate foods. Depending on the results of adequate clinical trials some of the products listed in this Appendix could qualify as medical foods under the definition suggested in this report (see p.5–6).*
<table>
<thead>
<tr>
<th>PRODUCT NAME(^1)</th>
<th>SUGGESTED USE(^1)</th>
<th>GENERIC DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compleat Modified Formula(^6)</td>
<td>General nutrition support.</td>
<td>Nutritionally adequate, ready-to-use liquid diet that is isotonic and formulated from natural foods including meat, vegetables, milk, and fruit.</td>
</tr>
<tr>
<td>Comply(^2) (flavored)</td>
<td>General nutrition support</td>
<td>Nutritionally adequate, high calorie diet.</td>
</tr>
<tr>
<td>Criticare HN(^2)</td>
<td>General nutrition support. Clinical studies cited.</td>
<td>Nutritionally adequate, ready-to-use, high nitrogen liquid diet that is low sodium and lactose-free. 40% of protein is supplied as small peptides.</td>
</tr>
<tr>
<td>Enrich(^7) (flavored)</td>
<td>General nutrition support.</td>
<td>Nutritionally adequate, ready-to-use liquid diet with high-fiber source.</td>
</tr>
<tr>
<td>Ensure(^7) (flavored)</td>
<td>General nutrition support.</td>
<td>Nutritionally adequate, ready-to-use liquid diet that is lactose free, low residue, low osmolality.</td>
</tr>
<tr>
<td>Ensure HN(^7) (flavored)</td>
<td>May be useful in support of the stressed patient. Such conditions may include trauma, burns, cancer, and other hypermetabolic states.</td>
<td>Nutritionally adequate, ready-to-use liquid diet that is lactose free, low residue, low osmolality and with additional nitrogen.</td>
</tr>
<tr>
<td>PRODUCT NAME\textsuperscript{1}</td>
<td>SUGGESTED USE\textsuperscript{1}</td>
<td>GENERIC DESCRIPTION</td>
</tr>
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</tr>
<tr>
<td>Ensure Plus\textsuperscript{7} (flavored)</td>
<td>May be useful in support of the stressed patient. Such conditions may include trauma, burns, cancer, and other hypermetabolic states.</td>
<td>Nutritionally adequate, ready-to-use liquid diet that is lactose free, low residue, low osmolality and with extra calories in a limited volume.</td>
</tr>
<tr>
<td>Ensure Plus HN\textsuperscript{7} (flavored)</td>
<td>May be useful in support of the stressed patient. Such conditions may include trauma, burns, cancer, and other hypermetabolic states.</td>
<td>Nutritionally adequate, ready-to-use liquid diet that is lactose free, low residue, low osmolality and with additional nitrogen and extra calories in a limited volume.</td>
</tr>
<tr>
<td>Entralife\textsuperscript{8}</td>
<td>General nutrition support. Clinical studies cited.</td>
<td>Nutritionally adequate, ready-to-use diet containing whey, isolated soy, corn oil, hydrolyzed corn starch, and sucrose.</td>
</tr>
<tr>
<td>Entralife HN\textsuperscript{8}</td>
<td>General nutrition support.</td>
<td>Nutritionally adequate, ready-to-use diet containing whey, isolated soy, corn oil, hydrolyzed corn starch, and sucrose. Contains additional protein.</td>
</tr>
<tr>
<td>Entralife HN-Fiber\textsuperscript{8}</td>
<td>General nutrition support</td>
<td>Nutritionally adequate, ready-to-use diet containing whey, isolated soy, corn oil, hydrolyzed corn starch, and sucrose. Contains additional protein and fiber source.</td>
</tr>
<tr>
<td>Entrition 1\textsuperscript{9}</td>
<td>General nutrition support</td>
<td>Nutritionally adequate diet in ready-to-deliver closed feeding system. It is isotonic, low residue, lactose free, and contains whole protein, vitamins and minerals.</td>
</tr>
<tr>
<td>PRODUCT NAME</td>
<td>SUGGESTED USE</td>
<td>GENERIC DESCRIPTION</td>
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</tr>
<tr>
<td>Entrition 1/2</td>
<td>General nutrition support</td>
<td>Nutritionally adequate diet in ready-to-deliver closed feeding system. It is isotonic, low residue, lactose free, and contains whole protein, vitamins and minerals. Not for extended use. It is ½ strength of Entrition 1.</td>
</tr>
<tr>
<td>Entrition HN</td>
<td>General nutrition support</td>
<td>Nutritionally adequate diet in ready-to-deliver closed feeding system. It is isotonic, low residue, lactose free, and contains added whole protein, vitamins and minerals.</td>
</tr>
<tr>
<td>Gevral</td>
<td>Vitamins, minerals, and protein supplementation.</td>
<td>Nutritionally incomplete protein, vitamin and mineral supplement.</td>
</tr>
<tr>
<td>High MCT Supplement</td>
<td>Readily absorbed lipid energy support.</td>
<td>Nutritionally incomplete powder fat supplement that is lactose-free. The MCT include the following fatty acids: caproic, caprylic, capric, and lauric, 0.3, 5.8, 5.5, 45.6% respectively of total fat.</td>
</tr>
<tr>
<td>Isocal</td>
<td>General nutrition support Clinical studies cited.</td>
<td>Nutritionally adequate, ready-to-use liquid diet that is lactose- and fiber-free.</td>
</tr>
<tr>
<td>Isocal HCN</td>
<td>General nutrition support Clinical studies cited.</td>
<td>Nutritionally adequate, high calorie and high nitrogen ready-to-use liquid diet that is lactose-free.</td>
</tr>
<tr>
<td>PRODUCT NAME</td>
<td>SUGGESTED USE</td>
<td>GENERIC DESCRIPTION</td>
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</tr>
<tr>
<td>Isocal HN</td>
<td>May be useful in support of the mildly stressed patient. Such conditions may include trauma, burns, surgery, and other hypermetabolic states.</td>
<td>Nutritionally adequate, high-nitrogen ready-to-use liquid diet that is lactose-free and low-residue.</td>
</tr>
<tr>
<td>Isosource</td>
<td>General nutrition support</td>
<td>Nutritionally adequate liquid diet.</td>
</tr>
<tr>
<td>Isosource HN</td>
<td>General nutrition support</td>
<td>Nutritionally adequate liquid diet with high protein.</td>
</tr>
<tr>
<td>Isotein HN</td>
<td>Useful in support of the stressed patient. Such conditions may include trauma, burns, and other hypermetabolic states.</td>
<td>Nutritionally adequate powder diet that is high protein, isotonic, and lactose- and gluten-free.</td>
</tr>
<tr>
<td>Jevity</td>
<td>General nutrition support</td>
<td>Nutritionally adequate, ready-to-use isotonic liquid diet that contains fiber, high nitrogen, ultra-trace minerals (Cr, Mo, Se), carnitine, and taurine.</td>
</tr>
<tr>
<td>Lonalec</td>
<td>Nephrosis, hepatic cirrhosis with ascites and other disorders requiring sodium restriction.</td>
<td>Nutritionally adequate diet powder low in sodium and high in protein.</td>
</tr>
<tr>
<td>MCT Oil</td>
<td>Readily absorbed fat calorie supplement.</td>
<td>Nutritionally incomplete fat supplement consisting of MCT.</td>
</tr>
<tr>
<td>PRODUCT NAME</td>
<td>SUGGESTED USE</td>
<td>GENERIC DESCRIPTION</td>
</tr>
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</tr>
<tr>
<td>Magnacal²</td>
<td>Management of patients with restricted fluid intake as may occur during hepatic or renal disease and hypermetabolic conditions including trauma, and other conditions listed by the manufacturer.</td>
<td>Nutritionally adequate, high calorie diet, low in sodium and lactose-free.</td>
</tr>
<tr>
<td>Meritene⁶ (flavored)</td>
<td>General nutrition support</td>
<td>Nutritionally adequate powder or liquid diet.</td>
</tr>
<tr>
<td>Microlipid²</td>
<td>Pulmonary failure, hypermetabolic states and other conditions listed by the manufacturer.</td>
<td>Nutritionally incomplete emulsified source of calories from safflower oil.</td>
</tr>
<tr>
<td>Moducal⁵</td>
<td>Energy source for patients on restricted diets, and other uses listed by the manufacturer. Clinical studies cited.</td>
<td>Nutritionally incomplete dietary powder carbohydrate supplement with low osmolality and low levels of electrolytes.</td>
</tr>
<tr>
<td>Nutrisource Modular System⁶</td>
<td>Hepatic, renal, and respiratory failure.</td>
<td>Nutritionally incomplete nutrient source module components that can be customized to meet specific nutritional needs.</td>
</tr>
<tr>
<td>Osmolite⁷</td>
<td>General nutrition support</td>
<td>Nutritionally adequate, ready-to-use isotonic liquid diet that is lactose and gluten free.</td>
</tr>
<tr>
<td>Osmolite HN⁷</td>
<td>General nutrition support</td>
<td>Nutritionally adequate, ready-to-use isotonic liquid diet that is lactose and gluten free and contains additional nitrogen.</td>
</tr>
<tr>
<td>PRODUCT NAME</td>
<td>SUGGESTED USE</td>
<td>GENERIC DESCRIPTION</td>
</tr>
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</tr>
<tr>
<td>&quot;P.C.&quot; Pure Carbohydrate Supplement</td>
<td>General nutrition carbohydrate supplement.</td>
<td>Nutritionally incomplete powder or liquid carbohydrate supplement that is lactose- and fat-free and low in sodium and potassium.</td>
</tr>
<tr>
<td>Peptamen</td>
<td>Hypermetabolic states such as multiple trauma and burns as well as other conditions listed by the manufacturer.</td>
<td>Nutritionally adequate, ready-to-use, liquid, isotonic peptide based diet.</td>
</tr>
<tr>
<td>Pepti 2000</td>
<td>May be useful in protein malabsorption and other conditions listed by the manufacturer.</td>
<td>Nutritionally adequate diet containing short-chain peptides as the primary protein source.</td>
</tr>
<tr>
<td>Portagen</td>
<td>Nutritional management of patients with fat malabsorption as may occur in hepatic conditions with decreased bile salt production, and other conditions listed by the manufacturer. Clinical studies cited.</td>
<td>Nutritionally adequate, powder diet that is lactose-free and contains MCT as the major source of fat.</td>
</tr>
<tr>
<td>Precision High Nitrogen Diet</td>
<td>General nutrition support</td>
<td>Nutritionally adequate, powder diet with high protein, low residue natural food source and high in nitrogen, fiber-, lactose-, gluten-, and cholesterol-free.</td>
</tr>
</tbody>
</table>
## Appendix B. Continued.

<table>
<thead>
<tr>
<th>PRODUCT NAME&lt;sup&gt;1&lt;/sup&gt;</th>
<th>SUGGESTED USE&lt;sup&gt;1&lt;/sup&gt;</th>
<th>GENERIC DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision Isotonic Diet&lt;sup&gt;6&lt;/sup&gt;</td>
<td>General nutrition support</td>
<td>Nutritionally adequate, isotonic powder diet with low residue, low sodium, lactose−, gluten−, purine−, and cholesterol− free.</td>
</tr>
<tr>
<td>Precision LR Diet&lt;sup&gt;6&lt;/sup&gt;</td>
<td>General nutrition support</td>
<td>Nutritionally adequate, powder diet with low residue, low sodium, lactose−, gluten−, and cholesterol− free.</td>
</tr>
<tr>
<td>Pre-Fortison&lt;sup&gt;2&lt;/sup&gt;</td>
<td>General nutrition support</td>
<td>Nutritionally adequate liquid diet with low osmolality and lactose− free. Suitable for starter tube feeding. Not for extended use.</td>
</tr>
<tr>
<td>Promod&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Nitrogen source for cancer therapy, stress, or trauma and other conditions listed by the manufacturer.</td>
<td>Nutritionally incomplete protein supplement.</td>
</tr>
<tr>
<td>Pro-Mix&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Protein supplementation.</td>
<td>Nutritionally incomplete powder protein supplement.</td>
</tr>
<tr>
<td>Propac&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Suitable for patients with hypermetabolic states as may occur in burns, or trauma. Other conditions listed by the manufacturer.</td>
<td>Nutritionally incomplete modular protein supplement.</td>
</tr>
<tr>
<td>Pulmocare&lt;sup&gt;7&lt;/sup&gt; (flavored)</td>
<td>For dietary management of respiratory insufficiency. Clinical studies cited.</td>
<td>Nutritionally adequate, ready−to−use liquid diet with a high fat and low carbohydrate profile to reduce CO&lt;sub&gt;2&lt;/sub&gt; production.</td>
</tr>
<tr>
<td>PRODUCT NAME</td>
<td>SUGGESTED USE</td>
<td>GENERIC DESCRIPTION</td>
</tr>
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</tr>
<tr>
<td>Reabilan&lt;sup&gt;12&lt;/sup&gt;</td>
<td>For use in hypermetabolic states (trauma, burns, cancer) and other conditions recommended by the manufacturer. Clinical studies cited.</td>
<td>Nutritionally adequate, ready-to-use liquid diet using a small peptide formula for improved protein absorption.</td>
</tr>
<tr>
<td>Reabilan HN&lt;sup&gt;12&lt;/sup&gt;</td>
<td>For use in hypermetabolic states (trauma, burns, cancer) and other conditions recommended by the manufacturer. Clinical studies cited.</td>
<td>Nutritionally adequate, ready-to-use liquid diet; includes small peptides for improved protein absorption and contains additional nitrogen.</td>
</tr>
<tr>
<td>Resource Instant Crystals&lt;sup&gt;6&lt;/sup&gt; (flavored)</td>
<td>General nutrition support and other conditions listed by the manufacturer.</td>
<td>Nutritionally adequate powder diet.</td>
</tr>
<tr>
<td>Ross SLD&lt;sup&gt;7&lt;/sup&gt; (flavored)</td>
<td>General nutrition support</td>
<td>Nutritionally adequate diet powder that is low-residue, low fat, lactose- and gluten-free, and forms a clear liquid.</td>
</tr>
<tr>
<td>Sumacal&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Energy source useful in renal disease and hepatic failure and other conditions listed by the manufacturer.</td>
<td>Nutritionally incomplete modular powder carbohydrate supplement with low electrolytes, and low osmolality.</td>
</tr>
<tr>
<td>Sustacal&lt;sup&gt;5&lt;/sup&gt; (flavored)</td>
<td>Nutritional support for malnutrition in cancer patients, stress, or surgical trauma and other conditions listed by the manufacturer. Clinical studies cited.</td>
<td>Nutritionally adequate, ready-to-use dietary liquid, pudding, or mixable powder that is low residue, lactose- and fiber-free.</td>
</tr>
<tr>
<td>PRODUCT NAME</td>
<td>SUGGESTED USE</td>
<td>GENERIC DESCRIPTION</td>
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</tr>
<tr>
<td>Sustacal HC&lt;sup&gt;5&lt;/sup&gt; (flavored)</td>
<td>Nutritional support for patients requiring volume restriction (e.g., lung disease), fluid restriction (e.g., liver disease), and other conditions listed by the manufacturer.</td>
<td>Nutritionally adequate, ready-to-use liquid diet with concentrated calories and high-quality protein in a limited volume and is low residue, lactose- and fiber-free.</td>
</tr>
<tr>
<td>Sustacal with Fiber&lt;sup&gt;5&lt;/sup&gt; (flavored)</td>
<td>General nutrition support. Clinical studies cited.</td>
<td>Nutritionally adequate, ready-to-use liquid diet with low osmolality, low sodium, lactose-free, and contains soy fiber.</td>
</tr>
<tr>
<td>Sustagen&lt;sup&gt;5&lt;/sup&gt; (flavored)</td>
<td>General nutrition support. Clinical studies cited.</td>
<td>Nutritionally adequate, powder diet that is high-calorie, high-protein, low in fat and residue.</td>
</tr>
<tr>
<td>Tolerex&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Maintenance nutritional support for patients with intractable diarrhea, impaired digestion and absorption, and other conditions recommended by the manufacturer including patients with known food sensitivities. Clinical studies cited.</td>
<td>Nutritionally complete powder diet containing essential nutrients in simple, readily absorbable form.</td>
</tr>
<tr>
<td>TraumaCal&lt;sup&gt;5&lt;/sup&gt;</td>
<td>May be useful in support of the moderately to severely stressed patient as in trauma, burns, cancer, and other hypermetabolic states. Also useful in obstructive pulmonary disease and ventilator-dependent patients. Clinical studies cited.</td>
<td>Nutritionally adequate, ready-to-use liquid diet that is high-calorie and high-nitrogen with restricted carbohydrates in a limited volume.</td>
</tr>
<tr>
<td>PRODUCT NAME</td>
<td>SUGGESTED USE</td>
<td>GENERIC DESCRIPTION</td>
</tr>
<tr>
<td>------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Travasorb HN&lt;sup&gt;14&lt;/sup&gt;</td>
<td>General nutrition support. Clinical studies cited.</td>
<td>Nutritionally adequate powder diet containing additional hydrolyzed protein that is readily digested and rapidly absorbed.</td>
</tr>
<tr>
<td>Travasorb MCT Diet&lt;sup&gt;14&lt;/sup&gt;</td>
<td>May be useful in lipid malabsorption. Clinical studies cited.</td>
<td>Nutritionally adequate, powder diet that contains medium chain triglycerides as the primary fat source, lactose-free, and easily digestible whole protein source.</td>
</tr>
<tr>
<td>Travasorb STD Defined Peptide Diet&lt;sup&gt;14&lt;/sup&gt;</td>
<td>General nutrition support. Clinical studies cited.</td>
<td>Nutritionally adequate, low residue powder diet. A partial list of contents includes hydrolyzed lactalbumin, glucose oligosaccharides, MCT, sunflower oil, minerals and vitamins.</td>
</tr>
<tr>
<td>Twocal HN&lt;sup&gt;7&lt;/sup&gt; (flavored)</td>
<td>For use in hypermetabolic states.</td>
<td>Nutritionally adequate ready-to-use high energy, high protein, lactose-free liquid diet.</td>
</tr>
<tr>
<td>Vital High Nitrogen&lt;sup&gt;7&lt;/sup&gt; (flavored)</td>
<td>For use in hypermetabolic states such as stress or trauma and other conditions recommended by the manufacturer. Clinical studies cited.</td>
<td>Nutritionally adequate, defined formula, powder diet that is ready-to-use, with low osmolality, low residue, low electrolyte levels, and with additional nitrogen from partially hydrolysed proteins.</td>
</tr>
<tr>
<td>Vitaneed&lt;sup&gt;2&lt;/sup&gt;</td>
<td>General nutrition support.</td>
<td>Nutritionally adequate diet.</td>
</tr>
</tbody>
</table>
Appendix B. Continued.

1 Product name and suggested use are identified from manufacturers' product labeling or information catalogs or from listings in available literature.

2 Information available from Sherwood Medical Company, St. Louis, MO.

3 Information available from Food Sciences Corporation, Mt. Laurel, NJ.

4 Information available from the Carnation Company, Los Angeles, CA. Also available from Clintec Nutrition Company, an affiliate of Baxter Healthcare Corporation, Deerfield, IL.

5 Information available from Mead Johnson Nutritionals, a Bristol-Myers Company, Evansville, IN.

6 Information available from Sandoz Nutrition, Minneapolis, MN.

7 Information available from Ross Laboratories, Columbus, OH.


9 Information available from Biosearch Medical Products, Inc., Somerville, New Jersey. These products are presently distributed by Baxter Healthcare Corporation, Deerfield, IL.

10 Information available from Lederle Laboratories, Pearl River, NY.

11 Information available from The Upjohn Company, Kalamazoo, MI.

12 These products are manufactured by Roussel UCLAF Nutrition, Paris, France and distributed in the United States by O'Brien Pharmaceuticals. Product information is available from O'Brien/KMI, Parsippany, NJ.


14 Information available from Travenol Laboratories, Inc., a division of Clintec Nutrition Company and an affiliate of Baxter Healthcare Corporation, Deerfield, IL.
APPENDIX C*

Technology Assessment Group, Harvard School of Public health
and
Clinical Trials Unit, Mt. Sinai School of Medicine

EVALUATING RANDOMIZED CLINICAL TRIALS

This is an update of our original paper detailing criteria for evaluating randomized clinical trials.

Editor's note: (the following refers to Form B)

1. **Selection Description**—A detailed description of both the entry and rejection criteria is required for a well-designed trial. This should permit replication of the patient selection project by other clinicians. A mere statement that so many patients with such and such diagnosis were randomized is unsatisfactory. Something in between these two extremes is given a score of "fair."

2. **Rejection Log**—Equally as important as the documentation of the population studied is a description of the eligible population not accepted for the trial before randomization. A log of those patients should be kept. RCTs are given full credit on the basis of the selection criteria in the protocol only when numbers of patients eligible but not randomized are given, in addition to reasons for non-randomization of each of these patients. A score of "fair" is given when the numbers rejected are not broken down into specific categories.

3. **Therapeutic Regimen**—The descriptions of both experimental and all ancillary therapies must be complete enough to allow proper interpretation of the results and replication in other studies or practice. A study should describe the exact timing and amount of daily therapies in the trial and all ancillary allowed other therapies. A description of the control regimen, including placebos, is also required for full credit.

4. **Control Appearance and/or Regimen**—Full credit can only be attained when the appearance of the control regimen is identical to the treatment. In trials involving parenteral medication, this should include vehicles and mode of administration as well as physical appearance of the drug. In any case, the dosage regimens must be identical for credit. This item is scored "not applicable" when both patients and observers are not blinded.

5. **Control Taste and/or Sensation**—Full credit, here, is given only when it is specified that taste of both treatment and control regimens involving oral administration are identical. In addition, sensation applies to the sensory attributes of regimens that do not involve oral administration. In trials where this is applicable, full credit can only be obtained if it is specified that sensation for both treatment and control are identical. This item is also scored "not applicable" when patients and observers are unblinded. While it is understood that documentation is often lacking in the publication of RCTs, the paper should mention that control is identical in both taste and sensation as well as appearance.

* Reproduced with permission of Dr. Thomas C. Chalmers, The Technology Assessment Group, Harvard School of Public Health, and the Clinical Trials Unit, Mt. Sinai School of Medicine (Chalmers, 1990).
6. **Blinding of the Randomization Process**—The crux of this issue lies in determining whether the investigators could discern which treatment is next in line. Blinding of randomization is assured by assignment via telephone communication, preferably by an individual not involved in the actual treatment, or with indistinguishable treatments randomly precoded by the pharmacy. Computer programs are now available which require insertion of name and identification number of patient before treatment assignment is determined, recorded and revealed. Use of patient chart numbers, birth dates, dates of admission, coin flips, or alternate (odd–even) allocation are all examples of unblinded, quasi-methods, randomization, and should receive no credit. It is necessary to reaffirm the imperfections of open tables of random numbers or sealed envelopes (regardless of opacity). In general, if it is impossible to predict the next treatment in line, full credit should be given. If there is a small chance of the next treatment being predicted (e.g., sealed envelopes) partial credit should be given. Mention of random numbers and coin flips could receive half credit if they are used by someone other than the person enrolling study participants. No credit for randomization blinding is given if pharmacy supplied tablets are labelled A and B, and any leak is possible.

7. **Blindability of Patients**—This refers to the fact that some treatments are easier to blind than others. Most studies are completely blindable, and are given maximum score only when completely blinded. Unblindable studies (e.g., patients cannot be blinded as to surgery vs. medicine) should be scored "not applicable." Partially blindable studies (e.g., studies in which only some patients can be blinded, perhaps because of specific, well known side effects) are given maximum score for partial blinding.

**Patients Blinded**—The confusion on this issue lies in determining whether a trial is blinded merely by its statement, regardless of contradictory evidence. Technique of blinding must be fully reported; there should be little chance of patient guessing which treatment they are getting. In the specific case where different dosages of the same drug are given without "dummies" to make up the difference, no credit can be given. When side effects clearly reveal the patient's group, the study should be considered partially blinded. Single-blindedness, unless otherwise specified, should be assumed to refer to patient blinding.

8. **Blindability of Observers**—Some treatments are easier to blind than others. Most studies are completely blindable, and are given maximum score only when completely blinded. Unblindable studies (e.g., surgery vs. medicine where the endpoint involves physical examination) should be scored "not applicable." Partially blindable studies (e.g., studies in which only some observers can be blinded, or trials using steroid therapy, where certain specific side effects are peculiar to the treatment group), are given maximum score for partial blinding. Scores are then assigned according to which column applies to the study in question.

**Observers Blinded to Treatment**—The same conditions for "Patients Blinded to Treatment" also apply to observers. A study is just classified by column as to whether or not all observers could have been blinded, some only, or none. Then these questions are answered as to whether complete, partial or no blinding was actually employed.

A stand-alone statement that a study was double-blind, without any details allowing judgement about the thoroughness, will only receive 4 points each for questions 2.7 and 2.8.

9. **Observers Blinded to Results**—Full credit is given solely when there is a separate data-monitoring person(s). Partial credit is given when less satisfactory attempts are made to blind the observers as to the results. A score of "partial" is also given when a coordinating or data-monitoring committee is mentioned but there is no specific statement about individual centers or observers being blinded to ongoing results. No credit is given when no effort is made to blind the observers as to the results. (Note: this item refers only to the ongoing results of the study, not to any individual patient's outcome.)
10. **Prior Estimate of Numbers**—There should be evidence that a prior estimate of the numbers of patients required was made. An excellent paper lists in its Methods section the expected rate of control outcomes, the largest improvement of clinical interest that should not be missed, the chosen levels of error (alpha and beta), and the numbers anticipated.

11. **Stopping Rules**—The explicit statement of any one of the following constitutes an "adequate" stopping rule. If there is inappropriate or incorrect application, it should be given a score of "fair." Note that a fixed sample size with proper estimate of numbers gets an "adequate" score.

   1. Proper estimate of numbers (see above)
   2. Sequential analysis
   3. Planned multiple looks with adjusted p values
   4. Relative betting odds (Monte Carlo method)
   5. Issues against continuing (e.g., side effects, subgroup response)

12. **Testing Randomization**—For an "adequate" score relevant demographic and prognostic features should be given. A fair score would present either prognostic or demographic variables, but not both. (Note: this item refers solely to the presentation of data; statistical analysis of these data is evaluated by the item "Results of Prerandomization".)

13. **Testing Blinding**—A score of "not applicable" is given if a trial is unblinded. Single blinding makes the item applicable. Full credit is given when both patients and observers are quizzed. Partial credit is given if not all the blinded groups are quizzed.

14. **Testing Compliance**—This item is scored "not applicable" for in-hospital studies except when a test of compliance (e.g., consulted nurses' notes) is specifically mentioned, in which case full credit is given. In addition, a score of "not applicable" is given for trials using parenteral medications or surgical procedures. Full credit is given for outpatient studies using pill counts or other similar tests of compliance. A score of "fair" reflects a flawed attempt to assess compliance (e.g., asking the patients if they took their medication). Measurements of biological equivalence will, in some cases, satisfy this item.

15. **Biological Equivalent**—When feasible, appropriate lab results not used as endpoints should be measured to receive credit. These may measure absorption (e.g., levels) or a known pharmacological effect of the drug (e.g., clotting time).

16. **Endpoint Duplicate Variability**—Studies should have more than one observer evaluating the endpoints when the endpoints are subjective. When more than one person makes an observation, the duplicate variability should be measured and interpreted. This item is not applicable when endpoints are objective.

**Form C**

1. **Dates of Study**—Studies should list the starting and stopping dates of accession so that the results can be interpreted in the light of other changes in therapy that may have been going on at the same time, as in the case of the advent of coronary care units. A half score is given when one date is mentioned.

2. **Results of Prerandomization**—Analyses done to assess the baseline comparability of the study groups may give the interpreter of the results of the trial reasons for being very cautious or even suspicious. Thus the issue here is whether the prognostic variables have been analyzed well and did the author(s) consider their impact on the results. Either statistical analysis or a statement that the groups are too similar to require statistical analysis is necessary for a score of adequate.
3. **Major Endpoints**—When significance is reported, it should be given in such a way that the reader can make the actual calculations. Both the test statistic (where applicable) and the observed probability values should be stated. If the observed probability level is presented but not the test statistic, or the test statistic is given without the probability level, the reader may have trouble verifying the statistical conclusions. The absence of both is unacceptable.

4. **Post-Beta Estimate (neg. trials only)**—If the difference between the compared treatments turns out not to be statistically significant, then a discussion of the Type II error and its probability should be included in the results or the discussion section of the trial. Actually estimating a posterior beta for a clinically interesting difference gets a score of "adequate," as does a comment about the confidence intervals around the differences. Mentioning the problem and admitting a necessity for more patients ("problem needs further study to be sure a difference is not being missed") get a score of "fair." Trials in which all differences measured are statistically significant warrant a score of "not applicable."

5. **Confidence Limits**—Confidence limits should be provided for differences in the proportions, rates, or means used as trial endpoints. Reporting standard deviation or standard error of endpoints by group gains 1.5 points.

6. **Life Table/Repeated Measures**—For all discrete endpoints, such as mortality or morbidity, even for trials of short duration, life-table or time-series analysis should be carried out. If more than one survival curve is reported, comparison of the curves should be done by the appropriate statistical procedure, e.g., long-rank test. The question specifically refers to the adequacy of the statistical analysis.

7. **Timing of Events**—This differs from the above question in that it only refers to the availability of the raw data on which the survival curves were based (e.g., in a survival analysis, the number entering each period, the number with an endpoint, and the number censored should be given). An "adequate" score is given when the data are fully presented in tabular or graph form. A "fair" score is given when incomplete data are provided.

8. **Regression/Correlation Analysis**—Regression is a measure of dependence and correlation is a measure of association. When the investigators evaluate the relationship between a continuous endpoint and predictor variable, a regression analysis should always be performed. Correlation analysis should always be performed when the association between two or more random variables is desired. In RCTs done since about 1982, some sort of regression analysis (e.g., Cox regression) is always applicable. In earlier studies, this item can be scored "not applicable" because regressions were not customary at that time. The determination of need for these analyses is based on what the investigators actually measured. This item is not meant to judge what variables should have been measured.

9. **Statistical Analyses**—This is an overall assessment of the statistical methods that are used in the trial. When all appropriate analyses have been performed and clearly and precisely reported, a score of "excellent" should be given. If many, but not all, analyses have been performed, or not all results of these analyses are reported, i.e., the test statistic or the name of the test (where no test statistic exists) and the p value, a score of "good" is appropriate. A score of "fair" should be given when more serious deficiencies exist. (Note that the answer to this question is highly subjective.)

10. **Withdrawals after Randomization**—Withdrawals are defined as patients who were randomized but did not receive the allocated treatment or complete the specified observation period, or who were removed from the study during the analysis period. If investigators specify the numbers of patients who withdrew from the trial and the reasons why, this would represent an adequate "list." If the numbers are listed without the reasons, two points are given. If there are no withdrawals, and it is so stated in the paper, this item would be scored as "none." "No list/unknown" means that no information is given. If >15% of these randomized withdraw from a study or are removed, the results are suspect and no points are given.
11. **Handling Withdrawals**—Depending on the type of study, withdrawals are handled in many different ways, for example: (a) The results are analyzed with the dropouts handled in more than one way. (b) Patients are included in the group to which they were originally assigned regardless of what happens to them. (By intention to treat, ITT.) Analyzing the data both according to treatment assigned and treatment received is the best procedure because a different result for each method strongly suggests an inconclusive study. (c) Patients can be ignored or eliminated from the study at the time of withdrawal—thus, not counted in the result. Although this is done most often, it is rarely a defensible procedure. It is often referred to as "on randomized treatment"—ORT. (d) Patients may change groups and be considered as an end result in the new group. This is never defensible as the only analysis.

12. **Side Effects Discussion**—To obtain a score of "adequate," side effects should be reported and discussed, and adequate statistical analyses carried out. Comparison of percentages with a statistical test of significance and the observed probability should be done if the sample size warrants it. The name of the test (and test statistic where applicable) and the p-value must be recorded. A score of "fair" reflects an incomplete report or discussion. When no attempt is made to deal with side effects beyond simply listing them, or not listing them at all, a score of "inadequate" should be given.

13. **Retrospective Analysis**—In a clinical trial, the post analysis of subgroups that were not specified at the outset of the trial is termed retrospective. For full credit the authors should recognize the limitations and usefulness of retrospective analyses. In addition, a good retrospective analysis will point out any inadequacies due to the randomization, dropouts, or compliance difficulties and consider their effect on outcomes.
Harvard School of Public Health, Technology Assessment Group
Mount Sinai School of Medicine, Clinical Trials Unit
Randomized Control Trials Evaluation Sheets

FORM A

ID# ___________________ Project # ___________________ Reader ________________

1.1 Author(s) ________________________________________________________________

1.2 Title ___________________________________________________________________

1.3 Journal __________________________________________________________________

1.4 Vol. and Year of publication ________________

1.5 Biostatistician
   a. Author
   b. Credits
   c. Neither

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   c. Coop >5

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C-6
### FORM B

#### STUDY PROTOCOL

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2.5 Control taste/sens

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2.6 Randomization blinding

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2.10 Prior estimate No.

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2.11 Stopping rules

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2.12 Testing randomization

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2.13 Testing blinding

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2.14 Testing compliance

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2.15 Biological equivalent

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2.16 Endpoint duplicate variable

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Total possible points 64

Accept paper for meta-analysis

Reject paper for meta-analysis

Reason for acceptance/rejection:
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<td>c. inadequate</td>
</tr>
<tr>
<td>B. Prognostically favors</td>
</tr>
<tr>
<td>a. treatment</td>
</tr>
<tr>
<td>b. controls</td>
</tr>
<tr>
<td>c. equivocal</td>
</tr>
<tr>
<td>d. unknown</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3.3 Major endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. test &amp; p</td>
</tr>
<tr>
<td>b. p no test</td>
</tr>
<tr>
<td>c. test no p</td>
</tr>
<tr>
<td>d. neither</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3.4 Post beta estimate (neg.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. adequate</td>
</tr>
<tr>
<td>b. fair</td>
</tr>
<tr>
<td>c. inadequate</td>
</tr>
<tr>
<td>d. n.a.</td>
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</table>

<table>
<thead>
<tr>
<th>3.5 Confidence limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. yes</td>
</tr>
<tr>
<td>b. partial</td>
</tr>
<tr>
<td>c. no</td>
</tr>
<tr>
<td>d. n.a.</td>
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</table>

<table>
<thead>
<tr>
<th>3.6 Life table/repeat. meas.</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. adequate</td>
</tr>
<tr>
<td>b. fair</td>
</tr>
<tr>
<td>c. inadequate</td>
</tr>
<tr>
<td>d. n.a.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>3.7 Which?</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. life table</td>
</tr>
<tr>
<td>b. repeated measures</td>
</tr>
<tr>
<td>c. neither</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>3.8 Timing of events</th>
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</thead>
<tbody>
<tr>
<td>a. adequate</td>
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<tr>
<td>b. fair</td>
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<tr>
<td>c. inadequate</td>
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<tr>
<td>d. n.a.</td>
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</table>

<table>
<thead>
<tr>
<th>3.9 Regression/correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. yes</td>
</tr>
<tr>
<td>b. no</td>
</tr>
<tr>
<td>c. n.a.</td>
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</table>

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<th>3.10 Which?</th>
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</thead>
<tbody>
<tr>
<td>a. regression</td>
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<tr>
<td>b. correlation</td>
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<td>c. neither</td>
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<thead>
<tr>
<th>3.11 Statistical analysis</th>
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</thead>
<tbody>
<tr>
<td>a. excellent</td>
</tr>
<tr>
<td>b. good</td>
</tr>
<tr>
<td>c. fair</td>
</tr>
<tr>
<td>d. poor</td>
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<thead>
<tr>
<th>3.12 Withdrawals</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. none</td>
</tr>
<tr>
<td>b. listed with reason</td>
</tr>
<tr>
<td>c. listed without reason</td>
</tr>
<tr>
<td>d. no list/unknown</td>
</tr>
<tr>
<td>e. &gt;15%</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>3.13 Handling withdrawals</th>
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</thead>
<tbody>
<tr>
<td>a. sevrl. ways</td>
</tr>
<tr>
<td>b. inc. orig.</td>
</tr>
<tr>
<td>c. discard</td>
</tr>
<tr>
<td>d. chng. grp/unknown</td>
</tr>
<tr>
<td>e. n.a.</td>
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</table>

<table>
<thead>
<tr>
<th>3.14 Side eff. discussion</th>
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</thead>
<tbody>
<tr>
<td>a. adequate</td>
</tr>
<tr>
<td>b. fair</td>
</tr>
<tr>
<td>c. inadequate</td>
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<tr>
<td>d. n.a.</td>
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<table>
<thead>
<tr>
<th>3.15 Retrospect. analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. adequate</td>
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<tr>
<td>b. fair</td>
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<tr>
<td>c. inadequate</td>
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</table>

**Total possible points**: 40
APPENDIX D

POSITION PAPER ON MEDICATION/ENTERAL FORMULA INTERACTIONS*

The combination of a medication with an enteral feeding product raises the potential for physical and or chemical interactions between the drug and the formula. For this reason, combining or co-administering these two products should only be ordered by appropriately trained health care professionals who are familiar with the drug package insert and have duly considered the following potential medication/formula interactions:

A. General Considerations:

1. As directed by the drug package insert, medications that should not be taken with foods should not be mixed or co-administered with enteral formulas.

2. Medications which might be mixed with foods may adversely affect the bioavailability of certain nutrients and or the taste acceptability of orally consumed formulas. Additionally, if GI intolerance to the mixture is observed, the cause of the intolerance is obscured.

3. The therapeutic effects of some medications depend on rapidly achieving high blood levels. If these medications are combined with a formula, chemical interactions with the mixture may reduce the effective amount of the drug provided. Further, if the mixture is slowly fed, drug administration is protracted and peak blood levels may be blunted.

B. Preparation and Feeding Considerations:

1. The addition of medications to enteral feeding products should be conducted in a clean, controlled environment to minimize the risks of microbiological contamination and the accidental administration of an incorrect medication. Enteral formulas that have been mixed with medications should be appropriately labeled.

2. The distal end of the feeding tube must be appropriately positioned for administering the medication being considered. Drugs that should be delivered to the stomach may not be effectively utilized if directly administered into the duodenum or the jejunum.

3. Administer the prescribed medication during, before, or after a feeding as recommended for the drug in use. If the preferred route of medication delivery is direct administration through a feeding tube, first rinse the feeding tube with a small amount of water to wash out residual formula, administer the medication via the tube, and then rinse the tube with water to assure complete drug delivery.

4. Although water-soluble medications offer more flexibility in mixing than do non-water soluble medications or tablets, consideration must be given to the pH of the drug being administered and the osmolality of the resulting combination product.

a. Strongly alkaline or acidic drugs will measurably affect the pH of the formula and may cause protein denaturation (curdling).

b. Medications which contain or consist of salts in solution or are highly concentrated, can be hypertonic. When hypertonic materials are rapidly administered, nausea, abdominal cramping, and diarrhea may result.

5. When non-water-based medications are added to enteral feeding products there is a high probability that the active drug will precipitate or separate from solution and inadvertently become highly concentrated. Under these circumstances, a portion of the drug may remain as a residue in the feeding container or may block the feeding tube. Further, the patient may receive irregular doses of the intended medication.

6. Viscous medications and thoroughly crushed tablets may be diluted or mixed with water provided there are no contraindications known and the drug is soluble in water. Enteric coated tablets and time-released capsules should not be crushed.
ADDENDUM

APPENDIX E

NOTE: The following persons and organizations submitted reference materials in response to announcement of the study in the Federal Register (55:39049–39050), September 22, 1989 and comments on a tentative report released April 30, 1990 as announced in the Federal Register (55:17672), April 26, 1990 [Docket 89N–0348]. Appendix E was inadvertently omitted from the final report. The LSRO sincerely regrets any inconvenience resulting from this omission.

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