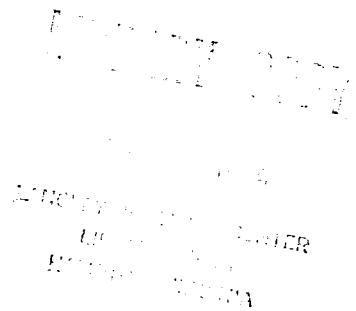
NASA-CR-3850 19850004253

NASA Contractor Report 3850

Nutritional Models for Space Travel From Chemically Defined Diets

Patricia A. Dufour

CONTRACT NASW-3165
NOVEMBER 1984



NASA

NASA Contractor Report 3850

Nutritional Models for Space Travel From Chemically Defined Diets

Patricia A. Dufour
The George Washington University
Washington, D.C.

Prepared for
NASA Office of Space Science and Applications
under Contract NASW-3165

National Aeronautics
and Space Administration

**Scientific and Technical
Information Branch**

1984

Foreword

The purpose of this report is to examine data on various types of formulated diets in order to uncover nutritional knowledge that may be applied to the design of diets assembled from fairly restricted groups of sources for long-term space travel. The study of these special diets is also of great benefit to the field of nutrition in general.

Compositions of representative commercial diets have been included to illustrate human dietary requirements. The inclusion of a dietary formulation is not an endorsement of a specific product. Many nutritional products that are not mentioned in this report are available. Exclusion of specific products was done to avoid repetition of similar formulations and because of space limitations. More complete descriptions of nutritional products can be obtained directly from the various manufacturers, as well as by consulting the latest edition of the Physician's Desk Reference and other sources.

I wish to thank James Bredt and Pat Groziak for reviewing this report and April Roy for her excellent typing and editorial assistance.

This report was prepared for the NASA Life Sciences Division under contract NASw-3165.

Table of Contents

List of Tables

CHAPTER I

INTRODUCTION

Purpose

One of the most complicated and frequently controversial areas in human health is nutrition. Although many of the major nutritional principles have been elaborated in this century, a large number of questions remain. The effects of specific nutrients are very difficult to study, due to the large number of other variables present. These variables include composition of the diet, genetic background, age, sex, environmental conditions, psychosocial factors, as well as many interactions between variables. Humans have been able to survive without understanding everything about nutrition by eating a varied diet. When a diet is more restricted, there is a greater risk of nutrient deficiencies developing over time.

A diet similar to what humans normally consume has been provided for space missions up to now because these missions have been of short duration. However, very long space missions are anticipated sometime in the future. These missions may require food and oxygen regeneration and waste recycling. The CELSS (Controlled Ecological Life Support Systems) Program of the National Aeronautics and Space Administration (NASA) is doing research on feasible approaches to food selection, food

production, and nutrient recycling. Due to the great practical and technical limitations on such missions, the number of species of plants and/or animals grown or raised will be quite restricted yet must furnish an adequate diet. It is essential that the best available understanding of human nutritional requirements be attained, so that an adequate combination of food sources can be selected.

The most extensive experience in humans with restricted diets is in the use of chemically defined diets (CDD's). In these diets, all of the nutrients are supplied in the form of relatively simple chemical compounds, so that the composition of each diet is more exactly determined than in a normal diet. It was thought that a review of the literature on CDD's would help the CELSS Program design space diets that could meet human nutritional requirements with a minimum number of components. An analysis of CDD's will also identify nutritional areas requiring further study, which will enable NASA to set the appropriate priorities.

It should be emphasized that CDD's are not being proposed as the actual diets for astronauts in this report. Although CDD's have been investigated by Winitz et al. (1965) for this potential application, the use of such an extreme diet is no longer being seriously considered for use in healthy individuals. Liquid diets tend to be monotonous and various morphological and physiological changes in the gastrointestinal tract have been observed in both humans and laboratory animals on CDD's. The

physiological effects of CDD's are discussed in detail later in this report. A number of unconventional food sources, such as algae, synthetic proteins and carbohydrates, bacteria, and others (Popov, 1975), have been investigated as food for space travel. These unusual sources will probably be combined with more conventional food sources in any actual system.

Scope

Chemically defined diets are reviewed in terms of the various types, nutrient compositions, clinical applications, physiological effects, and experimental studies in humans and laboratory animals. The major emphasis is on studies in healthy humans, and there are very few of these compared with those in seriously ill patients. Regarding the clinical studies, special consideration has been given to those in which the patients have been using CDD's for long durations. Human nutritional requirements that have been more clearly defined as a result of experience with CDD's are discussed. Current knowledge about nutrient requirements, toxicities, and interactions is summarized. Finally, areas are identified where more nutritional information is needed.

Early Development of CDD's

Chemically defined diets were developed for use in three situations: 1) in the prevention of starvation in severely ill patients; 2) in diets for astronauts in long-term space travel; and 3) in conducting precise metabolic and nutritional studies.

The provision of oral nutritional supplements in liquid form has been attempted throughout history. Certain synthetic nutrients, such as protein hydrolysates, and some liquid formula diets were being produced around 1950 (Kark, 1974). The development of CDD's can be traced through the use of intravenous (parenteral) feeding techniques, since the chemical composition of the fluids had to be formulated very precisely to avoid adverse reactions. The therapeutic use of intravenous fluids containing specific chemicals, such as salts and sugars, was first attempted in the 1800's (Shenkin and Wretlind, 1979).

Great advances in the use of parenteral feeding were made during World War II and in the decade following. Nutritional requirements for calories and nitrogen were established during this period (Shils, 1980). The major limitation on intravenous feeding in seriously ill patients, where the oral route is impossible, is that very large volumes of fluids are needed to furnish enough calories. Traditional intravenous techniques use isotonic fluids in peripheral veins (because these are more accessible); however, a very ill patient may not be able to tolerate over three liters of fluid per day (Dudrick and Rhoads,

1972). Since not enough calories may be delivered in three liters, the result of long-term total parenteral nutrition (TPN) under these conditions is starvation.

This problem was solved by Dudrick et al. (1968) by infusion of fluids into a catheter implanted in the superior vena cava through the external jugular (neck) or subclavian (shoulder) veins. The superior vena cava is large enough to dilute hypertonic glucose infusions, which would damage peripheral veins and alter the osmotic pressure of the blood. The technique was first tried successfully in puppies for as long as 256 days and then in humans for up to 200 days. Although the use of TPN has saved the lives of patients who cannot be fed through the gastrointestinal tract, it is a drastic measure which is associated with many complications, particularly infection. Oral CDD's are used when possible, depending on the patient. The clinical situations requiring CDD's are discussed in Chapter III.

In order to improve the liquid formula diets for clinical use, the National Institutes of Health began sponsoring a number of studies, in which various liquid diet compositions were tested in rats and mice during the 1950's (Birnbaum et al., 1957-1958; Greenstein et al., 1957; Winitz et al., 1957; and others). A nutritionally complete CDD was finally developed in rats (Greenstein et al., 1960). Further studies supported by NASA were begun with the goals of chemically improving this CDD for adaptation to humans and other species and of defining exact amino acid and trace element requirements (Winitz, 1962).

Various CDD's were then evaluated by Winitz et al. (1965) in healthy adult males with promising results.

The Air Force also became interested in improving formulated diets in the early 1960's in preparation for both long-term space travel and more precise nutritional studies. A series of projects were begun in order to develop CDD's after the Air Force found that none of the currently available liquid diets were either adequately defined chemically or palatable enough (Dymsza et al., 1968). The CDD's in these studies were developed at the Food Laboratory of the United States Army Natick Laboratories. In further studies, jointly sponsored by the Air Force and NASA, CDD's were tested in volunteers (college students) under simulated space conditions in a Life Support Systems Evaluator while the subjects wore space suits for 28-day trials (Katchman et al., 1967; Lotter et al., 1967; Katchman et al., 1970). The results of these studies in humans and laboratory animals are summarized in Chapter III.

A final development of CDD's is for the study of basic human nutrition, which is the major purpose of this report. Most of the studies on CDD's are clinical in nature, but all have uncovered information about nutrition that can be applied to normal individuals. The use of CDD's enables nutritionists to control dietary constituents more precisely, so that their effects can be more easily determined. In addition, the intravenous route of CDD's is useful in nutritional studies, because it bypasses the problem of differential absorption rates

of chemical compounds (Shenkin and Wretlind, 1979). Differential absorption means that different nutrients ingested at the same time will reach the bloodstream at different times, depending on the size and structure of each nutrient.

CHAPTER II

HUMAN NUTRIENT REQUIREMENTS AND CHEMICALLY DEFINED DIETS

All CDD's must supply water, energy, essential fatty acids, amino acids, vitamins, minerals, and trace elements in order to maintain health. The dietary requirements in healthy adults in the United States for these nutrient categories are discussed below. It should be noted that growing children, pregnant or nursing women, and the very ill generally have increased requirements. The need for energy and certain nutrients tends to be reduced in old age. Individual variations in requirements must also be considered in the design of diets. The various types of CDD's and the compounds used to satisfy these nutrient requirements in different formulations are reviewed, and the compositions of commercially available CDD's are compared.

Basic Requirements

Water

The adult fluid (water) requirement is 1 ml fluid per kcal (kilocalorie) diet per day (National Research Council, 1980). Human fluid needs are increased by high ambient temperature, greater physical exercise, and when certain disease symptoms (such as diarrhea, vomiting, or fever) are present.

Energy

The number of kilocalories of energy needed for growth, maintenance of body temperature, and other metabolic activities varies according to age, gender, amount of daily physical activity, body size, environmental conditions, and the presence of various stressful conditions, such as pregnancy, lactation, injury, or disease. The recommended energy intakes for adults in the United States are shown in Table 1.

Table 1

Recommended Daily Energy Intake:
U.S. Adults

	Age (years)	Mean (kcal)	Range (kcal)
Men (70 kg = 154 lb; 5 ft 10 in tall)	19-22	2900	2500-3300
	23-50	2700	2300-3100
	51-75	2400	2000-2800
	76 up	2050	1650-2450
Women (55 kg = 121 lb; 5 ft 4 in tall)	19-22	2100	1700-2500
	23-50	2000	1600-2400
	51-75	1800	1400-2200
	76 up	1600	1200-2000

Source:

National Research Council, 1980

Protein

Proteins are polymers composed of over 20 different amino acids, of which 9 are essential (see Table 2). There are a number of other naturally occurring amino acids that are not in proteins, but are found in cells and have various metabolic functions. The amino acids in proteins are all L-alpha-amino acids.

The amount of protein required per day is 0.8 g per kg body weight per day (National Research Council, 1980). This is equivalent to 56 g protein per day for a 70 kg man and 44 g protein per day for a 55 kg woman. Protein intake should be about 10 to 15% of the total diet (Harper, 1973). The American diet includes about 11 to 12% protein (National Research Council, 1980). The requirement for protein consists of a need for both nitrogen and specific essential amino acids (EAA's). The recommended daily intake of EAA's is listed in Table 3. Proteins also furnish sulfur and phosphorus in significant amounts.

Table 2

Amino Acids of Human Proteins

Essential	Nonessential
Histidine*	Alanine**
Isoleucine	Arginine**
Leucine	Asparagine
Lysine	Aspartic acid**
Methionine	Cysteine (from cystine)**
Phenylalanine	Cystine (can substitute for 80-90% methionine)
Threonine	Glutamic acid**
Tryptophan	Glutamine
Valine	Glycine (toxic at high levels)
	Hydroxylysine
	4-Hydroxyproline
	Proline**
	Serine**
	Tyrosine** (can substitute for 70-75% phenylalanine)

*Requirements not established for healthy adults; required in infants and nephritic adults (Calloway, 1975)
**Recommended for a CDD given IV (Shenkin and Wretlind, 1979)

Table 3

Recommended Daily Intake of
Essential Amino Acids

	g/day (for a 70 kg adult male)
Histidine	2.0
Isoleucine	1.4-1.68
Leucine	2.2-2.24
Lysine	1.6-1.68
Methionine	2.2
Phenylalanine	2.2
Threonine	1.0-1.12
Tryptophan	0.42-0.5
Valine	1.6-1.96

Sources:

Calloway, 1975
National Research Council, 1980

The nitrogen requirement (for synthesis of amino acids) is fulfilled by nonessential amino acids (NAA's). The terms "essential" and "nonessential" are somewhat misleading, because both types of amino acids must be supplied for an adequate diet. The main distinction is that EAA's cannot be synthesized by the human, and NAA's can be synthesized. The ability of the human to synthesize certain NAA's, such as arginine, is somewhat limited (Shenkin and Wretlind, 1979).

In addition to needing certain amounts of amino acids, humans also need a certain balance among the amino acids. There are a number of potential interactions among the amino acids, which

could create an imbalance if incorrect mixtures are supplied in a CDD. There are also some amino acids, such as glycine, which are toxic at high levels (Shenkin and Wretlind, 1979).
Physiologically balanced amino acid mixtures are those that have EAA patterns similar to proteins in the human body (Vander et al., 1975), i.e., animal proteins. Whole egg and milk proteins (casein is a major milk protein) are often used as standards with which to compare the quality of other proteins. These proteins are fully utilized by young rats in bioassays for protein quality.

Another aspect of overall protein quality is digestibility, which is determined by the amount of nitrogen in the feces (National Research Council, 1980). Plant proteins are usually less digestible than animal proteins due to too much fiber, lower solubility in human digestive fluids, and other factors (Hoff, Howe, and Mitchell, 1982; Vander et al., 1975). In general, single plant proteins (except for soybean protein) do not provide all EAA's. Combinations of plants, such as wheat and peanuts, cereals and green leafy vegetables and legumes, and corn or rice plus beans, can provide the right balance of amino acids (Howe and Hoff, 1982). The plants in each of the combinations should be ingested at the same time so that the body has all the EAA's for optimum protein synthesis (Phillips and Odgers, 1982).

Carbohydrate

Carbohydrates include sugars, starches, and cellulose and are the main energy sources in the normal diet. Carbohydrates should comprise about 55 to 70% of the total diet (Harper, 1973). The National Research Council (1980) states that the current amount of carbohydrate in the American diet is about 46%, and that carbohydrates made up a higher fraction of the diet earlier in this century. Fat intake has increased to nearly the carbohydrate intake in terms of calories. Although the absolute minimum intake of carbohydrate should be 50 to 100 g, Calloway (1975) recommends about 400 to 500 g per day, mainly as the complex carbohydrate, starch, because solutions with high levels of simple sugars have high osmolarities (large amounts of dissolved substances). A sudden increase in osmolarity can be stressful to the body, whether the substances are taken orally or intravenously. This is a critical consideration in CDD's and will be discussed in more detail later.

Fiber

Fiber includes indigestible carbohydrates and other substances, such as cellulose, lignin, gums, and pectins. Although there is no proof that a fiber requirement exists, beneficial effects of fiber have been observed. Fiber is known to enhance intestinal function, and there is some epidemiological evidence that people with diets containing very low amounts of

fiber have higher incidences of cancer of the colon and other ailments. Although this preventive aspect of fiber has not been validated, an intake of 2 to 3 g fiber per day is suggested (Calloway, 1975). Too much fiber, on the other hand, may interfere with mineral absorption (National Research Council, 1980).

Fat

Fats, or lipids, provide energy and essential fatty acids, improve food palatability, and act as carriers for the fat-soluble vitamins (A, D, E, and K). Most dietary fats are triglycerides (National Research Council, 1980), which consist of three fatty acids of various lengths attached to glycerol, a 3-carbon carbohydrate. The major essential fatty acid for humans is linoleic acid, which is abundant in vegetable oils. Although arachidonic acid is an essential fatty acid, it is produced from linoleic acid in the body and is not required in the diet (Martin et al., 1983). Linolenic acid may also be an essential fatty acid; however, this has not been confirmed in humans. Linolenic acid occurs in the same vegetable oils as linoleic acid, but in smaller amounts. Linolenic acid is not synthesized in the human, and possible linolenic acid deficiency symptoms have been observed in both humans and animals. If a linolenic acid requirement exists it is very small, and the dietary ratio of linoleic to linolenic acids may actually be more important in human nutrition. These questions are under investigation (Bivins

et al., 1983). Calloway (1975) states that 3 to 6 g linoleic acid per day will meet the requirements. The National Research Council (1980) recommends that at least 1 to 2% of the total daily caloric intake be essential fatty acids, which are polyunsaturated.

Other recommendations of the National Research Council (1980) include decreasing the total portion of fat in the diet from 42% (in the typical American diet) to 35% and increasing the ratio of polyunsaturated to saturated fats in the diets. High intake of saturated fats may be one of the risk factors in coronary artery disease, although this is still controversial. High intake of polyunsaturated oils may also be harmful and no more than 10% of the diet should be from this source. Too many polyunsaturated fatty acids may increase the vitamin E requirement and may hasten aging (Hoff, Howe, and Mitchell, 1982). These investigators recommend that total dietary fat be approximately 30%.

Vitamins

The vitamins are a group of chemical compounds of various structures, which are needed for normal metabolism and are either not synthesized at all in the human or are not synthesized in large enough amounts without dietary supplementation (Goodhart and Shils, 1980). The vitamins function as cofactors or coenzymes for a variety of metabolic reactions. Intestinal bacteria synthesize small quantities of vitamins. With the exception of biotin and vitamin K, intestinal vitamin synthesis

is not adequate to meet adult requirements (Harper, 1973; Vander et al., 1975). Although the vitamins are not chemically related, these nutrients are commonly divided into two categories: water-soluble and fat-soluble.

The water-soluble vitamins include the vitamin B complex (folacin, niacin--nicotinic acid and nicotinamide, pantothenic acid, riboflavin or B_2, thiamin or B_1, pyridoxine or B_6, cobalamins or B_{12}, biotin, and inositol), ascorbic acid or C, and choline. Although no recommended allowance for inositol has been established at this time in the United States, about 1 g per day is recommended in the Soviet Union (Calloway, 1975). Inositol is essential in mice and chicks and has been found to be necessary for growth in some experimental human cell cultures (Harper, 1973). Choline is synthesized by the human and an average of about 400 to 900 mg (milligrams) are ingested daily in the American diet (National Research Council, 1980). Because no choline deficiency symptoms have been reported in humans (although such symptoms have been found in various laboratory animals), there may not be a human dietary requirement for choline. The precursors for choline biosynthesis (methionine, folacin, and vitamin B_{12}) do have dietary requirements. The remaining question is whether deficiency symptoms might appear after long-term absence of dietary choline.

The fat-soluble vitamins are A (retinol), D (ergocalciferol and cholecalciferol), E (tocopherols), and K (phylloquinone and

the menaquinones). Human vitamin requirements from the National Research Council (1980) and Calloway (1975) are given in Table 4.

Table 4

Human Vitamin Requirements[1]

Vitamin	Daily Allowance Recommended for U.S. Adults
Water-soluble	
B complex	
Thiamin (B_1)	1.0 mg (per 2000 kcal)
Riboflavin (B_2)	1.2 mg (per 2000 kcal)
Pyridoxine (B_6)	2.2 mg (males); 2.0 mg (females)
B_{12}	3.0 mcg (micrograms)
Folacin (folic acid)	400 mcg
Niacin (nicotinic acid and nicotinamide)	13.2 mg/2000 kcal (60 mg tryptophan = 1 mg niacin)
Pantothenic acid	4.0-7.0 mg (estimated safe and adequate intake)
Biotin[2]	100-200 mcg (estimated safe and adequate intake)
Inositol	Not established in humans[3]
C (ascorbic acid)	60.0 mg
Choline	0.4-0.9 g (average intake--may not be a vitamin in humans)
Fat soluble	
A	1.0 mg (5000 IU) males; 0.8 mg (4000 IU) females
D	0 (for adults exposed to sunlight) 200.0 IU (with no exposure or inadequate exposure to sunlight)
E	10.0 IU (males); 8.0 IU (females); 30.0 IU for astronauts[3]
K[2]	70.0-140.0 mcg (estimated safe and adequate intake)

References:

1. From National Research Council (1980) unless indicated
2. No requirement established due to synthesis by intestinal microorganisms
3. Calloway (1975)

Minerals

Essential elements assist in the activation of various enzymes, in the electrophysiology of nerves and muscles, and in many other complex bodily functions. The minerals that are required in relatively large amounts are commonly called macronutrients and include calcium, chlorine, magnesium, phosphorus, potassium, and sodium. Sulfur is also required; however, this requirement is met by intake of the amino acids, cysteine and methionine. Calcium and phosphorus combine to form the structural part of bones and teeth and function in other metabolic processes. Magnesium is combined with calcium and phosphorus in bone, is involved in various enzyme systems, and maintains the electrical potential of nerves and muscles. These three minerals must be present in certain ratios for optimal health. The ratio of calcium to phosphorus should be about 1:1 and that of calcium to magnesium should be about 2:1 (Calloway, 1975). The condition of weightlessness in space travel has produced calcium losses and imbalances leading to bone loss in astronauts (Nicogossian and Parker, 1982; Rambaut, 1980).

The function of the electrolytes--sodium, potassium, and chlorine--is to regulate water metabolism. The requirements for sodium in particular are the subject of an ongoing controversy. The relationship of high sodium intake to the development of hypertension remains unresolved. Certain individuals are at least susceptible to developing hypertension and may be more

sensitive to sodium intake. Vander et al. (1975) estimate that the American intake of table salt (sodium chloride, which is the source of most dietary sodium) is an average of 10 to 15 g per day. The intake of sodium alone is estimated to be from 2.3 to 6.9 g per day in a typical American adult (National Research Council, 1980). The National Research Council recommends that this intake be reduced to between 1.1 and 3.3 g per day with a maximum of 5 to 6 g per day.

To complicate this issue, other minerals may be involved in hypertension. Kurtz and Morris (1983) have suggested that the intake of chloride rather than sodium alone, may be important in the development of hypertension. A pilot survey comparing the dietary habits of normotensive versus hypertensive individuals found that while the sodium and potassium levels between the two groups did not differ significantly, the calcium intake was significantly lower in hypertensives (McCarron et al., 1982). The daily mineral allowances for adults (National Research Council, 1980) are given in Table 5.

Table 5

Daily Mineral Allowances for U.S. Adults*

Calcium	0.8 g
Magnesium	0.35 g (males); 0.3 g (females)
Phosphorus	0.8 g
Chlorine (as chloride)**	1.7-5.1 g
Potassium**	1.875-5.625 g
Sodium**	1.1-3.3 g (5-6 g maximum)

*National Research Council, 1980
**Estimated safe and adequate intake

Trace Elements

The functions of and dietary requirements for the trace elements, or micronutrients, are still under study. For an element to be deemed essential, it must be naturally occurring and must be found in the newborn (or in breast milk), in the egg, and in various organs (Schwarz, 1977). Essentiality is further defined by discovery of a specific physiological function of the element. Essential trace elements are required in very small amounts and are toxic at higher levels. A number of trace elements have been added to the list of essential nutrients for humans in the past 20 to 30 years. Future research will undoubtedly uncover more essential trace elements, will more precisely define the requirements for them, and will clarify various interactions among them.

The trace elements whose requirements have been the most well-defined are iron, iodine, and zinc (Calloway, 1975). The

requirements for the trace elements are the result of studies in laboratory animals, limited experimental studies in humans, calculations of the normal daily dietary intake in the United States, calculations of the amounts excreted in healthy humans, and the presence of deficiency symptoms in certain individuals (which are ameliorated by administration of the element). Copper deficiency is relatively rare in healthy humans and is more commonly observed in individuals suffering from malnutrition, in premature infants, and after long-term total parenteral nutrition (Bozzetti et al., 1983; National Research Council, 1980). Deficiency symptoms in healthy humans are rare for chromium, manganese, molybdenum, and selenium, however, animal studies have provided evidence that these elements are required by humans (National Research Council, 1980).

The chromium requirement is not easily defined, because the element varies in form and availability, and the amount actually absorbed from the diet is very small. As with all nutrients, essentiality is best shown by observing deficiency symptoms in humans. The most clearly documented cases of chromium deficiency have been reported in TPN (Total Parenteral Nutrition) patients. One case occurred in a woman after 3 1/2 years with no chromium in the TPN solution. The woman lost weight, developed neuropathy, and had abnormal glucose, fat, and nitrogen metabolism. Large initial doses of chromium were given for 2 weeks, after which a daily dose of 20 mcg (micrograms) had been given for 18 months with no further symptoms at the time of

publication (Jeejeebhoy et al., 1977). Since normal plasma insulin levels occurred along with the deficiency symptoms, this case provided evidence of chromium's role as a possible cofactor for insulin.

Manganese deficiency has not been reported in either normal humans or in patients on CDD's (manganese is usually included in oral CDD's and TPN solutions). The functions of manganese in human enzymes have been well-documented, and deficiencies have been induced in animals. Manganese is involved in the enzymes that lead to the formation of oligosaccharides, proteoglycans (mucopolysaccharides), and glycoproteins. These classes of compounds contribute to the structure of connective tissue and cell membranes and are involved in the immune system and many other complex areas. Manganese is also needed for the enzyme superoxide dismutase, which appears to protect cells against the effects of oxygen (Martin et al., 1983). Deficiency of manganese in animals results in abnormal bones and cartilage, retarded growth, birth defects, and decreased reproductive capacity (National Research Council, 1980).

Molybdenum is needed for proper functioning of three enzymes: aldehyde oxidase, xanthine oxidase, and sulfite oxidase. The functions of these enzymes are, respectively, the metabolism of aldehyde and various nitrogenous compounds, conversion of xanthine to uric acid, and the metabolism of the sulfur amino acids, methionine and cystine. The only case of molybdenum deficiency in a human was reported by Abumrad et al. (1981). A

male patient aged 24 had been on TPN for about one year, after which he began experiencing severe symptoms from administration of various amino acid solutions. The physical symptoms included nausea, vomiting, headaches, increased pulse and breathing rates, and coma. The biochemical changes included high levels of methionine in the blood, decreased excretion of inorganic sulfate and uric acid, and increased excretion of organic sulfate and xanthine. These changes were not induced by other nutrient solutions, and the symptoms were reversible when the amino acid infusions were withdrawn. A daily dose of 300 mcg ammonium molybdate was able to correct the severe reactions to amino acid infusions.

Selenium deficiency has been reported recently in a male patient on TPN without selenium for over a year. There were no obvious symptoms; however, low selenium levels and low activity of the enzyme glutathione peroxidase (for which selenium is a cofactor) were detected in the blood. Selenium was administered at a dose of 400 mcg per day for one week and then 100 mcg per day. After 4 months of selenium therapy, the blood tests returned to normal (Baker et al., 1983).

A summary of the trace element requirements is given in Table 6. Elements have been included that are suspected to be essential for humans, but no requirements have been set due to insufficient data. Requirements for these elements are expected to be set in the future.

Table 6

Essential Trace Element Requirements

Element	Recommended Daily Intake[1]
Essentiality demonstrated[1]:	
Cobalt	In vitamin B_{12}
Copper	2.0-3.0 mg
Chromium	50.0-200.0 mcg
Fluorine (as fluoride)	1.5-4.0 mg (adult) 1.5-2.5 mg (younger groups)
Iodine	150.0 mcg
Iron	10.0 mg (males) 18.0 mg (females)
Manganese	2.5-5.0 mg
Molybdenum	0.15-0.5 mg
Selenium	50.0-200 mcg
Sulfur	in methionine and cysteine
Zinc	15.0 mg
Essentiality suspected[1-5]:	
Aluminum	Not established
Arsenic	"
Cadmium	"
Nickel	75.0 mcg (hypothetical)[5]
Silicon	Not established
Tin	"
Vanadium	"

References:

1. National Research Council, 1980
2. Rambaut, 1980
3. Schwarz, 1977
4. Mertz, 1981
5. Solomons et al., 1982

Types of CDD's and Sources of Nutrients

The phrase, "chemically defined diet," as used in the biomedical field, is somewhat ambiguous. This is because there are different degrees to which a CDD may be defined and because none of these diets are completely specified down to the last molecule. Both Heymsfield et al. (1979) and Bloch and Shils (1980) have suggested that DFD (defined formula diet) would be more accurate. For the purposes of this report, the term CDD includes diets administered in liquid form that are purified or semipurified, are low residue, and may include intact protein and small amounts of lactose. This type of diet is in contrast to either a diet of solid food or a liquid diet made entirely from homogenized solid food.

Chemically defined diets differ in the way they are administered, in the specific compounds used in each nutrient category (i.e., protein, fat, carbohydrate, etc.), and in the amounts of each nutrient used. There are different types of CDD's for clinical use in order to meet the needs of patients with specific diseases. For example, those patients with the inability to absorb fat properly would need diets lower in fat than normal, and diabetics would need diets lower in simple sugars. Similarly, patients with a functioning gastrointestinal (GI) system would be able to receive liquid CDD's orally (by mouth or by stomach tube). Patients with large portions of their GI systems removed may have to be fed intravenously. Intravenous (IV) feeding of a complete diet is commonly called total

parenteral nutrition (TPN) or IV hyperalimentation. The latter term is misleading, because not all TPN patients receive excess calories (Shils, 1980). Nevertheless, the term is still used in the literature. TPN serves as an artificial intestinal tract (Grundfest et al., 1979). The normal intestine absorbs nutrients from digested food and transfers them into the bloodstream. TPN performs this function by putting nutrients directly into circulation via a central vein (usually the superior vena cava in the chest).

Fats

The compositions of oral and intravenous CDD's are similar; the major differences are in the fats and micronutrients (Voitk, 1975). Since fats are not water-soluble, they are supplied in the form of an emulsion. For IV administration, the fat emulsions must be very stable, so that large fat particles (which could lead to blocked blood vessels in major organs) do not form. An early fat emulsion, Lipomul, was associated with serious side effects and had to be taken off the market in 1964 by the United States Food and Drug Administration (Dudrick and Rhoads, 1972). Safer fat emulsions were developed and approved for use in the United States beginning in 1977 (Shils, 1980). The fat emulsions in current use consist of 100 to 200 g vegetable oil (soybean or safflower oil), 12 to 20 g of an emulsifier (egg-yolk phospholipids, soybean lecithin, or soybean phospholipids), 25 to 50 g of a compound (sorbitol, xylitol, or glycerol) to make the

emulsion isotonic (same osmotic pressure) with blood, and enough distilled water to make one liter, allowing for the volume displaced by the other substances (Shenkin and Wretlind, 1979).

The fats used in oral CDD's are similar, although the suspensions do not have to be as stable, since there would be no possibility of blocked blood vessels. Vegetable oils, such as safflower, soy, or corn, are used alone or in combination with mono- or diglycerides to stabilize the suspension and medium chain triglycerides (MCT's). The MCT's are formed from the fractional distillation of coconut oil and contain fatty acids with 6 to 10 carbon atoms. They are very easily digested and increase the absorption of the long chain triglycerides (Chernoff, 1981; Phillips and Odgers; 1982), which contain fatty acids of 16 to 18 carbons and are found in vegetable oils (Phillips and Odgers, 1982; Smith and Heymsfield, 1983).

Vitamins and Trace Elements

Vitamin and trace element doses for TPN solutions have been based on oral doses. The requirements for these nutrients in parenteral nutrition are less understood, and there are potential problems with both inadequate and excessive doses (Voitk, 1975). With oral intake of food, there is a regulatory system in the intestine that prevents excess absorption of certain nutrients, depending on the individual's needs. In IV intake of nutrients, this regulatory system is bypassed, and all nutrients administered get into the bloodstream (Shenkin and Wretlind,

1979).

The American Medical Association (AMA) issued some guidelines for parenteral vitamin doses in 1975 and then updated these statements 4 years later (American Medical Association, 1979b). The updated recommendations are similar to the original ones. The major point is that in 1979 none of the parenteral or intramuscular multivitamin products satisfied all of the guidelines. The available products contained excesses or deficiencies of certain essential vitamins, lacked other essential vitamins, and were not specific to the requirements of children versus adults. The manufacturers have subsequently reformulated many of the products to reflect AMA guidelines. General recommendations for adults included increased levels of the water-soluble vitamins (to compensate for stress in patients) and decreased amounts of vitamin A (the oral requirement is larger because it is based on absorption and conversion of carotenes to vitamin A) compared with levels recommended by the National Research Council in 1974. The AMA stated that its guidelines are preliminary until more accurate scientific data on vitamin requirements for long-term parenteral nutrition are available. Some of the current parenteral vitamin formulations will be discussed later in this chapter.

Vitamins and trace elements are generally included with all other substances in one solution for oral CDD's. Modular vitamins, minerals, and trace elements are available for both parenteral and oral use. In TPN, these nutrients tend to be

added separately and may not be included on a daily basis. The dose schedule depends on the physician's judgment and the needs of the patient. For example, Greig et al. (1982) give most of the vitamins 6 days per week; on day 7, vitamins A and D are given. Vitamin E, which is fat-soluble, is included in the fat component of the TPN solution. Biotin was not generally supplied by this group, and this appears to have been standard practice. Since biotin deficiency in TPN patients has been reported recently (Innis and Allardyce, 1983; Levenson, 1983) biotin supplementation is becoming standard practice. Howard et al. (1983) have found in their clinical experience that TPN patients can be given larger supplements of vitamin C, thiamin, niacin, pyridoxine, and folic acid twice weekly. Adding substances less frequently in home TPN prevents possible contamination of the solutions, which are made up by the patients. Since TPN is being used in more and more cases, a better understanding of human micronutrient needs can be expected in the near future.

An additional problem with micronutrients in CDD's is that trace elements are widely distributed in nature and are often present as contaminants in water and other substances. An analysis of various standard nutrient solutions (amino acids, lipids, carbohydrates, and salts) for TPN showed that zinc, copper, chromium, iron, and manganese were present (other trace elements were not being tested). Zinc and copper were present in almost every solution tested; the other three were found less often (Shils, 1980). The exact amount of each element will thus

be different in every CDD, even if supplemental elements are added in carefully measured amounts. Hauer and Kaminski (1978) reported that the chromium present as a contaminant in standard TPN nutrient solutions may be adequate for human nutritional needs. Zinc levels were low in the majority of TPN solutions tested, and all of the commercial solutions were deficient in iron and copper.

Guidelines for the trace element amounts in TPN solutions were issued by a panel of experts of the AMA (American Medical Association, 1979a). At that time, commercial solutions containing iron, iodine, and cobalt (as vitamin B_{12}) were already available. The AMA recommended that zinc, copper, chromium, and manganese be produced commercially as separate solutions, to avoid possible overdoses and to meet individual requirements. The AMA gave the following recommendations for daily IV intake of each of these elements in clinically stable adults: zinc, 2.5 to 4.0 mg; copper, 0.5 to 1.5 mg; chromium, 0.01 to 0.015 mg; manganese, 0.15 to 0.8 mg. The AMA also stated that manufacturers should be required to analyze their TPN solutions to determine the exact amounts of each trace element present as a contaminant.

The AMA did not recommend including in TPN therapy other trace elements that are suspected of being essential, until further information on human requirements is available. These trace elements are selenium, vanadium, molybdenum, nickel, tin, silicon, and arsenic. Since deficiencies of both selenium and

molybdenum have been reported (Abumrad et al., 1981; Baker et al., 1983) and since recommended dietary allowances of these two elements are now available (National Research Council, 1980), these elements are becoming part of long-term TPN and oral CDD therapy. Current practice in TPN tends to include zinc, chromium, copper, and manganese (Seltzer, 1983); the others have been included only when indicated. Zinc, copper, and manganese are included in most oral CDD's.

Minerals and Proteins

The levels of macronutrients, including minerals and electrolytes, are of great importance in CDD's. This is especially the case in critically ill patients on TPN, because many of these individuals have a metabolic imbalance of water and electrolytes. Human requirements for calcium, phosphorus, and magnesium may be lower IV than orally (Heymsfield et al., 1979). The commercial amino acid solutions made from protein hydrolysates contain various amounts of the macronutrients (and micronutrients) as contaminants and as normal parts of the amino acid solutions. The commercial crystalline amino acids tend to have lower amounts of electrolytes (Shils, 1980). Separate electrolyte solutions for supplementation are also available.

Amino acids in all types of CDD's are given as either protein hydrolysates or crystalline (synthetic) amino acid solutions. Positive nitrogen balance has been attained in patients receiving either amino acid source (Shils, 1980). The

use of synthetic amino acids allows more flexibility in the composition of the CDD, because a single amino acid can be added in a smaller or larger amount to meet individual requirements. Some protein hydrolysates have been found to have amino acid imbalances, and these solutions contain some D-forms of amino acids, most of which humans cannot use. The crystalline amino acids are now used more commonly in TPN (Phillips and Odgers, 1982). Protein hydrolysates, crystalline amino acids, and intact proteins are all used in complete CDD's for oral administration. The advantages of intact proteins are better taste and fewer GI upsets. Synthetic amino acid solutions have a bitter taste and higher osmolality, which is increased by the addition of flavoring ingredients (Smith and Heymsfield, 1983).

Carbohydrates

The carbohydrate components of CDD's must be carefully selected to avoid exceeding safe osmolarities. Osmolarity is a measure of how many substances are dissolved in a solution. It is defined as the number of separate solute particles in the total volume of solution. The units are in osmoles (Osm) per liter of solution. The solute concentration is also expressed as the osmolality--the number of solute particles per unit solvent measured in osmoles per kg solvent. These units are more commonly expressed in terms of milliosmoles (mOsm). Substances that ionize create more solute particles. For example, sodium chloride breaks into sodium and chloride ions in solution. A one

molar solution of sodium chloride (one molecular weight in grams of sodium chloride per liter) is 2 Osm per liter. Glucose, proteins, and amino acids do not ionize in solution--a one molar solution of each of these types of compounds would have an osmolarity of 1 Osm per liter. Osmolarity only includes the number of particles in solution, not the sizes or chemical properties of the particles (Vander et al., 1975).

Plasma has an osmolarity of about 280 mOsm per liter, and human red blood cells have an osmolarity of about 300 mOsm per liter (Vander et al., 1975). If a large amount of a solution with a higher osmolarity than blood (i.e., a hypertonic solution) rapidly gets into the bloodstream, a number of adverse physiological effects can result. Intravenous administration of very hypertonic solutions can cause inflammation of the veins, blood clots (Dudrick and Rhoads, 1972), dehydration, and coma from acute hyperglycemia (Shils, 1980). Oral intake of solutions with high osmolarities (or osmolalities) may result in GI upsets, such as nausea and abdominal cramps, diarrhea, vomiting, sweating, and fainting. These symptoms are the result of the "dumping syndrome," in which large amounts of fluid enter the upper intestine in order to dilute the hyperosmolar environment (Case et al., 1981a; Vander et al., 1975). Normal, solid-food diets include hypertonic meals with no adverse effects, and a moderate degree of osmolarity (700 mOsm per liter) has been reported to be beneficial in promoting nutrient absorption (Case et al., 1981b). These investigators hypothesized that problems

with moderate osmolarity may be due to the presence of substances that are difficult to absorb. The recommended osmolality range for a complete enteral diet is from 300 to 700 mOsm per kg (Smith and Heymsfield, 1983).

Despite problems with high osmolarity, glucose (dextrose) is currently the best carbohydrate source for intravenous feeding. This is because glucose is needed by the brain, it can be metabolized by all cells, and it may be monitored easily by blood tests. Under severe stress, less insulin may be produced by the body, leading to glucose intolerance. This problem can be corrected by the addition of insulin to the TPN solution (Shenkin and Wretlind, 1979). Various substitutes for intravenous glucose, such as maltose, sorbitol, xylitol, and fructose, have been tested in humans and laboratory animals (Young and Weser, 1975). Further research is needed before an alternative carbohydrate becomes used clinically. Since fats can be an excellent source of energy, combinations of fat and glucose have been used successfully. Although the ideal ratio is unknown, the use of 30 to 50% fat and the rest glucose as the energy sources has produced very promising results, such as increased protein synthesis (Greig et al., 1982). MacFie et al. (1983) compared glucose (25%) alone with glucose plus Intralipid (20%) as the energy sources in two groups of TPN patients. When glucose alone was the energy source, more energy was used for fat synthesis and less was available for protein synthesis.

A greater variety of carbohydrates can be used in oral

CDD's, without the adverse effects observed in IV administration. Some of the carbohydrates in common use are combinations of glucose or sucrose with oligosaccharides (composed of 2 to 10 simple sugars), glucose alone, and maltodextrin. Maltodextrin is formed from the hydrolysis of corn starch and contains mainly glucose polymers and a few simple sugars such as maltose (Mead Johnson & Company, 1984). No starch modules are available as energy sources (Smith and Heymsfield, 1983). In addition to carbohydrates added as energy sources, others serve as flavorings and other additives. The flavor additives increase the osmolarity of the CDD's (Young et al., 1975), but are of obvious psychological benefit to the patient.

Commercially Available CDD's

Due to the increasing use of CDD's, a large variety of nutrient formulations are being manufactured. These include products providing a complete diet, various combinations of two or more nutrients, and single-nutrient modules that can either be combined to form a complete diet or used as supplements. Low residue CDD's contain proteins of a nonmilk (lactose-free) origin, including egg albumin, soy protein, or casein. "Low-residue" refers to the fact that less bulky feces are produced, placing less strain on the intestines. Polymeric CDD's contain intact protein, have higher molecular weight components, low osmolalities, and are less costly. Patients receiving polymeric CDD's must be able to digest protein and fat normally.

Monomeric CDD's have high osmolalities, are low or lacking in starches and triglycerides, are more costly, and can be used with patients who cannot digest protein and fat normally. Monomeric CDD's are typically prescribed for patients with inflammatory bowel disease and with chronic diarrhea (Heymsfield et al., 1979).

The cost of an oral CDD can be less than $50 per day for 2000 kcal (Chernoff, 1981). Wholesale prices in 1978 (per 1000 kcal) for several of the complete CDD's were as follows: Flexical, $3.99; Vital, $4.43; Vivonex, $4.50 (Koretz and Meyer, 1980). Flavoring packages are available at additional cost. Home TPN can be considerably more expensive, and there is a greater potential for medical complications (see Chapter III). The cost for the TPN solutions plus the infusion pump and other equipment was estimated by Shils (1980) to be from $13,000 to $24,000 per year. Malcolm et al. (1980) reported that yearly costs for home TPN in various patients ranged from $10,000 to over $50,000.

Although space does not allow for a complete discussion of the composition of each CDD available, representative CDD's have been summarized. The data for the CDD's discussed are shown in Tables 7 through 22 at the end of this chapter. Table 22 lists all of the CDD's mentioned, giving the nutrient type and manufacturer's name and address. The compositions are compared, and nutrient deficiencies and excesses are discussed where relevant.

It should be noted that there is a very high turnover among nutritional products. During the preparation of this report, some of the products listed below were discontinued and/or reformulated. A major reason for the turnover is that pharmaceutical companies change their products to reflect new medical findings regarding nutritional requirements, side effects, patient acceptance, and other factors. Those products that were no longer available at time of publication are so noted in Table 22.

Comparison of Nutrients in Commercial CDD's

The compositions of four complete enteral CDD's--Flexical, Vital High Nitrogen (to be referred to as Vital), Standard Vivonex (to be referred to as Vivonex), and Precision Isotonic--are shown in detail. Precision Isotonic is a polymeric diet; the others are monomeric. Compositions of a number of modular nutrient formulations for both IV and enteral use are also given. The CDD's selected for inclusion in the tables are basic diets and solutions not designed for patients with highly specialized or unusual dietary needs (beyond the inability to tolerate solid food). For example, a number of commercial diets are available for various metabolic diseases, such as Maple Syrup Urine Disease, phenylketonuria, and tyrosinemia (Bloch and Shils, 1980). The CDD's are commonly diluted to 1 kcal per ml or about 1000 kcal per liter (Heymsfield et al., 1979), although the dilution varies, particularly in the modular preparations. Many

of the nutrient levels in the tables below are given per 1000 kcal. It should be noted that about 2000 kcal of a CDD would be administered.

Carbohydrates

Tables 7 and 8 list the carbohydrates in some commercial diets and modular preparations, respectively. The percentage of calories contributed by the carbohydrate sources to the whole diets ranges from 60 to 90.5, compared with about 46% in a typical diet in the United States (National Research Council, 1980). The National Research Council recommends that carbohydrates be 55 to 70% of the diet. The carbohydrates in the complete CDD's include sucrose, glucose polymers, and maltodextrin. The modular carbohydrate solutions available include maltodextrin (in Moducal), glucose polymers (in Polycose), or glucose alone (for parenteral use).

Fats

The fat components in some common CDD's are given in Tables 9 to 11. The percentage of fat in the complete diets ranges from 1.3 to 30%, and the percentage of total kilocalories which are essential fatty acids varies from 1 to 10%. These amounts are acceptable nutritionally, although the 1% essential fatty acids in Vivonex is at the lower limit of the range (1 to 2%) recommended by the National Research Council (1980). Most of the complete diets and modular fat solutions include emulsifiers.

Greater stability is attained when maltodextrins or other larger carbohydrates are also used in the diet, when the fat components comprise less than 30% of the total kilocalories, when the fat is added at room temperature, or when the complete diet is mixed every day (Smith and Heymsfield, 1983). The breakdown of individual fatty acids in the oils used as fat sources is given in Table 11. Linoleic acid is the main constituent of the polyunsaturated oils, safflower and corn. Both oils also contain significant amounts of oleic and palmitic acids, and soybean oil also contains almost 8% linolenic acid (Phillips and Odgers, 1982). Soybean oil is used in Flexical, Precision Isotonic, and the parenteral solution Intralipid. Safflower oil is found in Vital and Vivonex. Medium chain triglycerides are utilized, in addition to the polyunsaturated oils stated above, in Flexical and Vital.

Proteins

The proteins in CDD's include synthetic or crystalline amino acids, hydrolyzed natural proteins, and intact proteins (Tables 12 and 13). As stated earlier in this chapter, those diets containing intact protein (e.g., Precision Isotonic) are polymeric and are not considered to be chemically defined in the strict sense, but have been included for comparison purposes. This type of diet contains more well-defined carbohydrate and fat components. The proteins in the complete CDD's (see Table 12) contribute from 8.2 to 16.7% to the total energy in the diet.

This range is comparable to that--10 to 15%--recommended by Harper (1973), as well as to that of the typical American protein intake--about 11 or 12% of the total diet (National Research Council, 1980).

Synthetic (crystalline) amino acids are the protein sources in Vivonex (a complete oral CDD) and in the parenteral protein solutions, Travasol and Freamine III. The synthetic amino acid solutions are available in different concentrations from 5.5 to 10%. Hydrolyzed casein is found in Flexical, and a combination of hydrolyzed meat, soy, and whey proteins is in Vital. The modular oral protein products, Pro Mix and Casec, contain the intact proteins, whey and calcium caseinate, respectively. Precision Isotonic contains intact protein in the form of egg albumin (from pasteurized egg white solids). Single synthetic amino acids are also available (Smith and Heymsfield, 1983).

The nutritional value of the intact milk proteins, whey and casein, is very high. Intact protein solutions also have lower osmolalities and a superior taste compared with other protein sources, as stated previously. The natural mineral and electrolyte levels of intact proteins and hydrolyzed proteins are higher than those of synthetic amino acid solutions. The modular intact protein products are subjected to a demineralization treatment, which lowers but does not completely remove all the minerals (Smith and Heymsfield, 1983). Residual mineral levels for Casec and Pro Mix have been included in Table 13. The electrolyte levels added to the parenteral amino acids are also

given. Mineral and trace element levels of specific CDD's will be discussed in more detail later.

The amino acid levels of the complete CDD's and the modular protein sources are listed in Tables 14 and 15. The essential amino acid levels can be compared with the recommended daily intakes in Table 3. The minimum daily requirement for each essential amino acid is half the recommended daily intake (Harper, 1973). All of the essential amino acids are provided in the CDD's listed. There is greater variability in the nonessential amino acids provided, and there are some unanswered questions about the desirable amount of each one. Research from the parenteral administration of amino acids (Shenkin and Wretlind, 1979) has suggested which nonessential amino acids should be included (see Table 2) and which ones are toxic at very high levels (aspartic acid, glutamic acid, and glycine). Of the recommended nonessential amino acids, cystine and glutamic acid are not included in Vivonex and Travasol, glutamic acid and tyrosine are absent in Freamine III, and serine is absent in Travasol. The above suggestions regarding nonessential amino acids may not apply to orally administered proteins, either intact or hydrolyzed.

Vitamins

The levels of vitamins (per 1000 kcal) in the complete oral CDD's are shown in Table 16. These levels may be compared with the recommended daily intakes listed in Table 4. About twice the

levels listed in Table 16 (2000 kcal) would normally be ingested. All four CDD's contain amounts of vitamins that either meet or exceed the recommended intakes in Table 4. Choline may not be a vitamin for humans because the body can synthesize it. The average daily dietary intake of choline is about 400 to 900 mg. Of the three complete CDD's, only Flexical provides this amount in 2000 kcal. The effects of a lower than average intake of choline over long periods are unknown. Until there is more information, lower dietary intakes of choline may be considered adequate, as long as the choline precursors (methionine, folacin, and vitamin B_{12}) are provided in the diet.

Three of the modular vitamin preparations are listed in Table 17. As explained previously, the requirements for parenteral vitamins differ from those of enteral vitamins. The American Medical Assocation (1979b) has set guidelines for parenteral vitamin doses, and both multivitamin products listed in the table (Berocca Parenteral Nutrition and M.V.C. 9+3) conform to these guidelines. Another parenteral product, M.V.I.-12, has the same vitamin levels (Physician's Desk Reference, 1984). The vitamin levels are identical in Berocca and M.V.C. 9+3; only the additives and manufacturers differ. Vitamin K is not included in these products because it can interact with anticoagulants used in certain patients. It is recommended that vitamin K be given separately 2 to 4 mg per week in patients not receiving anticoagulants. The parenteral products do not include choline. NUTRISOURCE is a new group of products, which includes intact

protein, amino acid, carbohydrate, fat, vitamin, and mineral/trace element modules for enteral feeding. The vitamin levels in the NUTRISOURCE module conform to the National Research Council (1980) guidelines (see Table 4) except in choline. The average daily intake of choline in the American diet is estimated at 400 to 900 mg. Since choline is synthesized by the human, it is not certain that there is a dietary need for choline. For a patient on a formulated diet for long periods, the 100 mg daily level of choline in NUTRISOURCE may be adequate, but this is uncertain.

Minerals, Electrolytes, and Trace Elements

The minerals and electrolytes (per 1000 kcal) in complete CDD's are given in Table 18. See Table 5 for the recommended daily allowances of these substances. The levels recommended for sodium, potassium, and chlorine have not yet been determined. The levels in Table 5 thus are estimated safe and adequate intakes rather than specific requirements. Vivonex contains 1.444 g chloride in 2000 kcal, compared with the 1.7 to 5.1 g listed in Table 5. Precision Isotonic is the only diet in Table 18 that contains sodium at the safe and adequate intake level indicated in Table 5. The other three CDD's contain under a gram of sodium in 2000 kcal. This may not be harmful because the minimum requirement for sodium in adults may be as low as 58 mg per day to maintain health (National Research Council, 1980).

The trace element levels (per 1000 kcal) of the complete

CDD's are given in Table 19. The requirements for these elements are in Table 6. Copper, iodine, iron, manganese, and zinc are provided within the required ranges in the four CDD's. Vivonex and Precision Isotonic (Sandoz Nutrition, 1984; Physician's Desk Reference, 1984) include chromium, molybdenum, and selenium. These elements would need to be supplemented in long-term use of Flexical or Vital. Cobalt and sulfur are not added to any of the diets, because these elements are present in other nutrients (in vitamin B_{12} and in cysteine and methionine, respectively). None of the CDD's contain added fluoride. Fluorine is present as fluoride in many drinking water supplies (also soils, plants, and animals) and is associated with reduced dental caries at a total intake level of 1.5 mg per day or more. A water supply containing 1 mg per liter fluoride would produce the desired total daily intake from food plus water. Fluoride maintenance levels from 0.4 to 2.0 mg per day (for a 70 kg human) have been suggested by various authors (as reviewed by Phillips and Odgers, 1982) for total parenteral nutrition.

As shown in Table 20, the minerals and trace elements are available either separately or in combined mineral and trace element modules. Separate NUTRISOURCE enteral modules are formulated for use with intact protein and with synthetic amino acids, because intact protein has a higher natural mineral content. Thus, the mineral levels added to the module for use with amino acids (as the protein source) must be higher. These mineral and trace element amounts correspond closely to the

requirement levels listed in Tables 5 and 6. The module for use with intact protein contains lower levels of the electrolytes, but the same levels of trace elements. LyphoMed, Inc. produces a module M.T.E.-5, containing small doses of copper, chromium, manganese, selenium, and zinc, bulk solutions of various electrolytes (RAP or Rapid Additive Pak), and single element modules, such as Iodopen (iodine), Molypen (molybdenum), and Selepen (selenium). These modules are for parenteral use. A parenteral iron module (Imferon) is produced by Merrell Dow and other companies (Physician's Desk Reference, 1984).

Osmolalities

As Table 21 indicates, the solutions with the highest osmolarities or osmolalities are the more concentrated synthetic amino acids (10% Travasol, 1000 mOsm per liter), the carbohydrate modules (Polycose, 850 mOsm per kg), and the complete CDD's with flavorings added (595 to 723 mOsm per kg). Precision Isotonic, a polymeric CDD, has an osmolality of 300 mOsm per kg. The monomeric CDD's (Flexical, Vital, and Vivonex) are more chemically defined with lower molecular weight substances and have higher osmolalities as a result (460 to 550 mOsm per kg unflavored). Other CDD's in Table 21 which are approximately isotonic are 10% Intralipid (280 mOsm per kg), 5% dextrose (278 mOsm per kg), and the single trace element modules--Chrometrace, Coppertrace, Mangatrace, and Zinctrace (300 mOsm per liter).

List of Products Cited

The final table (22) includes a list of the modular and complete CDD's discussed in this chapter. The names and locations of the manufacturers are also given. The companies producing CDD's should be consulted for more complete information and for updated formulations.

Table 7

Carbohydrates in CDD's
A. Complete Enteral Diets

	Flexical[1-3]	Vivonex[1-3,5]	Vital[4,5]	Precision Isotonic[6]
% of Total kcal as carbohydrate	61.0	90.5	74.0	60.0
Total grams carbohydrate per 1000 kcal	152.5	230.6	188.0	150.0
Carbohydrate sources	Sucrose Oligosaccharides Citrate	Glucose oligosaccharides	83.2% Glucose polymers (oligo- and polysaccharides) from hydrolyzed corn starch 16.8% Sucrose Lactose (1.7 mg/1000 kcal)	Sucrose Maltodextrin Citrate
Flavors	Unflavored	Vivonex Flavor Packets (lemon-lime, orange-pineapple, strawberry, or vanilla	Preflavored vanilla or add Vari-Flavors Flavor Pacs (orange, cherry, lemon, pecan, or strawberry)	Preflavored orange or vanilla

Table 7 (continued)

	Flexical[1-3]	Vivonex[1-3,5]	Vital[4,5]	Precision Isotonic[6]
Flavor ingredients (nonnutritive)	None	Artificial flavors and colors Citric acid Dextrose Saccharin Silicon dioxide (adds about 8-9 kcal carbohydrate)	Artificial and natural flavors (produce no significant change in the nutritional status)	Artificial and natural flavors Citric acid

References:

1. Bloch and Shils, 1980
2. Young et al., 1975
3. Young et al., 1982
4. Vital High Nitrogen, 1981
5. Physician's Desk Reference, 1984
6. Sandoz Nutrition, 1984

Table 8

Carbohydrates in CDD's
B. Modular Carbohydrate Solutions

Parenteral[1]

Carbohydrate source	Glucose (dextrose) as glucose monohydrate
Concentrations	10% (isotonic): 10 g glucose/100 ml water
	50% (hypertonic): 50 g glucose/100 ml water

Enteral[2,3,4]

	Polycose Liquid	Moducal[5]
Carbohydrate source(s)	Glucose oligosaccharides	Maltodextrin (glucose polymers mainly; some glucose, maltose, and isomaltose)
Total carbohydrate	50 g/100 ml Polycose	95 g/100 g Moducal
Minerals/electrolytes (maximum level)	per 100 ml:	per 100 g:
Chloride	140 mg	170 mg
Potassium	6 mg	5 mg
Sodium	70 mg	70 mg
Calcium	20 mg	not listed
Phosphorus	3 mg	" "

References:

1. Shils, 1980
2. Bloch and Shils, 1980
3. Physician's Desk Reference, 1984
4. Smith and Heymsfield, 1983
5. Mead Johnson & Company, 1984

Table 9

Major Fat Components in CDD's
A. Complete Enteral Diets

	Flexical[1-3]	Precision Isotonic[4-5]	Vital[1,3-6]	Vivonex[1-3,6]
Major fat source(s)	Soybean oil MCT oil[7]	Soybean oil	Safflower oil MCT oil[7]	Safflower oil
% of Total kcal as Fat	30	28	9.3	1.3
% of Total kcal as Essential Fatty Acids	10	4.5	7.0	1
Total g Fat/1000 kcal	34	31	10.8	1.45
Emulsifiers and other additives	Soy lecithin	Mono- and diglycerides Carrageenan BHA	Soy lecithin Mono- and diglycerides	Not listed

References:

1. Bloch and Shils, 1980
2. Young et al., 1975
3. Young et al., 1982
4. Physician's Desk Reference, 1984
5. Sandoz Nutrition, 1984
6. Vital High Nitrogen, 1981
7. Medium Chain Triglyceride oil

Table 10

Major Fat Components in CDD's
B. Modular Fat Emulsions

	Intralipid[1-4]	Microlipid[1,5]	MCT (Medium Chain Triglyceride) oil[1,5,6]
Major fat source(s)	Soybean oil (contains vitamin E), 100-200 g/liter	74% Linoleic acid, 44 g/120 ml Other unsaturated fatty acids	Fractionated coconut oil (contains fatty acids of 6-10 carbons), 93.3 g fat/100 ml
Route of administration	IV	Enteral	Enteral
Emulsifiers	Egg-yolk phospholipids, 12 g/liter	Soy lecithin	--
Other additives Glycerol (to make it isotonic with blood)	22.5 g/liter	--	--
Amount of fat in emulsion	10-20%	50%	93.3%
Trace elements[4]		Not listed	Not listed
Zinc	33-46 mcg/liter		
Copper	20-28 "		
Chromium	0.9 "		
Iron	<100 "		

References:

1. Bloch and Shils, 1980
2. Phillips and Odgers, 1982
3. Shenkin and Wretlind, 1979
4. Shils, 1980
5. Smith and Heymsfield, 1983
6. Mead Johnson & Company, 1984

Table 11

Major Fat Components in CDD's
C. Fatty Acids in CDD Fat Sources

	Medium Chain Triglyceride Oil[1,2]	Safflower Oil[1]	Soybean Oil[1]
Fatty acids, essential (polyunsaturated)			
Linoleic	--	77.0%	54.27%
Linolenic	--	--	7.81%
Arachidonic	--	--	--
Fatty acids, non-essential			
Monounsaturated			
Oleic	--	13.0%	26.41%
Palmitoleic	--	--	0.026%
Saturated			
Palmitic	--	7.0%	9.18%
Myristic	--	--	0.035%
Stearic	--	2.5%	2.87%
Arachidic	--	--	0.12%
Behenic	--	--	0.059%
	6-10 carbon fatty acids (saturated):		
	<8 carbons 6%		
	8 carbons 67%		
	10 carbons 23%		
	>10 carbons 4%		

References:

1. Phillips and Odgers, 1982
2. Physician's Desk Reference for Nonprescription Drugs, 1982

Table 12

Proteins in CDD's
A. Complete Enteral Diets

	Flexical[1-3]	Precision Isotonic[4]	Vital[1,3,5,6]	Vivonex[1-3,6]
% of Total kcal as protein	9.0	12	16.7	8.2
Total grams protein per 1000 kcal	26.4	30	41.7	20.6
Protein sources	Hydrolyzed casein (amino acids, small peptides)	Egg albumin (pasteurized egg white solids)	87% Partially hydrolyzed proteins (soy, whey, meat) as small peptides 13% essential amino acids	Crystalline amino acids (synthetic)

References:

1. Bloch and Shils, 1980
2. Young et al., 1975
3. Young et al., 1982
4. Sandoz Nutrition, 1984
5. Vital High Nitrogen, 1981
6. Physician's Desk Reference, 1984

Table 13

Proteins in CDD's
B. Modular Protein Solutions

	Pro Mix[1,2] (enteral; dry)	Casec[1-4] (enteral; dry)	Travasol[5,6] (8.5%; parenteral)	Freamine III[5] (8.5%; parenteral)
Protein amount	227 g/ 1000 kcal; 88 g/ 100 g Pro Mix	237.6 g/ 1000 kcal; 88 g/100 g Casec	85 g/ 1000 ml solution	85 g/ 1000 ml solution
Protein source	Whey (intact protein)	Calcium caseinate (intact protein)	Crystalline amino acids	Crystalline amino acids
Kcal/concentration	1000 kcal/ 284 g Pro Mix; 360 kcal/ 100 g Pro Mix	1000 kcal/ 270 g Casec; 370 kcal/ 100 g Casec	8.5 g/100 ml (5.5% and 10% also available)	8.5 g/100 ml (10% also available)
Other nutrients				
Carbohydrate	22.7 g/ 1000 kcal	0	0	0
Fat	0	2 g/100 g Casec	0	0
Minerals/ Electrolytes	mEq/1000 kcal:	per 100 g Casec:		
Sodium	18.52	150 mg	70mEq/liter	Available with or without electrolytes
Potassium	116.51	10 mg	60mEq/liter	
Magnesium	Not listed	Not listed	10mEq/liter	
Chloride	" "	10 mg	70mEq/liter (also available without electrolytes)	
Calcium	" "	1.6 g	Not listed	
Phosphorus	" "	0.8 g	see next page	

Table 13 (continued)

	Pro Mix[1,2]	Casec[1-4]	Travasol[5,6]	Freamine III[5]
Other additives				
Acetate (as sodium acetate and acetic acid for pH adjustment)	Not listed	Not listed	5.94 g/liter (sodium acetate); 135 mEq/liter (acetate)	Not listed
Sodium bisulfite (as stabilizer)	Not listed	Not listed	3 mEq/liter	Not listed
Phosphate	Not listed	see previous page	60 mEq/liter	Not listed

References:

1. Bloch and Shils, 1980
2. Smith and Heymsfield, 1983
3. Mead Johnson & Company, 1984
4. Physician's Desk Reference for Nonprescription Drugs, 1982
5. Phillips and Odgers, 1982
6. Physician's Desk Reference, 1983

Table 14

Amino Acids in CDD's
A. Complete Enteral Diets

	Flexical[1,2]	Precision Isotonic[3]	Vital[2,4,5]	Vivonex[1,5]
Total protein	26.4 g/1000 kcal	30 g/1000 kcal	41.7 g/1000 kcal	20.6 g/1000 kcal
Essential amino acids (g/1000 kcal)				
Histidine	0.705	0.669	1.0842	0.455
Isoleucine	1.425	2.000	1.9182	0.937
Leucine	2.410	2.670	3.3360	1.483
Lysine	2.015	1.812	2.2101	1.115
Methionine	1.060	1.209	1.5012(ref.6)	0.960
Phenylalanine	1.120	1.941	3.4611(ref.7)	1.067
Threonine	1.095	1.335	1.5846	0.937
Tryptophan	0.355	0.477	0.4587	0.290
Valine	1.770	2.352	2.3352	1.034
% of Total protein	45	45	40	40
Nonessential amino acids (g/1000 kcal)				
Alanine	0.845	2.289	see ref.8	0.999
Arginine	0.935	1.782	"	1.827
Cystine	0.100	0.732	With methionine	0
Glutamic acid	5.485	4.260	see ref.8	0
Glycine	0.560	1.146	"	1.629
Proline	2.555	1.146	"	1.335
Serine	1.490	2.385	"	0.688
Tyrosine	0.590	1.272	With phenylalanine	0.194
Aspartic acid	1.895	2.385	see ref.8	2.132
Glutamine	0	0	"	3.516
% of Total protein	55	55	60	60

References:

1. Young et al., 1975
2. Young et al., 1982
3. Sandoz Nutrition, 1984
4. Vital High Nitrogen, 1981
5. Physician's Desk Reference, 1984
6. Total sulfur-containing amino acids (methionine and cystine)
7. Aromatic amino acids (phenylalanine and tyrosine)
8. 13% free amino acids; 87% of protein as small peptides; amounts of individual amino acids not specified

Table 15

Amino Acids in CDD's
B. Modular Protein Solutions

	Pro Mix[1] enteral:	Casec[1] enteral:	Freamine III[2] parenteral:	Travasol 8.5%[3] parenteral:	
Total protein	88 g/100 g Pro Mix	88 g/100 g Casec	101.5 g/ 16 g nitrogen (N)	8.404 g/ 100 ml	
Essential amino acids	g/100 g of the module:		g/16 g N (100 g protein):	g/100 ml:	g/ liter:
Histidine	2.5	2.76	2.96	0.372	3.72
Isoleucine	5.8	5.01	7.26	0.406	4.06
Leucine	12.8	8.8	9.47	0.526	5.26
Lysine	10.6	7.51	7.63	0.394	3.94
Methionine	3.7	2.5	5.54	0.492	4.92
Phenylalanine	4.3	4.83	5.90	0.526	5.26
Threonine	5.8	3.63	4.18	0.356	3.56
Tryptophan	2.5	1.12	1.60	0.152	1.52
Valine	6.1	6.3	6.89	0.390	3.90
Nonessential amino acids					
Alanine	5.5	3.28	7.38	1.760	17.60
Arginine	3.5	3.54	9.96	0.880	8.80
Cysteine	In cystine	In cystine	In cystine	0	0
Cystine	4.1	0.26	<0.25	0	0
Glutamic acid	18.2	21.06	0	0	0
Glycine	2.3	1.73	14.64	1.760	17.60
Proline	6.2	10.27	11.69	0.356	3.56
Serine	5.1	4.4	6.15	0	0
Tyrosine	4.1	5.01	0	0.034	0.34

References:

1. Smith and Heymsfield, 1983
2. Phillips and Odgers, 1982
3. Block and Shils, 1980

Table 16

Vitamins in Complete Enteral CDD's

	Flexical[1,2] per 1000 kcal:	Precision Isotonic[3] per 1000 kcal:	Vital[2,4,5] per 1000 kcal:	Vivonex[2,5] per 1000 kcal:
Water-soluble				
B complex				
Thiamin (B_1)	2.5 mg	1.3 mg	1.0 mg	0.8 mg
Riboflavin (B_2)	2.2 mg	1.7 mg	1.13 mg	0.9 mg
Pyridoxine (B_6)	2.5 mg	2.0 mg	1.47 mg	1.1 mg
B_{12}	7.5 mcg	4.0 mcg	4.0 mcg	3.3 mcg
Folacin	200.0 mcg	270.0 mcg	266.7 mcg	222.2 mcg
Niacin (nicotinic acid and nicotinamide)	25 mg	13.3 mg	13.3 mg	11.1 mg
Pantothenic acid	12.5 mg	6.7 mg	6.7 mg	5.6 mg
Biotin	150 mcg	200 mcg	200 mcg	170 mcg
Inositol	0	0	0	0
C (ascorbic acid)	150 mg	60 mg	60 mg	33.3 mg
Choline	250.0 mg	66.7 mg	133.3 mg	40.9
Fat-soluble				
A	2500 IU	3333 IU	3333 IU	2778 IU
D	200 IU	266.7 IU	266.7 IU	222 IU
E	23 IU	20 IU	40 IU	17 IU
K	125 mcg	67 mcg	186.7 mcg	37 mcg (as K_1)

References:

1. Young et al., 1975
2. Young et al., 1982
3. Sandoz Nutrition, 1984
4. Vital High Nitrogen, 1981
5. Physician's Desk Reference, 1984

Table 17

Vitamins in Modular CDD's

	NUTRISOURCE[1] Vitamins	Berocca Parenteral[2] Nutrition	M.V.C. 9+3[2-4]
	Complete daily enteral dose/ 10 g powder	Complete daily IV dose/2 ml solution	Complete daily IV dose/10 ml solution
Water-soluble			
B complex			
Thiamin (B_1)	1.4 mg	3.0 mg	3.0 mg
Riboflavin (B_2)	1.6 mg	3.6 mg	3.6 mg
Pyridoxine (B_6)	2.2 mg	4.0 mg	4.0 mg
B_{12}	3.0 mg	5.0 mcg	5.0 mcg
Folacin (folic acid)	400 mcg	400 mcg	400 mcg
Niacin (nicotinic acid and nicotinamide)	18.0 mg	40.0 mg	40.0 mg
Pantothenic acid	5.5 mg	15.0 mg	15.0 mg
Biotin	150 mcg	60 mcg	60 mcg
Inositol	0	0	0
C (ascorbic acid)	60.0 mg	100.0 mg	100.0 mg
Choline	100.0 mg	0	0
Fat-soluble			
A	5000 IU	3300 IU[5]	3300 IU[5]
D	200 IU	200 IU	200 IU
E	10 IU	10 IU	10 IU
K	70 mcg	0[6]	0[6]

Table 17 (continued)

	NUTRISOURCE Vitamins[1]	Berocca Parenteral Nutrition[2]	M.V.C. 9+3[2-4]
Additives			
Carrier	maltodextrin (9 g carbohydrate)	0	0
pH correction	0	Sodium hydroxide Citric acid	Sodium hydroxide Monobasic potassium phosphate Benzyl alcohol
Solubilizer	0	Polyoxyethylated vegetable oil	Polysorbate-20
Antioxidants	Not listed	Not listed	BHA BHT
Stabilizers and preservatives	Not listed	Propylene glycol Gentisic acid Ethanolamide Ethyl alcohol Sodium citrate Benzyl alcohol Disodium edetate	Propylene glycol Gentisic acid Ethanolamide

References:

1. NUTRISOURCE Technical Information Manual, 1982
2. Physician's Desk Reference, 1984
3. Feroz et al., 1982
4. M.V.I.-12 (Armour Pharmaceutical Company) is almost identical
5. Recommended for parenteral route (American Medical Association, 1979b)
6. 2-4 mg once per week recommended if no anticoagulant therapy is being given (American Medical Association, 1979b)

Table 18

Minerals/Electrolytes in Complete Enteral CDD's

	Flexical[1,2]	Precision Isotonic[3]	Vital[4,5]	Vivonex[2,5]
mg/1000 kcal				
Calcium	600	666.7	666.7	556
Chlorine (as chloride)	1000	1070	900	722
Magnesium	200	267	266.7	222
Phosphorus	500	666.7	666.7	556
Potassium	1250	1000	1333.3	1172
Sodium	350	800	466.7	468

References:

1. Young et al., 1975
2. Young et al., 1982
3. Sandoz Nutrition, 1984
4. Vital High Nitrogen, 1981
5. Physician's Desk Reference, 1984

Table 19

Essential Trace Elements (Per 1000 kcal)
in Complete CDD's

	Flexical[1,2]	Precision Isotonic[3]	Vital[2,4,5]	Vivonex[1,2,5]
Cobalt[6]	--	--	--	--
Copper (mg)	1.0	1.3	1.33	1.1
Chromium (mcg)	0	100	0	28
Fluorine as (fluoride)	0	0	0	0
Iodine (mcg)	75.0	100	100.0	83.3
Iron (mg)	9.0	12	12.0	10.0
Manganese (mg)	2.5	2.7	2.5	1.6
Molybdenum (mcg)	0	200	0	83
Selenium (mcg)	0	66.7	0	83
Sulfur[7]	--	--	--	--
Zinc (mg)	10	10	10	8.3

References:

1. Young et al., 1975
2. Young et al., 1982
3. Sandoz Nutrition, 1984
4. Vital High Nitrogen, 1981
5. Physician's Desk Reference, 1984
6. Part of vitamin B_{12}
7. Part of the amino acids, cysteine and methionine

Table 20

Minerals and Trace Elements in Modular CDD's

	NUTRISOURCE Minerals for Protein Formulas[1] Complete daily enteral dose/ 24 g powder:	NUTRISOURCE Minerals for Amino Acid Formulas[1] Complete daily enteral dose/ 24 g powder:	M.T.E.-5[2] Parenteral trace elements:	RAP(Rapid Additive Pak)[2] Parenteral electrolytes:
A. Mixtures				
Calcium	0.65 g	0.80 g	0	Calcium gluconate
Chlorine (chloride)	1.8 g	2.0 g	0	Potassium chloride, etc.
Magnesium	0.35 g	0.35 g	0	
Phosphorus	0.65 g	0.80 g	0	
Potassium	1.75 g	2.2 g	0	
Sodium	1.0 g	1.3 g	0	
Copper	2.0 mg	2.0 mg	0.4 mg/ml	
Chromium	125 mcg	125 mcg	4 mcg/ml	
Fluorine	0	0	0	
Iodine	150 mcg	150 mcg	See below	
Iron	18.0 mg	18.0 mg	See below	
Manganese	4.0 mg	4.0 mg	0.1 mg/ml	
Molybdenum	325 mcg	325 mcg	See below	
Selenium	125 mcg	125 mcg	20 mcg/ml	
Zinc	15.0 mg	15.0 mg	1 mg/ml	
Additive				
Carrier	maltodextrin (6 g carbohydrate)	maltodextrin (3 g carbohydrate)	--	--

Table 20 (continued)

B. Single elements (parenteral solutions):

Chrometrace (as chromic chloride)	4 mcg chromium/ml[3]
Coppertrace (as cupric chloride)	0.4 mg copper/ml[3]
Mangatrace (as manganese chloride)	0.1 mg manganese/ml[3]
Zinctrace (as zinc chloride)	1 mg zinc/ml[3]
Iodopen (as sodium iodide)	100 mcg iodine/ml[2]
Molypen (as ammonium molybdate)	25 mcg molybdenum/ml[2]
Selepen (as selenious acid)	40 mcg selenium/ml[2]
Imferon - iron dextran complex (as ferric hydroxide and dextran in sodium chloride solution)	50 mg iron/ml[3]

References:

1. NUTRISOURCE Technical Information Manual, 1982; NUTRISOURCE Minerals also available in electrolyte-restricted formulations
2. LyphoMed, Inc., 1983
3. Physician's Desk Reference, 1984

Table 21

Osmolarities/Osmolalities of CDD's

	Osmolarity[1] mOsm/liter water:	Osmolality[1] mOsm/kg water:
A. Complete Oral CDD's		
Flexical	723 (flavored[2])	550[3,4]
		723 (flavored[5])
Precision Isotonic		300[6]
Vital High Nitrogen		460 (unflavored[7])
		475-490 (flavored[7])
Standard Vivonex		595-600 (flavored[8])
		550 (unflavored[8])
B. Modular CDD's		
Intralipid		10%: 280[9] 20%: 330
Moducal		725[10]
Polycose		850[8,10]
Dextrose (glucose)[9]		
5%		278
10%		523
20%		1250
30%		2100
50%		3800

Table 21 (continued)

	Osmolarity[1] mOsm/liter water:	Osmolality[1] mOsm/kg water:
Travasol[12]		
2.75%	425 (with electrolytes)	
10%	1000 (without electrolytes)	
Chrometrace	300[8]	
Coppertrace	300[8]	
Mangatrace	300[8]	
Zinctrace	300[8]	

References:

1. Listed as reported by the source referenced: milliosmoles/liter water = milliosmoles/kilogram (kg) water (1 liter pure water weighs 1 kg)
2. Koretz and Meyer, 1980
3. Bloch and Shils, 1980
4. Young et al., 1982
5. Young et al., 1975
6. Sandoz Nutrition, 1984
7. Vital High Nitrogen, 1981
8. Physician's Desk Reference, 1984
9. Shenkin and Wretlind, 1979
10. Smith and Heymsfield, 1983
11. Phillips and Odgers, 1982
12. Physician's Desk Reference, 1983

Table 22

List of CDD's
Included in Chapter II

CDD	Type	Manufacturer
A. Complete		
Flexical*	Monomeric	Mead Johnson & Company Nutritional Division Evansville, IN
Precision Isotonic	Polymeric	Sandoz Nutrition Minneapolis, MN
Standard Vivonex	Monomeric	Norwich-Eaton Laboratories Norwich, NY
Vital High Nitrogen	Monomeric	Ross Laboratories Columbus, OH
B. Modular		
Moducal	Carbohydrate source (enteral)	Mead Johnson & Company Nutritional Division Evansville, IN
Polycose	Carbohydrate source (enteral)	Ross Laboratories Columbus, OH
Dextrose IV solutions	Carbohydrate source (IV)	Abbot Pharmaceuticals North Chicago, IL American McGaw Division of Hospital Supply Corp. Irvine, CA Cutter Laboratories Energyville, CA
MCT (medium chain triglyceride) Oil	Fat source (enteral)	Mead Johnson & Company Nutritional Division Evansville, IN
Intralipid	Fat source (IV)	Vitrum Stockholm, Sweden

Table 22 (continued)

CDD	Type	Manufacturer
Microlipid	Fat source (enteral)	Biosearch Medical Products Summerville, NJ (formerly produced by Organon Inc. West Orange, NJ)
Casec	Protein (enteral)	Mead Johnson & Company Nutritional Division Evansville, IN
Pro Mix	Protein (enteral)	Navaco Industries Phoenix, AZ
Freamine III	Amino acids (IV)	American McGaw Division of Hospital Supply Corp. Irvine, CA
Travasol	Amino acids (IV)	Travenol Laboratories, Inc. Parenteral Products Deerfield, IL
NUTRISOURCE	Vitamins; Minerals with trace elements (enteral)	Sandoz Nutrition Minneapolis, MN
Berocca Parenteral Nutrition	Multivitamins (IV)	Roche Laboratories Division of Hoffmann-LaRoche Inc. Nutley, NJ
M.V.C. 9+3 (Multivitamin Concentrate for Infusion)	Multivitamins (IV)	LyphoMed, Inc. Chicago, IL
RAP	Electrolytes (IV)	"
M.T.E.-5	Trace elements (IV)	"
Iodopen	Iodine (IV)	"
Molypen	Molybdenum (IV)	"
Selepen	Selenium (IV)	"

Table 22 (continued)

CDD	Type	Manufacturer
Chrometrace; Coppertrace; Mangatrace; Zinctrace	Trace elements	Armour Pharmaceutical Company Tarrytown, NY
M.V.I.-12	Multivitamins (IV)	"
Imferon	Iron source (IV)	Merrell Dow Pharmaceuticals Inc. Cincinnati, OH

*No longer available (reformulated as Criticare HN)

Summary

Human adults require fluid; energy; protein containing 8 to 9 essential amino acids; carbohydrate; fat containing the essential fatty acid, linoleic acid; about 13 vitamins; 6 minerals and electrolytes; and about 11 trace elements in the daily diet. These represent the minimum number of dietary nutrients humans need to be healthy. Additional vitamins and trace elements may be added as more is learned about human nutrition.

Chemically defined diets (CDD's) in this report include liquid diets that are formulated so that the components can be quantified and reproduced to a much greater degree than a typical, solid food diet. Various types of CDD's have been developed for oral, tube, or intravenous administration, depending on the degree of function of the patient's gastrointestinal system. The relative proportions of fat, carbohydrate, and protein can be adjusted in a CDD, and the specific types of fats, carbohydrates, and proteins vary. Both nutritionally complete CDD's and modular CDD's containing a single nutrient or a combination of nutrients, are available. The compositions of representative CDD's are shown in Tables 7-22. Experience with the administration of various types of CDD's in humans and laboratory animals is described in Chapter III.

CHAPTER III

CLINICAL AND EXPERIMENTAL USE OF CHEMICALLY DEFINED DIETS

CDD's have been used therapeutically in seriously ill patients, in nutritional studies in healthy humans, and in laboratory animals. Most of the work has been in connection with the therapeutic application of special diets. Relevant studies for each application of CDD's are summarized below. The emphasis in these summaries is on the nutritional knowledge that has been gained from experience with various types of formulated diets. Short- and long-term effects of these diets are also outlined.

Clinical Studies

The use of various types of formulated liquid diets has been increasing. There is a medical journal devoted entirely to the subject (Journal of Parenteral and Enteral Nutrition). Although the majority of CDD's are used for a few weeks, some patients need to be fed these diets on a long-term basis. A growing number of people, who can never return to solid food, are being discharged on home TPN (total parenteral nutrition) via a permanently implanted catheter in a neck or shoulder vein. From 1970 to 1977 at least 400 patients were placed on home TPN, and an international organization to record data on home TPN patients has been established (Shils, 1980). This organization, the

Registry of Patients on Home Parenteral Nutrition at the New York Academy of Sciences (2 East 103 St., New York, NY 10029), estimates that 1500 or more people in the United States have begun home TPN since about 1973 (Howard et al., 1983).

There are many medical reasons for using various types of CDD's either through peripheral or central veins (parenteral) or via the gastrointestinal (GI) tract (enteral). The GI tract can be reached orally, when the patient simply drinks the diet, by nasogastric tube feeding, or by a catheter surgically implanted in the stomach or small intestine. A combination of parenteral and enteral nutritional support may also be used. The use of a central vein for all nutrients (TPN) is to be undertaken only when the other methods cannot meet the patient's needs. This is because the procedures for implanting the catheter in a central vein are tricky and uncomfortable and because there can be serious complications.

Phillips and Odgers (1982) report that the conditions most often requiring parenteral nutrition are inflammatory bowel diseases, enterocutaneous fistulas, and before and after various abdominal operations. The many conditions that may require some type of CDD for nutritional support are listed in Table 23.

TABLE 23

Clinical Applications of CDD's

1. Gastrointestinal (GI) Problems
   - fistulas*
   - malabsorption
   - short bowel syndrome
   - inflammatory bowel disease* (Crohn's disease, ulcerative colitis)
   - obstruction in GI tract
   - liver diseases
   - pancreatitis
   - congenital defects
2. Hypermetabolic States
   - traumatic injuries
   - severe burns
   - surgery
3. Prolonged Coma
4. Preparation for Diagnostic Procedures of the GI Tract
5. Pre- and Postoperative Management
   - abdominal surgery*
   - colon and rectum operations
   - head and neck surgery
6. Persistent Nausea/Vomiting
7. Anorexia
8. Food Allergies (diagnosis/treatment)
9. PKU (phenylketonuria)--to maintain special diet
10. Mental Retardation--to facilitate nursing care
11. Cancer
12. Transition from TPN to Solid Food (enteral CDD's)

*most common reasons for use of parenteral nutrition

References:

1. Sandoz Nutrition, 1984
2. Heymsfield, et al., 1979
3. Howard et al., 1983
4. Koretz and Meyer, 1980
5. Phillips and Odgers, 1982
6. Russell, 1975
7. Shils, 1980
8. Voitk, 1975

The value of using enteral CDD's in many of the conditions in Table 23 has been questioned by Koretz and Meyer (1980) on the grounds that very few controlled studies comparing enteral CDD's with solid food have been conducted. The authors conclude that the benefits of CDD's over regular solid (or blenderized) food need to be substantiated, due to the high costs, unpleasant tastes, and side effects of these special diets. Another controversy concerns when to use enteral versus parenteral diets. Heymsfield et al. (1979) report that, at least in their experience, a large number of patients on TPN could tolerate either enteral diets or combinations of enteral and parenteral. More well-controlled clinical trials might clarify this. However, as Randall (1984) points out, improved studies may not always be feasible, due to the number of subjects needed for statistical purposes, the great expense involved, and the large number of CDD's being developed.

Due to the life threatening nature of the patients' conditions and the technical complexity of (TPN), more clinical attention has been given to this type of CDD in the medical field. Recently, there has been increasing interest in enteral CDD's, because of the greater medical risks associated with TPN. The physiological and psychological effects of CDD's are summarized below. Mechanical problems in the administration of CDD's and potential drug interactions with CDD ingredients are covered briefly.

Medical Complications

The major categories of complications associated with CDD's are similar, regardless of the route of administration. These include mechanical and other problems related to administering the diets, gastrointestinal side effects and changes, physiological imbalances that frequently involve either nutrient excess or deficiency (Cataldi-Betcher et al., 1983), and psychological problems. These complications are summarized in Table 24.

Complications that are unique to TPN involve the central veinous catheter for the most part and special problems in providing the correct balance of nutrients intravenously, as discussed in Chapter II. Hazards of the catheter include infection from contamination of the catheter as well as phlebitis, thrombosis, pneumothorax, and punctured blood vessels from incorrect catheter position (Shils, 1980).

Nasogastric feeding is the most common route for tube-fed enteral CDD's (Cataldi-Betcher et al., 1983). A serious mechanical complication that is unique to enteral CDD's administered by nasogastric tube is aspiration or regurgitation of the stomach contents. The patient can choke to death, because some of the fluid inevitably reaches the lungs (aspiration pneumonia). Some tubes can damage the throat and esophagus (Heymsfield et al., 1979). The problem of aspiration can be avoided by surgically attaching the feeding tube directly to various points in the GI tract (such as the stomach or jejunum).

Other risks are associated with these surgical routes (Randall, 1984).

Other mechanical problems with both TPN and enteral CDD's are blockage of the catheters or tubes, due to thickening of the nutrient solutions. The ingredients must be mixed correctly to avoid interactions, either among the CDD constitutents or with other medications. Antibiotics, nutrients, antipsychotic drugs, cold medicines and other agents (that might be given to patients in enteral feeding solutions) were mixed with several common enteral diets in the laboratory by Cutie et al. (1983). Pharmaceutical syrups were associated with frequent incompatibility reactions. Other potential drug interactions include adverse effects on stability, bioavailability, and effectiveness.

Contaminated nutrient solutions, as well as feeding tubes or catheters, can lead to serious, life-threatening infections in TPN or GI disturbances in enteral or oral CDD's (Cataldi-Betcher et al., 1983; Jeejeebhoy et al., 1976). The risk of a systemic infection has been a major complication of TPN (Voitk, 1975).

A review of the 12-month medical records of 253 patients on tube-fed (various entry routes for the tubes) CDD's showed that 52% of the complications (in 6.2% of the patients) were gastrointestinal, mechanical problems occurred in 3.5% of the patients (aspiration pneumonia in 0.8% of the patients), and metabolic complications in 2% of the patients. Diarrhea was the most common GI complaint. Other complaints included vomiting, GI bleeding, and incomplete or retarded emptying of the stomach.

Besides contaminated solutions, other factors contributing to GI upsets during CDD intake are high velocity feeding rates, feeding large quantities at once, highly concentrated (high osmolality) solutions, and too little bulk in the very low residue diets (Cataldi-Betcher et al., 1983). Other GI problems reported include nausea, halitosis, and abdominal cramps (Koretz and Meyer, 1980). It is somewhat ironic that some of the medical conditions that warrant use of CDD's may be aggravated by some aspect of the CDD itself. This points to the fact that altering a normal, solid food diet is a complex precedure, and that patient response to a certain CDD is subject to considerable individual variation. Although Randall (1984) states that only a small number of published studies have been done on the effects of enteral CDD's in patients, his clinical experience has shown that most patients with 60 cm or more of small intestine can tolerate these diets.

A number of investigators have looked at the effects of CDD's on the anatomy and physiology of the GI tract. Most of the studies dealing with the effects of CDD's on the GI system have been in laboratory animals, which are discussed later in this chapter. The results are somewhat conflicting; however, some of the major findings will be summarized. Because the digestive system is bypassed, one might expect some reduction in normal GI functioning during TPN. The presence of food and its chemical composition in the GI tract stimulate the release of various digestive system hormones and enzymes, such as from the stomach

(gastrin and pepsins), duodenum (secretin and cholecystokinin), pancreas (enzymes, insulin, and glucagon), and liver (bile) (Vander et al., 1975). Reduced secretions of some of these hormones and enzymes have been observed during parenteral nutrition (Phillips and Odgers, 1982; Shenkin and Wretlind, 1979).

Greenberg et al. (1981) investigated the plasma levels of intestinal hormones in 17 patients with Crohn's disease before, during, and after TPN therapy. Nine of the patients, who had been on TPN for an average of 25 days and were deemed ready to eat solid food, were given test breakfasts during which several blood samples were collected from 30 minutes before to 3 hours after. The first test breakfast (orange juice, eggs, toast, and jam) was given the morning after TPN was discontinued. The patients then began eating regular meals for an average of 156 days, after which they were given the same test breakfast and blood samples were collected. Plasma glucose and nine intestinal hormones (gastrin, motilin, secretin, gastric inhibitory peptide, pancreatic glucagon, enteroglucagon, insulin, pancreatic polypeptide, and vasoactive intestinal peptide) were assayed in the blood samples. No significant differences in hormones were found except in insulin and enteroglucagon. The peak insulin response was significantly reduced after the first test meal following the end of TPN, than following the second test meal after eating normal meals. Because the glucose increase following both test meals was similar, there may have been

peripheral insulin hypersensitivity due to TPN. A significantly higher peak enteroglucagon level was found following the first test meal after TPN than after the second test meal. The enteroglucagon levels were similar before each of the test meals. The greater response after the first test meal may have been due to a decrease in the time for food transport through the intestine, causing nutrient stimulation of the small intestine. Another study was done in the remaining 8 patients on TPN for an average of 22 days. Blood samples were taken before TPN was started, at various points during, and 3 days after TPN was discontinued. The same intestinal hormones were measured as in the first study. No significant hormonal fluctuations due to TPN were detected.

A recent case study by Bivins et al. (1984) was in a TPN patient with a pancreatic fistula, which enabled the investigators to collect and measure pancreatic output every 8 hours for 12 days. The output was measured first during dextrose and saline administration for 3 days, then dextrose and crystalline amino acids (and safflower oil on the sixth and eighth days) for the next 6 days, and finally during oral intake for 3 days. Pancreatic output decreased during parenteral nutrition, compared with the output when the patient was on solid food prior to the study, the output remained about the same for one day on a diet of clear liquids, and a large increase in pancreatic output occurred on both a high protein oral diet and a high fat oral diet over the next 2 days. Because the data are

from only one patient and because some other clinical reports have shown increased pancreatic secretions in certain cases, these results should be taken with caution until more research has been done. Also, individual variations occur with many physiologic parameters, particularly nutritional/digestive responses.

In addition to physiological changes in the GI system during TPN, structural changes have also been reported. These changes include hypoplasia of the intestinal mucosa (reduced length, weight, and thickness) and lowered numbers of intestinal microbes (Shenkin and Wretlind, 1979). The effects on the intestinal mucosa have been described in more detail by studies in laboratory animals.

Enteral CDD's might be expected to alter gastrointestinal functions less drastically than parenteral CDD's. Nevertheless, a number of changes have been reported. Monomeric CDD's have been reported to produce lower pancreatic output than polymeric diets, although others have found increased pancreatic output. Some studies have also reported reduced microbial populations in the intestines with enteral CDD's while other studies have found no effects (Koretz and Meyer, 1980; Winitz et al., 1970b). The implication of reduced intestinal bacteria is that synthesis of vitamin K and biotin might also be reduced, and this could create deficiencies of these vitamins unless the CDD's contain them. Depending on the diet composition, enteral CDD's produce reduced fecal output and decreased number of bowel movements (Russell,

1975).

The effectiveness of an elemental (monomeric) diet (Vivonex HN) versus a polymeric diet (Clinifeed 400) was assessed in 70 hospital patients, matched for race, age, sex, diagnosis, nutritional status, etc. (Jones et al., 1983). All 70 patients had normal GI system functions. In the prospective, 1-year study each of the 70 patients was randomly assigned to one of the diets. Thirty-four patients received High Nitrogen Vivonex, and 36 received Clinifeed 400. The Vivonex group was fed for an average of about 14 days (with a range of 1 to 35 days), and the Clinifeed group was fed for an average of about 15 days (with a range of 2 to 60 days). The effectiveness of the CDD's was compared on the basis of nutritional status and nitrogen balance, GI upsets, metabolic problems, and effects on liver enzymes. There were no clinical differences of major importance between isonitrogenous and isocaloric doses of the diets. Less nitrogen was excreted in the polymeric diet group (although not statistically significant) suggesting slightly better nitrogen balance. Increased liver enzymes occurred in both groups, but were within normal limits at the end of the study. The investigators concluded that less expensive polymeric diets rather than monomeric diets should be used in patients with normal GI systems who need nutritional support. In another study, the use of polymeric instead of monomeric CDD's after major abdominal operations was also found to be effective by Riley et al. (1980).

Physiological imbalances are a potential hazard whenever CDD's are used, particularly in people with existing health problems. Water must be given in addition to the enteral CDD solutions to prevent fluid and electrolyte upsets, such as dehydration (Russell, 1975). Adverse metabolic reactions occurred least often in a survey of 253 patients on enteral CDD's. Only 2% of the patients experienced these problems, which included hyperkalemia (serum potassium too high), hypokalemia (serum potassium too low), and hyperosmolality/dehydration. Various nutrient deficiencies or excesses and other physiological imbalances seem to be more frequent during TPN (Cataldi-Betcher, 1983).

Some of the most frequent physiological problems during TPN include hyperglycemia (excess glucose), hypokalemia (low potassium), and hypophosphatemia (low phosphate) (Phillips and Odgers, 1982). Vitamin and trace element deficiencies have been encountered a great deal in patients on TPN for long periods, as discussed in Chapter II. These deficiencies may become less common as more is established about parenteral micronutrient requirements. Howard et al. (1983) state that parenteral folic acid requirements may be higher than those for the oral route and that extreme deficiencies of this vitamin in TPN have been reported. Although the American Medical Association (1979b) recommended 0.4 mg per day parenterally (the same as the oral requirement), the requirement may be higher in some patients.

A vitamin that has not been included in routine TPN solutions

is biotin. The American Medical Association (1979b) recommends 60 mcg per day IV. Levenson (1983) reported that a patient on TPN for over 5 months with no biotin developed depression, threatened suicide, insomnia, vomiting, headaches, gray skin color, dermatitis, and other symptoms. After 300 mcg biotin supplements were given for a week, the symptoms were relieved. Innis and Allardyce (1983) reported 2 patients on TPN for 5 to 6 months, both of whom began experiencing extensive hair loss. After 2 months of daily biotin, their hair was restored. The authors stated that severe intestinal diseases or antibiotics can interfere with intestinal biotin synthesis.

Although knowledge of nutrient requirements can help prevent many imbalances during nutrition with CDD's, nutrient requirements vary considerably among individuals. For example, Thompson and Hodges (1984) surveyed the medical records of TPN patients to investigate the occurrence of hypophosphatemia. This complication has been a problem even when phosphate supplements are given according to published requirements. Urinary phosphate losses are increased due to hyperglycemia, use of diuretics or steroids, severe burns, and other conditions, and phosphate doses may have to be increased in these cases.

Trace metal deficiencies may take many months to develop and can be associated with severe overt symptoms and/or more subtle biochemical changes. Kien and Ganther (1983) report a case of selenium deficiency in a 10-year-old boy on TPN for 1-1/2 years. Symptoms included unusual white nail beds, recurrent leg muscle

pains, and elevated liver and skeletal muscle enzymes. Baker et al. (1983) reported the following biochemical evidence of selenium deficiency in a patient on TPN for 14 months: low erythrocyte selenium content, low erythrocyte glutathione peroxidase (which needs selenium for its activity), and other biochemical changes.

Chromium deficiency developed in a patient on TPN for 3-1/2 years before chromium became routinely given. Symptoms included peripheral neuropathy, glucose intolerance, and a 15% weight loss with the same caloric intake (Jeejeebhoy et al., 1977). Molybdenum deficiency appeared after another patient was on TPN for over a year. The severe symptoms were psychological problems, coma, vomiting, headaches, night blindness, and other reactions after infusion of a commercial amino acid solution. Molybdenum is a cofactor for enzymes involved in amino acid metabolism, and supplements of ammonium molybdate reversed the symptoms. There are many more examples of nutrient imbalances caused by CDD's. These types of case studies have made the refinement of CDD components possible.

Long-term TPN

The first clinical test of TPN was done by Dudrick et al. (1968) in 30 patients with serious diseases of the GI tract. The TPN solution included 20% glucose, 5% protein hydrolysate, electrolytes, vitamins, and trace elements. The patients were given TPN for 10 to 200 days, and all 30 improved with respect to

nutritional status and disease stage.

One of the best-documented case studies of a permanent home TPN patient is by Jeejeebhoy et al. (1973). At time of publication, the woman had been on TPN for 2-1/2 years and had made remarkable social and medical adjustments. Her intestines had been almost completely destroyed due to mesenteric vein thrombosis in 1970 at age 36, and she spent the first 9 months after surgery in the hospital. She then began home TPN, after which her condition has been monitored periodically. The same catheter was in place for 30 months with no infections, due to the use of special Millipore filters to prevent solution contamination. The medical team concluded that a mixture of half the kcal as lipid and half the kcal as carbohydrate was preferable to all of the energy requirement from carbohydrate. They also found that lipid infusions are needed both to supply essential fatty acids and to prevent fatty liver deposits. Fatty changes were observed in liver biopsies when carbohydrate alone was the energy source. These changes were reversed with the combined lipid and carbohydrate energy sources. Although periodic nutrient imbalances have been reported for this patient (Jeejeebhoy et al., 1977), she has been in a fairly healthy state on home TPN, and this was still the case as of the report by Shenkin and Wretlind (1979).

Jeejeebhoy et al. (1976) reviewed the case histories of 12 home TPN patients, including the one above. The total time on TPN varied from 3 months to 3 years. Daily fluid requirements

were about 3-1/2 liters per patient. Results of a variety of laboratory tests are tabulated in the review.

Psychological Aspects

Because CDD's represent a total change in diet, they are not well tolerated by all patients. The monomeric enteral CDD's, in particular, are reported to have unpleasant tastes and odors, which are still a problem with the addition of flavoring agents (Koretz and Meyer, 1980). The synthetic amino acids seem to be the main contributors to the bad tastes (Smith and Heymsfield, 1983). Nasogastric tube feeding is often required for enteral CDD's, because the patient is unable to drink enough of the diet to satisfy nutrient requirements (Heymsfield et al., 1979).

The most extreme therapeutic CDD is TPN, which may be required on a permanent basis by certain individuals. Those who are on permanent home TPN can be compared with people on kidney dialysis--they face significant changes in their lifestyles. Although the appetite is lowered on TPN (Shenkin and Wretlind, 1979), Malcolm et al. (1980) state that one of the most common complaints of TPN patients is the obvious one--that they still miss eating regular food. The appetite reduction is temporary and returns after TPN is ended. The amount of time these patients are connected to the TPN solutions may be a few times per week (partial TPN) or up to 18 hours per day. Psychiatric problems that have been encountered in long-term TPN patients include extremely negative body image, psychosomatic ailments,

family problems, noncompliance with TPN, and in rare cases, psychotic reactions. Nutritional deficiencies or excesses of vitamins, trace elements, or amino acids can lead to neurological disturbances, creating psychological problems such as depression.

Healthy Human Volunteers

NASA and Air Force Studies

As outlined in the introduction to this report, some early studies on CDD's in the 1960's were sponsored by NASA. The test subjects were human volunteers and laboratory animals (discussed in the next section). A liquid diet was tested for 8 days in a two-person space cabin simulator by Welch (1964). Eight Air Force volunteers tried the diet, which included toasted soy protein, powdered skim milk, homogenized oats, and vitamin A. The subjects also drank orange-grapefruit juice that had dextrin in it, and they were allowed to eat some hard candy. The diet was unflavored, and the subjects complained that it lacked taste, variety, had a bad odor, and that they wanted solid food. The subjects lost an average of 45 grams body weight per day.

One of the major NASA-sponsored projects to develop oral CDD's began in 1961: the principal investigator was Milton Winitz (1962). The main diet included L-amino acids, vitamins, minerals, linoleic acid as ethyl linoleate, and glucose as the main energy source. A review of this project (Winitz et al., 1965) indicates that the diet was tested in hospital patients with good results. The major test in healthy humans was

conducted at a prison using 24 male inmates selected from 160 volunteers.

Detailed results of the 10-month study were reported by Winitz et al. (1970a). The study was conducted from 1963 to 1964 in the California Medical Facility in Vacaville. The 24 inmates were from 24 to 43 years old. This CDD had been tested mainly in laboratory animals (predominantly rats). The subjects consumed several variations of the liquid diet for 25 weeks. Medical data were also collected for 4 weeks before and 13 weeks after the CDD test while the subjects were eating normal meals. The CDD was administered 4 times per day, 3 hours apart. Distilled water was taken as needed, and the subjects were allowed to drink the amounts of the CDD that suited them at each of the 4 presentations. Their actual caloric intakes varied from 2300 to 3400 kcal. Fifteen of the original 24 inmates continued to the end of the study. Six of the volunteers dropped out due to dislike of the diets. Three others dropped out for reasons unrelated to the study.

Bowel movements were significantly reduced compared to experience with normal meals. Weekly urinalyses of the subjects were within normal limits. Periodic batteries of blood tests were performed before, during, and after the study. Fasting blood sugar levels were at the low range of normal for all subjects and were significantly lower than the levels before the study or after returning to normal meals. Another alteration during intake of the CDD was a decrease in serum cholesterol with

glucose as the carbohydrate source. Cholesterol levels increased when sucrose was substituted for 25% of the glucose and went down again after a return to all glucose. Weekly medical checkups were done and no adverse effects were found. Other tests, such as electrocardiograms, chest x-rays, eye exams, and dental reports, were normal. Some subjects experienced halitosis, which may have happened because less saliva was produced. Weight losses were observed in all subjects during the first week, which the investigators stated was due to a loss in the intestinal bulk present on a solid-food diet. Six initially overweight subjects lost from 3-1/2 to 24-1/2 pounds by the end of the study. All of the subjects had normal blood pressures at the beginning of the study. After several days on the CDD, the systolic and diastolic blood pressures decreased. Within a week after their return to regular solid food, the subjects' blood pressures were up to the initial levels. No degeneration of teeth or gums due to lack of solid food was observed. The CDD's were deemed nutritionally acceptable as a result of this study.

Winitz et al. (1970b) conducted several short-term feeding studies with adult volunteers, both males and females, who were not institutionalized. The purpose of the studies was to monitor the effects of CDD's of various types on the populations of intestinal microorganisms. The populations and the number of species were rapidly reduced after a few days on the CDD's. The intestinal microorganisms returned to normal after the subjects ate regular food again. The changes were more pronounced on

glucose-based than sucrose-based CDD's in a 43-day study in one subject.

The Air Force also sponsored projects to develop CDD's in the 1960's, several of which were joint projects with NASA. Hollender et al. (1965) described one of the CDD's, which required vitamin/mineral supplements in capsule form. The diet consisted of sodium caseinate, egg albumin, and other intact proteins, sucrose, glucose, starch, corn oil, and various additives and flavoring agents. The various flavored versions were taste-tested by panels. On a scale of 1 to 9, some of the liquid CDD's received scores of 6 or more. Vanilla and chocolate were preferred to strawberry, cherry, coffee, orange, cream soda, banana, butterscotch, caramel, or coconut. The investigators noted that the Space Science Board of the National Research Council had recommended the use of liquid diets for space travel.

Four college males tested a fresh food diet for 30 days and then a liquid diet for the next 20 days in a study by Katchman et al. (1967). The subjects were confined to a Controlled Activity Facility (CAF) for the first 6 days, a Life Support Systems Evaluator (LSSE, a simulated aerospace environment) for the next 28 days, and then the CAF for the remaining 6 days. The subjects were under metabolic control during the study. Two of the subjects wore an unpressurized space suit 8 hours per day for the 28 days in the LSSE. The flavors of the liquid diet were varied from cherry to vanilla, chocolate, and strawberry. The subjects disliked the monotony of the liquid diet versus the fresh foods

(various meats, bread and butter, fresh lettuce with oil and vinegar, fruits, and tea with sugar). The 2444 kcal liquid diet (approximately 204 g carbohydrate, 70 g protein, 167 g fat plus supplements of vitamins and minerals) was similar in chemical composition to the fresh food diet. A number of laboratory tests on urine, feces, blood, heart rate, and blood pressure were found to be within normal limits. The liquid diet had a 5.5% lower overall degree of digestibility than the solid diet, and weight losses were produced in 2 subjects. A negative balance state was found for calcium, potassium, and phosphorus. The liquid diet increased the frequency of bowel movements compared with the fresh food.

The above study was repeated with another group of 4 college males (Katchman et al., 1970). All 4 subjects wore the space suits. This time the liquid diet had 6 flavors (served alternately): cherry, vanilla, chocolate, strawberry, raspberry, and butterscotch. The digestibility was about 3% lower with the liquid diet than the fresh food. Nitrogen digestibility was slightly improved in this study. The subjects were in negative balance for calcium, potassium, and magnesium, but were otherwise clinically normal. The subjects in this study disliked the diets even more than in the previous series.

Dymsza et al. (1968) reviewed the development and compositions of a number of different formulated diets, including liquid, freeze-dehydrated, compressed tablets, bite-size pieces, candy, and cookies. It was noted that solid, more normal forms

of CDD's would be more acceptable. There has been little interest in the use of CDD's for space travel in recent years.

Other Studies

Some of the medically oriented evaluations of CDD's will be summarized in the remainder of this section. Eighteen medical students (15 males, 3 females) were randomly assigned to consume a monomeric diet (Mead Johnson 3200-AS), containing hydrolyzed casein and medium chain triglycerides, or a polymeric diet (Mead Johnson 3200-AU) which contained intact casein and no medium chain triglycerides, for 12 days. The osmolarity of the monomeric diet was about 700 mOsm per liter. The vitamin and mineral contents were similar. The subjects disliked the consistency and taste of both the monomeric and the polymeric diet, and all subjects lost 2 to 3 pounds. Decreased serum cholesterol was found in both groups after the diet study. Most other blood test values were normal. Fourteen of the subjects were given duodenal perfusions in order to study the effects on bile salts and pancreatic enzymes (pancreatic trypsin, lipase, and amylase). No pancreatic damage could be found with respect to pancreatic enzyme secretions. Reduced bile salt secretion (with pancreozymin stimulation) was found in the subjects on the monomeric diet; however, the reduction was not statistically significant. The 15 males swallowed radio-opaque markers of vinyl tubing on day 7 of the diet. Delayed transit times (due to the liquid aspects) were found in subjects ingesting both diets,

when compared with data on normal diets from other studies. The authors stated that the results indicate that the monomeric diet is safe (Perrault et al., 1973).

McCamman et al. (1977) compared 3 CDD's in 10 volunteers (1 male and 9 females). The CDD's tested were Standard Vivonex (monomeric), Flexical (monomeric), and Precision LR (low residue, polymeric, Sandoz Nutrition). Each subject was given a standardized control diet for 3 days, then one of the CDD's for 10 days, then ate a normal diet for at least 5 days. Each subject tested all 3 diets in randomized order using this schedule. The subjects consumed calorie- and caffein-free beverages and water as needed during the study. Stool weight on Vivonex was significantly reduced compared with Precision LR. Flexical produced stool weights between those of the other 2 diets. Differences in the frequency of bowel movements were not significant. Both stool weight and frequency were lower than data from subjects on normal diets. In general, the longer a person is on a CDD, the more stool weight and frequency is reduced. The reduction in stool weight indicates greater nutrient utilization on CDD's. No significant differences in the fecal fat, ash, or moisture were detected on the 3 diets, indicating normal absorption. Subjects excreted more nitrogen than they took in (negative nitrogen balance) on all 3 diets and experienced weight losses of an average of 1.92 to 2.59 pounds. Weight losses of a couple of pounds are typical on beginning intake of CDD's, possibly due to lowered weight of intestinal

contents. The investigators reported that there was a miscalculation of the amounts of each CDD required for the subjects in this study. Due to the low protein to calorie ratios of the 3 diets, at least 2000 kcal of each CDD should have been given to the females. However, they received only 1500 to 1800 kcal.

The subjects ranked the CDD's according to taste, side effects, and degree of difficulty in mixing the diets. Vivonex was ranked as the best, and Precision LR was the second best. Flexical was preferred by only 2 subjects. The subjects mixed their CDD's with various beverages, which no doubt improved the taste of these diets. It took all subjects a few days to get used to the taste of the CDD's, especially Flexical. Side effects included headache, sweating, weakness, constipation, and diarrhea. The subjects experienced sensations of being too full, when they returned to solid food after being on the liquid CDD's during the study (McCamman et al., 1977).

The effects of 2 polymeric CDD's on fecal weight, fat absorption, nitrogen excretion, and other factors were assessed in 10 healthy college students (6 males, 4 females) by Kien et al. (1981). The subjects ate normal diets for the first 12 days of the study, after which they were randomly assigned to either Isocal or Sustacal (Mead Johnson Company) for 12 days. They could also drink unlimited water and carbonated beverages. The subjects were given fecal markers to swallow on the 1st, 11th, 16th, and 26th days. The subjects maintained adequate body

weights on both CDD's; no GI upsets were reported. The fecal weights were slightly lower on Isocal than on the normal diet, but the differences were not statistically significant. There was significantly less fat in the stools of subjects on the CDD's than the normal diets, indicating greater absorption. Nitrogen absorption was 95% for Isocal and 98% for Sustacal.

Table 24

Health Effects of CDD's in Humans
(Probable Causes Included Where Relevant)

Mechanical Problems

- tube/catheter contamination leading to infection, GI upsets
- aspiration pneumonia with nasogastric tube feeding (due to regurgitation)
- esophageal erosion/irritation (nasogastric tube)
- technical errors in administration of CDD's
- tube/catheter clogging (ingredient interactions, contaminated CDD's, incorrect CDD's)

Psychological Problems

- depression
- psychoses
- negative body image
- psychosomatic ailments
- noncompliance with TPN routine
- unpleasant taste/odor of CDD's (especially those with crystalline amino acids)

GI Effects (contaminated CDD's, high osmolality, rapid infusion rate)

- nausea
- vomiting
- bloating
- cramping
- diarrhea
- halitosis (crystalline amino acids especially)
- slower emptying of stomach
- unpleasant taste and odor
- reduced fecal bulk
- fewer bowel movements
- reduced microbial populations in intestine
- alterations in GI tract hormones and enzymes

Chemical Reactions

- unstable nutrient solutions
- drug/ingredient interactions

Table 24 (continued)

Physiological Changes

enzyme activity
hormone secretions
nutrient excesses/deficiencies
fluid/electrolyte imbalances
serum cholesterol reduction with glucose as sole carbohydrate source;
serum cholesterol increase with sucrose as carbohydrate source (oral CDD's)
blood pressure reduction (oral CDD's)
lower fasting blood sugar (oral CDD's)

References (partial list of reports on health effects of CDD's):

1. Cataldi-Betcher et al., 1983
2. Greenberg et al., 1981
3. Heymsfield et al., 1979
4. Jeejeebhoy et al., 1976
5. Koretz and Meyer, 1980
6. Malcolm et al., 1980
7. Randall, 1984
8. Shenkin and Wretlind, 1979
9. Smith and Heymsfield, 1983
10. Winitz et al., 1970a
11. Winitz et al., 1970b

Laboratory Animals

Studies to Develop CDD's

Representative studies of CDD's in various animal species are presented below. The classical work in TPN was the demonstration that nutrition could be successfully maintained by the parenteral route in beagle puppies by Dudrick et al. (1968). At 8 weeks of age each of 6 test puppies was compared to a litter mate control puppy of similar size. Both test and control animals were given standard oral diets until 12 weeks of age. At this time, the 6 test puppies were started on TPN, which had an equivalent number of kilocalories to the standard diet. The TPN solutions included fibrin hydrolysate, glucose, vitamins, minerals, and a fat emulsion, and the nutrients were given over 21 to 23 hours per day. The duration of TPN was from 72 to 256 days. The puppies on TPN had greater weight gain and similar skeletal growth compared to the controls.

The team of Winitz, Greenstein, Birnbaum, and others at the National Institutes of Health developed oral CDD's in the 1950's using rats for the most part. The CDD consisted of glucose, vitamins, amino acids, minerals, and corn oil. The diet was basically 80% glucose and 20% amino acids by weight. Several variations of the CDD were tested in at least 5 to 6 weanling, Sprague-Dawley rats of each sex. The animals were allowed to feed *ad libitum* from 2 bottles containing tap water and the CDD in each cage. The feeding studies were continued through the

second generation for some of the CDD's. The original weanling rats were mated at 120 or 186 days of age; offspring from these rats were mated at 120 days of age in the first series of studies (Greenstein et al., 1957).

Both fecal weight and frequency were reduced on the CDD's. No evidence of degeneration of the teeth, gums, pancreatic secretions, or other GI secretions was found in rats fed on CDD's for over a year. These rats were then returned to normal rat chow with no ill effects or adjustment problems. Growth of weanling rats was best with a CDD containing more of the nonessential amino acids (No. 26), in a ratio similar to those of casein. Reproduction and lactation were also improved on this diet.

Although the CDD's were readily accepted by the rats, during the reproduction study an unexpected problem occurred. The rats had never had solid food and had been raised in metabolic cages with metal floors. After being mated, the females were given nesting materials of wood shavings. The rats ate such large quantities of the shavings that a number died before having their litters. The problem was avoided by using foam rubber as a nesting material; however, this certainly suggests that rats have a preference for solid food.

Birnbaum, Greenstein, and Winitz (1957) performed metabolic studies in male rats, using various CDD's. They found that nitrogen retention (for protein synthesis) can only be increased to a certain point, beyond which greater dietary intake results

in less nitrogen retention. Birnbaum, Winitz, and Greenstein (1957) then investigated the essential and nonessential amino acid requirements in weanling male rats using CDD's to allow for quantitative dietary manipulation. They concluded that nonessential amino acids are actually needed in certain proportions for optimum health.

The investigators also studied the effect of varying the carbohydrate source in CDD's on growth in weanling, male, Sprague-Dawley rats. The sugars tested included D-glucose, D-sucrose, D-fructose, and D-glucosamine (tested for 3 weeks with the first 3 and 6 weeks for the last one). Weight gains were highest in the CDD containing sucrose, mainly because the rats ate much more of this diet. The amount of D-glucosamine in the diet was varied from 2.5 to 16%, with the remainder of the carbohydrate source being glucose. Increased D-glucosamine was correlated with decreased growth rates, due to decreased ingestion of the diet (Winitz, Birnbaum, and Greenstein, 1957). Similar studies were conducted over 3 weeks to test the effect of various forms of arginine on growth in weanling male rats. The best growth response was produced by L-arginine, although D-arginine also promoted growth compared to CDD's without arginine. The addition of L-arginine to a diet deficient in nonessential amino acids greatly improved growth and tended to mask nutrient deficiencies (Winitz, Greenstein, and Birnbaum, 1957).

Some growth studies were also done on weanling white mice

(N.I.H. strain) of both sexes. The mice were given one of 2 CDD's (No. 3 or No. 26) ad libitum for 3 weeks. Control mice were given Purina laboratory chow. The mice readily consumed the CDD's. Growth rates were much better with CDD No. 26 than with No. 3. The growth of mice fed No. 26 was similar to control animals. The weanling mice did poorer on No. 3 than weanling rats (Birnbaum et al., 1958).

The final report in the above series of studies (Greenstein et al., 1960) summarizes the final CDD's that were developed and results of various growth studies. The major difficulty in designing the CDD was the ability to incorporate the fat and fat-soluble vitamins successfully in a stable, water-soluble form. Earlier CDD's had employed separate fat supplements of corn oil. The problem was overcome by adding a Polysorbate 80 (an emulsifier) and ethyl linoleate mixture to an alcohol solution of fat-soluble vitamins. This formed an oil and water emulsion, which could be mixed with the other components in aqueous solution. Various forms of the fat component were added to CDD No. 26 and compared with No. 26 plus separate corn oil supplements in weanling rats for 82 days. Too much Polysorbate 80 (12 grams per 2 liters CDD) produced diarrhea in the rats. The diet was reformulated to contain 6 grams Polysorbate 80 and 4 grams ethyl linoleate per 2 liters diet. This CDD was designed for eventual application to parenteral CDD's in humans.

Studies to Evaluate the Effects of CDD's

The effects of enteral CDD's on the GI tract of rats were studied by Young et al. (1980). Control rats were fed Lab Blox Chow at the same caloric level. Male, Sprague-Dawley rats were fed the CDD through a surgically implanted intragastric tube for 2 weeks. Control animals were given distilled water through the intragastric tubes. The CDD's tested included Vivonex, Vivonex HN, Flexical, and Ensure. Rats in the control group gained more weight than rats fed any of the CDD's. The lower weight gains were statistically significant in rats fed Flexical or Vivonex. The percentage of fat in the livers of animals fed Vivonex or Flexical was significantly higher than in the controls. The weight of the pancreas was significantly lower in Vivonex and Flexical animals than in the controls, and the activity of certain pancreatic enzymes was significantly lower in these groups and the Ensure group as well. Maltase activity of proximal small intestinal sections was significantly greater in the Vivonex, Vivonex HN, and Ensure rats than in the controls. Mucosal weights in intestines of all CDD groups were significantly lower than controls on regular chow. The lack of fiber in the CDD's may have contributed to the reduced mucosal weight. Total protein and DNA levels in the intestinal muscosa were also lower in CDD groups. The authors stated that the fatty liver development (due to Vivonex and Flexical) may have been because of an inadequate nitrogen to calorie ratio, preventing

the production of phospholipids that carry fats out of the liver. Either the use of the intragastric route for administering CDD's or the compositions may account for some of the other intestinal changes (pancreatic enzyme activity reduction, decreased weight of small intestinal mucosa, and increased intestinal maltase activity). Stimulation from normal, oral food intake may also affect the release of various secretions in the GI tract.

In order to test the effects of oral versus intragastric administration of CDD's on the GI tract, Young et al. (1982) fed equivalent caloric levels of Vital, Vivonex, Vivonex HN, and Flexical to rats by these routes. Controls were given a liquid casein diet (116EC from Grand Island Biochemical Company) by both routes. Oral intake was achieved via measured animal drinking tubes; all animals in these groups were also implanted with intragastric tubes. The duration of the feeding study was 2 weeks. In general, the GI tract changes were greater due to CDD composition than from route of administration, although effects of the route were noted. The intragastric groups all had lower body weight gains, especially in the Flexical, Vivonex, and control liquid casein groups. Fat content of livers was higher in rats given Vivonex and Vivonex HN, as opposed to Vital, Flexical, or the control liquid; effects of route were not significant. Pancreatic amylase activity was significantly affected by both diet composition and route. Enzyme activity was significantly higher in intragastric route rats given Vital, Flexical, and Vivonex HN. Proximal intestinal mucosa sections

had significantly lower weights, lower protein, and DNA in rats fed all CDD's compared with control liquid, regardless of route. The authors indicated that a complete understanding of the complex interactions of nutrient influences on the GI system await further research.

The effects of parenteral versus oral administration of CDD's on the structure and enzymes of the intestinal mucosa were investigated by Levine et al. (1974) in male, Sprague Dawley rats. Equivalent CDD's were given to 2 groups of rats for 7 days. One group was allowed to feed orally, ad libitum; the other received the diet by TPN. Intestinal hypoplasia and atrophy (statistically significant) due to the intravenous CDD route were found. Effects due to TPN included a reduction in the total amount of the small intestine, decreases in proximal mucosal weight, total mucosal protein, mucosal DNA, mucosal height, reduced amounts and specific activities of maltase and sucrase, and a reduced amount of lactase. The results indicate that oral intake of food is important in at least certain aspects of normal intestinal structure and function.

The effects of CDD osmolality on nutrient absorption, GI side effects, and other factors were investigated in pigs by Case et al. (1981a; 1981b). Pigs have GI systems similar to those of humans. In the first study, 20 Yucatan miniature pigs were given oral CDD's of 5 different osmolalities from 250 to 700 mOsm per kg. A commercial polymeric CDD, Ensure (Ross Laboratories), was adjusted to the different osmolalities by changing the sucrose to

corn syrup solids ratio. The CDD's were ingested (usually in one minute) by the pigs 3 times per day for 3 days. On the fourth day, part of the first meal contained water and sucrose labelled with radioactive tracers. Samples of plasma were taken from the pigs at various intervals from 10 minutes to 4 hours after the meal. Carbohydrate absorption rates and amounts absorbed increased as the osmolalities increased, particularly during the first hour. Plasma glucose levels increased quickly in the first 20 minutes and were significantly less in pigs who ate the 250 mOsm per kg diet. Water absorption rate and amount were significantly greater at the 700 mOsm per kg level in the first 30 minutes. Water absorption rates and amounts were not significantly different at the other osmolalities. Rapid detection of labelled water, sucrose, and glucose in the plasma at all osmolalities was noted and suggests increased rate of gastric emptying due to the CDD's.

A second, similar study by Case et al. (1981b) was performed in 48 Yucatan miniature pigs. CDD's having osmolalities from 340 to 700 mOsm per kg were fed to the pigs for 3 days as in the first study. On the fourth day labelled doses of water, sodium chloride, sucrose, and chromium were included in the first meal. Plasma samples were collected during the following hour, after which the carbohydrate levels and osmolalities of the stomach and small intestine contents were determined. Average osmolalities of the contents of various segments of the intestine were significantly reduced at 60 minutes compared with 30 minutes

after the meal in all CDD's. Stomach emptying and dilution of contents were determined by comparing nonabsorbable chromium marker recovery rates with those of the absorbable markers (sodium chloride, water, and sucrose). CDD osmolality had no significant effects on stomach emptying (unlike the first study) or dilution. Carbohydrate, sodium, potassium, and water absorption increased as CDD osmolality increased. The osmolalities of the intestinal contents and stomach of pigs ingesting the different CDD osmolalities reached similar levels (453 mOsm per kg in the duodenum) within an hour after the meal. The authors concluded that a moderate osmolality of 700 mOsm per kg may be clinically advantageous, because nutrient absorption is enhanced, and nutrients can be given in smaller fluid levels. The 700 mOsm per kg level was not considered responsible for many reported GI upsets in other studies. The results of studies in healthy animals may differ from results in those with GI system diseases.

Summary

The reasons for using some type of CDD include gastrointestinal problems, traumatic injuries, severe burns, major surgery, coma, persistent vomiting, anorexia, preparation for GI tract diagnostic procedures, food allergies, mental retardation, and cancer. The most common medical reasons for using parenteral CDD's include inflammatory bowel diseases, fistulas of the GI tract, and abdominal surgery. The necessity of using CDD's for some of these reasons is controversial, as well as the type of CDD and route of administration. The major categories of CDD complications involve mechanical problems with administering the diets (such as contamination or blockage of catheters or nutrient solutions, aspiration of stomach contents, etc.), physiological changes (nutrient deficiencies or excesses, fluid shifts, alterations in hormone or enzyme levels, etc.), gastrointestinal side effects (diarrhea, nausea, vomiting, cramping, constipation, etc.), interactions with ingredients or drugs, and psychological problems associated with the unnaturalness and inconvenience of the CDD's.

An area of disagreement regarding the effects of CDD's in humans involves changes in the GI tract. For example, CDD's have been found to reduce intestinal microbial populations, particularly with glucose as the carbohdydrate source (Winitz et al., 1970b). Other studies have contradicted this finding (Koretz and Meyer, 1980); however, variations in diet composition may account for the opposite results. Similarly, opposing data

are available on the CDD-induced changes in enzyme and hormone secretions of the pancreas, stomach, and other organs in the GI system. Since there are few well-controlled studies on many of these effects, this controversy cannot be resolved at this time.

Total parenteral nutrition (TPN) has been used clinically since the late 1960's. This extreme form of CDD is to be utilized when enteral administration is impossible for some reason. Documentation of patients on home TPN for long periods has helped improve the design of nutrient solutions and has increased general knowledge of human nutrient requirements. Despite increased knowledge, nutritional needs can vary considerably among both healthy and diseased individuals.

A review of CDD studies in healthy humans shows that a major disadvantage of liquid diets involves aesthetic aspects, such as bad taste and odor, monotony, and consistency. The reduction in frequency and amount of fecal elimination has been bothersome to some subjects, and others have had some GI upsets. Weight losses have also been reported due to inadequate dietary intake and to the lack of bulk from solid food on the intestine.

Only a few of the available feeding studies in laboratory animals have been summarized in this report. Early work with puppies (TPN) and weanling rats (oral CDD's) proved that CDD's of the correct composition could substitute completely for normal diets in these species. Atrophy of the GI system due to inactivity during TPN or lack of solid foods with enteral CDD's, has been of concern to many researchers. Some changes, such as a

reduction in the weight of the intestinal mucosa and decreased gut hormone secretions, have been reported in rats and other species on TPN. Oral CDD's have been reported to increase GI hormone and enzyme secretions or mucosal weights in some studies and to decrease these parameters or exert no effects in others. Composition and also route of administration have been found to influence many of the effects of CDD's.

CHAPTER IV

NUTRIENT TOXICITY AND INTERACTIONS

The selection of foods to be used during space missions will be constrained by safety considerations arising both from potential hazards of the various nutrients and from their interactions with other nutrients or other substances.

Nutrient Toxicity

Much of the attention in nutrition is to nutrient deficiencies, particularly of vitamins and trace elements. Also there has been much public concern over unhealthy dietary levels of various fats, sugar (sucrose), and sodium. It should be noted that almost any substance can be harmful at high enough levels in the diet. The idea that if a certain amount is good, twice that amount is twice as beneficial, has been common regarding both vitamins and trace elements.

In order to clarify this issue, the effects of high doses of various nutrients and toxic levels and/or maximum recommended dietary levels of these nutrients are summarized in Table 25. The emphasis is not on acute doses of nutrients, in which one very large dose produces adverse symptoms, but on chronic intake of excess levels. In most cases, the exact maximum safe intake for periods of months or years has not been determined. It may

take a very long time for symptoms to develop when the safe intake level of a nutrient is exceeded on a daily basis. A useful indication of a safe nutrient intake level is the estimated amount in a typical diet. This level has been included in Table 25, if available.

The fat-soluble vitamins are potentially toxic if overingested, because these vitamins tend to be stored in the liver or in fat deposits. Vitamins A and D have been most commonly associated with toxic effects.

The water-soluble vitamins are generally less toxic, because of their rapid excretion, although toxic effects of megadoses (g per day) of nicotinic acid, vitamin C, and pantothenic acid have been reported. Adverse neurological effects of excess vitamin B_6 were also reported recently by Schaumburg et al. (1983). Daily ingestion of 2 to 6 g over periods of 2 to 40 months gradually produced extreme loss of coordination and feeling in 7 adults. These individuals had trouble walking and manipulating objects with their hands. The severity of the symptoms improved slowly 2 months after the vitamin B_6 supplements were discontinued. This was one of the first reports of vitamin B_6 toxicity, although chronic large doses (200 mg per day) of vitamin B_6 have been found to induce dependency in healthy humans (National Research Council, 1980).

The toxicity of some water soluble vitamins could be due to the presence of a small impurity, the effect of which is magnified at very high doses (Rudman and Williams, 1983). In the

vitamin B_6 case study above, the affected individuals took supplements ranging from 1000 to about 3000 times the recommended daily allowance of 2.0 to 2.2 mg vitamin B_6. A recent biochemistry book states that "There is no known toxicity of vitamin B_6" (Martin et al., 1983, page 105). Before self-prescribed megavitamin usage became common after 1970, few people would have encountered such excess amounts of a single vitamin. Vitamin B_6 has been reported to be helpful in treating premenstrual fluid retention, certain behavioral problems, and for increasing muscle development in weight-lifters (Rudman and Williams, 1983). These beneficial effects have not been adequately researched at this time.

Except for the controversial role of sodium in hypertension (discussed in Chapter II), the minerals and electrolytes (calcium, chlorine, magnesium, and potassium) are not toxic in normal humans, due to rapid excretion. Most of the trace elements can have toxic effects when large doses are taken (Martin et al., 1983). Some of the heavy metals, such as chromium and manganese, are more frequently associated with occupational toxicity by inhalation (Hawley, 1971; National Research Council, 1980).

Table 25

Toxic Limits of Ingested Nutrients

Nutrient	Approximate Maximum Safe Chronic Intake; Amount in Typical U.S. Diet	Some Reported Toxic Levels	Adverse Effects
Vitamins			
A	maximum: 25,000 IU/day[3]; typical: not specified[3]	>50,000 IU/day[3]	headache, bone pain, dizziness, skin peeling[2]; excess carotenes: yellow skin, no other known effects[3]
D	maximum: 200 IU/day[3]; typical: not specified[3]	100,000 IU/day for several months[1]	elevated serum calcium, nausea vomiting, kidney damage[1]
E	maximum: not specified[3]; typical: 10-20 IU/day[3]	400-1000 IU[3]	blurred vision,[2] headaches[2]
K	oral therapeutic dose for vitamin K deficiency: 1.5-2 mg/day[1], 5-10 mg/day[4]; typical: 300-500 mcg/day[3]	large doses of varying amounts[1,2]	hemolytic anemia, liver damage by synthetic water-soluble vitamin K[1,2]
Thiamin	maximum: not specified[3]; typical: not specified[3]	usually nontoxic[2]	--
Riboflavin	maximum: not specified[3]; typical: not specified[3]	usually nontoxic[2]	no cases reported[3]

Table 25 (continued)

Nutrient	Approximate Maximum Safe Chronic Intake; Amount in Typical U.S. Diet	Some Reported Toxic Levels	Adverse Effects
B_6	maximum: not specified[3]; typical: not specified[3]	200 mg/day for 1 mo.[3]; 2-6 g/day for 2-40 mo.[6]	induced dependency[3]; severe loss of feeling and coordination[6]
B_{12}	maximum: not specified[3]; typical: 5-15 mcg/day[3]	usually nontoxic[2]	--
Folacin	maximum: at least 1-2 mg/day acceptable in diet[3]; typical: .379-1.097 mg/day[3]	usually nontoxic	--
Niacin	maximum: 34 mg/day (including tryptophan, 60 mg = 1 mg niacin); typical: 8-17 mg niacin/day (plus 500-1000 mg tryptophan)[3]	3 g/day nicotinic acid[3]	flushing of skin, decrease in serum lipids, GI upsets[3]
Pantothenic acid	maximum: intakes to 20 mg/day reported with no toxicity[3]; typical: 5-20 mg/day[3]	10-20 g/day[3]	diarrhea, fluid retention[3]
Biotin	maximum: not specified; typical: 100-300 mcg/day[3]	usually nontoxic[2]	--

Table 25 (continued)

Nutrient	Approximate Maximum Safe Chronic Intake; Amount in Typical U.S. Diet	Some Reported Toxic Levels	Adverse Effects
C	maximum: not specified[3]; typical: not specified[3]	megadoses in grams/day[2]	kidney stones, diarrhea, impaired vitamin B_{12} absorption[2]; absorption of unsafe amounts of iron[3]
Minerals			
Calcium	maximum: up to 1500 mg/day with no reported problems[3]; typical: not specified[3]	excess usually excreted in healthy persons[2,3]	--
Chlorine	maximum: 5.1 g/day[3] typical: 1.95-5.9 g/day[3]	none specified (2,3)	-
Magnesium	maximum: not specified[3]; typical: 240 mg/2000 kcal[3]	relatively nontoxic orally if kidneys are operating adequately[2]; 3-5 g at once[3]	breathing problems, impaired reflexes[2]; diarrhea from very large doses[3]
Phosphorus	maximum: not specified[3]; typical: 1.5-1.6 g/day[3]	relatively nontoxic with normal kidney function; low calcium: phosphorus ratio (should be 1:1) may be hazardous[2,3]	low ratio of calcium:phosphorus--bone loss, calcium loss[2,3]

Table 25 (continued)

Nutrient	Approximate Maximum Safe Chronic Intake; Amount in Typical U.S. Diet	Some Reported Toxic Levels	Adverse Effects
Potassium	maximum: 5.6 g/day[3]; typical: 1.95-5.9 g/day[3]	>18 g/day (sudden increased intake especially)[3]	high doses can be fatal (cardiac arrest); ulcers; altered sodium: potassium ratio be factor in hypertension[2,3]
Sodium	maximum: 3.3-6 g/day[3]; typical: 2.3-6.9 g/day[3]	chronic high intake (exact levels unknown)	hypertension in susceptible persons[3]
Trace elements			
Chromium	maximum: 200 mcg/day[3]; typical: 60 mcg/day[3]	most toxic when inhaled[5]	chromium poisoning[1]
Copper	maximum: 3 mg/day[3]; typical: <1-5 mg/day[3]	low dietary toxicity in healthy persons[3]	copper poisoning: polyneuritis[1]
Fluorine	maximum: 4 mg/day[3]; typical: 1-4 mg/day[3]	>20 mg/day for long periods[3]	fluoride toxicity[3]: weakness, nausea, vomiting, tremors, hypotension, coma, breathing problems[1]
Iodine	maximum: 300 mcg/day[3]; typical: 64-677 mcg/day[3]	>300 mcg/day, exact level not specified[3]	goiter[2,3]; iodine poisoning: vomiting, metallic taste in mouth, thirst, clammy skin, breathing problems, convulsions[1]

Table 25 (continued)

Nutrient	Approximate Maximum Safe Chronic Intake; Amount in Typical U.S. Diet	Some Reported Toxic Levels	Adverse Effects
Iron	maximum: 75 mg/day[3]; typical: not given[3]	lethal dose (as ferrous sulfate) about 200-250 mg/kg or about 14-17.5 g iron in a 70 kg adult[3]	iron poisoning: vomiting, diarrhea, hypotension, rapid heart rate, shock[1]
Manganese	maximum: 5 mg/day[3]; typical: 2-9 mg/day[3]	more toxic when inhaled or injected[3]	manganese poisoning: polyneuritis[1]; psychosis[2]
Molybdenum	maximum: 500 mcg/day[3]; typical: 100-460 mcg/day[3]	10-15 mg/day; 540 mcg/day[3]	gout symptoms--higher intake; copper losses--lower intake[3]
Selenium	maximum: 200 mcg/day[3]; typical: 50-200 mcg/day[3]	mainly reported in laboratory animals[3]	selenium poisoning[1]
Zinc	maximum: 15 mg/day plus dietary intake = 30 mg/day[3]; typical: 6-15 mg/day[3]	2 g or more (as zinc sulfate) in one dose[3]	vomiting, other GI upsets[3]; polyneuritis[1]

References:

1. Holvey, 1972
2. Martin et al., 1983
3. National Research Council, 1980
4. Physician's Desk Reference, 1984
5. Hawley, 1971
6. Schaumburg et al., 1983

Dietary Interactions

Some examples of the known interactions in the diet are given in Table 26. Nutrient requirements may be altered because of environmental stress (such as extremes of temperature), injury, disease, or major surgery. In addition, the high intake of nutrient A may cause increased excretion or utilization of nutrient B, which would raise the requirements for B. As an example, higher protein levels from purified protein sources can increase calcium excretion (National Research Council, 1980).

High protein intake also can increase the need for zinc and vitamin B_6. A higher intake of kilocalories (energy) increases the need for thiamin, because thiamin is necessary for a number of metabolic functions. The requirement for vitamin E varies with the amount of polyunsaturated fatty acids in the diet. A higher requirement exists when intake is high and vice versa. Sodium loss in sweat during work at extremely high temperatures may raise the sodium requirement. High zinc intake may increase an existing copper deficiency (National Research Council, 1980), and high phosphate and calcium levels can make a zinc deficiency worse (Martin et al., 1983).

Another type of interaction is alteration in nutrient absorption or bioavailability. The presence of at least 30 to 90 g of meat, fish, or poultry or at least 25 to 75 mg vitamin C in a meal increases iron absorption. A meal with the highest iron availability is attained when greater than 90 g of meat, fish, or poultry are present, when greater than 75 mg vitamin C are

present, or when both 30 to 90 g meat, fish, or poultry and 25 to 75 mg vitamin C are present (Monsen et al., 1978). Excess zinc, copper, manganese, calcium or phosphate salts, and tannic acid (in tea) can decrease iron absorption. The fiber and phytate in plants (especially whole grain cereals and legumes) decrease the absorption of trace elements (zinc, iron, copper, manganese, and chromium), magnesium, and calcium. Soy protein also inhibits the utilization of minerals (Howe and Hoff, 1982). Mineral absorption can also be inhibited by high protein, fat, or oxalate levels. A high copper level may block zinc absorption whereas a high molybdenum intake may disrupt copper metabolism (Martin et al., 1983).

Suppression or inactivation of one nutrient by ingestion of another substance is a third type of interaction. This may involve a direct chemical inactivation, such as thiaminase in raw fish inactivating thiamin, avidin in raw egg white inactivating biotin, or vitamin C inactivation by heat or oxidation. This type of interaction can also be the indirect result of a substance on the production or utilization of a nutrient. A typical example of this is the reduction in the number of intestinal bacteria that occurs during antibiotic therapy, which may lead to deficiencies of biotin or vitamin K (Martin et al., 1983; National Research Council, 1980). Many other therapeutic drugs can alter the nutrient balance of the body.

Table 26

Some Interactions in the Human Diet

A. Alterations in Nutrient Requirements

1. High protein intake increases requirements for zinc (Martin et al., 1983), calcium, and vitamin B_6 (National Research Council, 1980)

2. Increase in total energy (kcal) intake (especially carbohydrate) increases the need for thiamin, because this vitamin is needed for many metabolic reactions, especially those involving carbohydrates (National Research Council, 1980)

3. Lower intake of polyunsaturated fatty acids lowers both intake of and requirement for vitamin E (National Research Council, 1980)

4. Severe environmental or other stress, such as severe injury or illness, (note that abnormal eating habits may be associated with stress) increases the vitamin C requirement (Howe and Hoff, 1982; National Research Council, 1980)

5. Some B vitamin requirements may also be increased by stressors, such as severe illness or trauma (Shenkin and Wretlind, 1979)

6. Large amounts of zinc may make a copper deficiency worse (National Research Council, 1980)

7. High phosphate and calcium levels in the diet could make a zinc deficiency worse (Martin et al., 1983)

8. Extremely vigorous work in high temperatures may lead to increased sodium losses in sweat, which would raise the sodium requirement (National Research Council, 1980)

Table 26 (continued)

B. Effects on Nutrient Absorption/Bioavailability

1. Vitamin C increases iron absorption (Howe and Hoff, 1982) in a meal containing at least 25-75 mg vitamin C (Monsen et al., 1978); vitamin C decreases copper absorption (Martin et al., 1983)

2. Meat, fish, or poultry (at least 30 to 90 g) in a meal increases iron absorption (Monsen et al., 1978)

3. Excess zinc, copper, manganese, salts of calcium and phosphate, and tannic acid in tea decrease iron absorption (Howe and Hoff, 1982; National Research Council, 1980)

4. Zinc, iron, copper, manganese, chromium, magnesium, calcium--absorption of these elements decreased by fiber and phytate in plants, particularly whole grain cereals and legumes (Howe and Hoff, 1982)

5. Mineral absorption adversely affected by excess protein, fat, and oxalates (Martin et al., 1983)

6. Dietary soy protein--decreased utilization of minerals (calcium, magnesium, phosphorus, copper, and manganese) (Howe and Hoff, 1982)

7. Excess molybdenum may disrupt copper metabolism (Martin et al., 1983)

8. High copper level in diet may block zinc absorption (Martin et al., 1983)

C. Suppression/Inactivation of Nutrients

1. Large intake of raw egg white, prevents biotin from being utilized due to the protein, avidin (National Research Council, 1980)

2. Antibiotic therapy reduces intestinal microorganisms and consequently biotin and vitamin K synthesis (Martin et al., 1983)

3. Thiamin--destroyed by thiaminase in raw fish (Martin et al., 1983)

4. Vitamin C becomes nonfunctional due to heat and oxidation (National Research Council, 1980)

CHAPTER V

CONCLUSIONS

There are approximately 40 nutrients known to be required in the daily diet. Additional essential substances may be identified in the future. Liquid alternatives to a normal, solid diet have been used most frequently for medical reasons, and the scientifically formulated, chemically defined diets (CDD's) have been in use for about 20 years. The administration of CDD's to humans has saved lives and has also increased our knowledge of human nutrition. The health of people fed by CDD's for long periods (months to years) will continue to be a source of information on requirements for nutrients needed in very small amounts. In the past decade, requirements for selenium, molybdenum, chromium, and biotin have been refined from experience with long-term intravenous CDD's (TPN, or Total Parenteral Nutrition).

There is a vast amount of literature on both CDD's and nutrition in general, and only a portion of the available sources has been reviewed in this report. For more details on the various aspects of CDD's, the original references cited should be consulted. The reviews on TPN include Phillips and Odgers (1982), Shenkin and Wretlind (1979), and Shils (1980). Enteral CDD's are covered by Cataldi-Betcher et al. (1983), Heymsfield et

al. (1979), Koretz and Meyer (1980), Randall (1984), and Smith and Heymsfield (1983). The definitive source for nutrient requirements in the United States is the National Research Council (1980). Detailed biochemical information on the nutrients is available in the text by Martin et al. (1983) and in many other sources.

The effects of various types of CDD's in humans demonstrate an important consideration in designing diets for long-term space missions. This is that adverse reactions can occur with any alteration in the normal eating pattern, even if the new diet is nutritionally complete. Adverse effects can either be psychological or physiological, and gastrointestinal symptoms would probably be the most likely physiological ones encountered in space travel. The psychological effects might include extreme dislike of the taste and reduced variety of a space diet, depression, hostility, loss of appetite, and psychosomatic complaints. Another nutritional consideration is the effect of possible decreases in the number of intestinal bacteria, which could lead to deficiencies of biotin or vitamin K; nutrient toxicities; and adverse nutrient interactions.

A final note is that many of the adverse effects of CDD's are related either to the liquid form or to the method of administration (nasogastric tubes, IV, etc.). Fewer problems might be encountered with a special diet that is as nutritionally complete as the currently available CDD's, but with more interesting texture and improved taste, so that the diet would be

more readily accepted. Now that many of the technical problems in providing all of the essential nutrients have been solved, more attention can be focused on making the diets more pleasant to consume.

References

Abumrad, N.N., A.J. Schneider, D. Steel, and L.S. Rogers. Amino acid intolerance during prolonged total parenteral nutrition reversed by molybdate therapy. American Journal of Clinical Nutrition 34:2551-2559, 1981.

American Medical Association Department of Foods and Nutrition. Guidelines for essential trace element preparations for parenteral use: a statement by an expert panel. JAMA 241(19):2051-2054, 1979a.

American Medical Association Department of Foods and Nutrition. Multivitamin preparation for parenteral use: statement by the Nutrition Advisory Group. Journal of Parenteral and Enteral Nutrition 3:258-262, 1979b.

Baker, S.S., et al. Reversal of biochemical and functional abnormalities in erythrocytes secondary to selenium deficiency. Journal of Parenteral and Enteral Nutrition 7(3):293-295, 1983.

Birnbaum, S.M., J.P. Greenstein, and M. Winitz. Quantitative nutritional studies with water-soluble, chemically defined diets. II. Nitrogen balance and metabolism. Archives of Biochemistry and Biophysics 72:417-427, 1957.

Birnbaum, S.M., M. Winitz, and J.P. Greenstein. Quantitative nutritional studies with water-soluble, chemically defined diets. III. Individual amino acids as sources of "non-essential" nitrogen. Archives of Biochemistry and Biophysics 72:428-436, 1957.

Birnbaum, S.M., M.E. Greenstein, M. Winitz, and J.P. Greenstein. Quantitative nutritional studies with water-soluble, chemically defined diets. VI. Growth studies on mice. Archives of Biochemistry and Biophysics 78:245-247, 1958.

Bivins, B.A., R.M. Bell, R.P. Rapp, and W.O. Griffen. Linoleic acid versus linolenic acid: what is essential? Journal of Parenteral and Enteral Nutrition 7(5):473-478, 1983.

Bivins, B.A., R.M. Bell, R.P. Rapp, and W.H. Toedebusch. Pancreatic exocrine response to parenteral nutrition. Journal of Parenteral and Enteral Nutrition 8(1):34-36, 1984.

Bloch, A.S. and M.E. Shils. Appendix. pages 1244-1330. In: Goodhart, R.S. and M.E. Shils (eds.). Modern Nutrition in Health and Disease. 6th Ed. Philadelphia: Lea & Febiger, 1980.

Bozzetti, F., M.G. Inglese, G. Terno, A. Pupa, C. Sequeira, and S. Migliavacca. Hypocupremia in patients receiving total parenteral nutrition. Journal of Parenteral and Enteral Nutrition 7(6):563-566, 1983.

Calloway, D.H. Basic data for planning life-support systems. pages 3-21. In: Calvin, M. and O.G. Gazenko (eds.). Foundations of Space Biology and Medicine. Volume III. Space Medicine and Biotechnology. Washington, DC: National Aeronautics and Space Administration, 1975.

Case, G.L. et al. Effects of osmolality of liquid nutrient diets on plasma equilibration of water and carbohydrate in Yucatan miniature swine. American Journal of Clinical Nutrition 34:1861-1867, 1981a.

Case, G.L. et al. Effects of osmolality of liquid nutrient diets on meal passage and nutrient absorption in Yucatan miniature swine. American Journal of Clinical Nutrition 34:1868-1878, 1981b.

Cataldi-Betcher, E.L., M.H. Seltzer, B.A. Slocum, and K.W. Jones. Complications occurring during enteral nutrition support: a prospective study. Journal of Parenteral and Enteral Nutrition 7(6):546-552, 1983.

Chernoff, R. Nutritional support: formulas and delivery of enteral feeding. I. Enteral formulas. Journal of the American Dietetic Association 79:426-429, 1981.

Cutie, A.J., E. Altman, and L. Lenkel. Compatibility of enteral products with commonly employed drug additives. Journal of Parenteral and Enteral Nutrition 7(2):186-191, 1983.

Dudrick, S.J. and J.E. Rhoads. Total intravenous feeding. Scientific American 226(5):73-80, May 1972.

Dudrick, S.J., D.W. Wilmore, H.M. Vars, and J.E. Rhoads. Long-term parenteral nutrition with growth and development, and positive nitrogen balance. Surgery 64:134-142, 1968.

Dymsza, H.A., G.S. Stoewsand, and H.A. Hollender. Nutrient-Defined Formula Diets for Aerospace Metabolic Experimentation. Final Report: December 31-September 30, 1967. Report No. SAM-TR-68-20. USAF Contract No. AF MIPR AM5-40037; AF MIPR AM6-40061. Natick, MA: U.S. Army Natick Laboratories, 1968.

Feroz, R.M., S. Puppala, M.A. Chaudry, and J.N. Kapoor. Compatibility of M.V.C. 9+3 (Multivitamin Concentrate for Infusion) in different large volume parenteral solutions. Paper presented in the Poster Session at the Midyear Clinical Meeting, American Society of Hospital Pharmacists, Los Angeles, CA, December 1982.

Goodhart, R.S. and M.E. Shils (eds.). Modern Nutrition in Health and Disease. 6th Ed. Philadelphia: Lea & Febiger, 1980.

Greenberg, G.R., S.L. Wolman, N.D. Christofides, S.R. Bloom, and K.N. Jeejeebhoy. Effect of total parenteral nutrition on gut hormone release in humans. Gastroenterology 80: 988-993, 1981.

Greenstein, J.P., S.M. Birnbaum, M. Winitz, and M.C. Otey. Quantitative nutritional studies with water-soluble, chemically defined diets. I. Growth, reproduction and lactation in rats. Archives of Biochemistry and Biophysics 72:396-416, 1957.

Greenstein, J.P., M.C. Otey, S.M. Birnbaum, and M. Winitz. Quantitative nutritional studies with water-soluble, chemically defined diets. X. Formulation of a nutritionally complete liquid diet. Journal of the National Cancer Institute 24:211-219, 1960.

Greig, P.D., J.P. Baker, and K.N. Jeejeebhoy. Metabolic effects of total parenteral nutrition. Annual Review of Nutrition 2:179-199, 1982.

Grundfest, S., E. Steiger, L. Sattler, S. Washko, and L. Wateska et al. The current status of home total parenteral nutrition. Artificial Organs 3(2):156-160, 1979.

Harper, H.A. Review of Physiological Chemistry. 14th Ed. Los Altos, CA: Lange Medical Publications, 1973.

Hauer, E.C. and M.V. Kaminski, Jr. Trace metal profile of parenteral nutrition solutions. American Journal of Clinical Nutrition 31:264-268, 1978.

Hawley, G.G. (ed.). The Condensed Chemical Dictionary. 8th Ed. New York: Van Nostrand Reinhold Company, 1971.

Heymsfield, S.B., R.A. Bethel, J.D. Ansley, D.W. Nixon, and D. Rudman et al. Enteral hyperalimentation: an alternative to central venous hyperalimentation. Annals of Internal Medicine 90:63-71, 1979.

Hoff, J.E., J.M. Howe, and C.A. Mitchell. Nutritional and Cultural Aspects of Plant Species Selection for a Controlled Ecological Life Support System. NASA CR-166324. Moffet Field, CA: Ames Research Center, National Aeronautics and Space Administration, 1982.

Hollender, H., H.A. Dymsza, and M. Klicka (U.S. Army Natick Laboratories, Natick, MA). Development of Nutritionally Defined Metabolic Diets for Aerospace Travel. Final Report: January-December 1964. Report No. AMRL-TR-65-218. USAF Contract MIPR No. AMD-AM 4-40011. Wright-Patterson Air Force Base, OH: Aerospace Medical Research Laboratories, 1965.

Holvey, D.N. (ed.). The Merck Manual. 12th Ed. Rahway, NJ: Merck & Co., Inc., 1972.

Howard, L., J. Bigaouette, R. Chu, B.E. Krenzer, D. Smith, and C. Tenny. Water soluble vitamin requirements in home parenteral nutrition patients. American Journal of Clinical Nutrition 37:421-428, 1983.

Howe, J.M. and J.E. Hoff. Plant Diversity to Support Humans in a CELSS Ground-Based Demonstrator. NASA CR-166357. Moffett Field, CA: Ames Research Center, National Aeronautics and Space Administration, 1982.

Innis, S.M. and D.B. Allardyce. Possible biotin deficiency in adults receiving long-term total parenteral nutrition. American Journal of Clinical Nutrition 37:185-187, 1983.

Jeejeebhoy, K.N., W.J. Zohrab, B. Laner, M.J. Phillips, A. Kuksis, and G.H. Anderson et al. Total parenteral nutrition at home for 23 months, without complication, and with good rehabilitation. Gastroenterology 65:811-820, 1973.

Jeejeebhoy, K.N., R.C. Chu, E.B. Marliss, G.R. Greenberg, and A. Bruce-Robertson et al. Total parenteral nutrition at home: studies in patients surviving 4 months to 5 years. Gastroenterology 71(6):943-953, 1976.

Jeejeebhoy, K.N. et al. Chromium deficiency, glucose intolerance, and neuropathy reversed by chromium supplementation, in a patient receiving long-term total parenteral nutrition. American Journal of Clinical Nutrition 30:531-538, 1977.

Jones, B.J.M., R. Lees, J. Andrews, P. Frost, and D.B.A. Silk. Comparison of an elemental and polymeric enteral diet in patients with normal gastrointestinal function. Gut 24: 78-84, 1983.

Kark, R.M. Liquid formula and chemically defined diets. Journal of the American Dietetic Association 64:476-479, 1974.

Katchman, B.J., G.M. Homer, J.P.F. Murphy, C.A. Linder, and V.R. Must (Department of Research, Miami Valley Hospital, Dayton, OH). The Biochemical, Physiological, and Metabolic Evaluation of Human Subjects in a Life Support Systems Evaluator and on a Liquid Food Diet. Report No. NASA-CR-94860, AMRL-TR-67-72. Joint NASA/USAF Study. Contract No. AF 33(657)-11716. Wright-Patterson Air Force Base, OH: Aerospace Medical Research Laboratories, 1967.

Katchman, B.J., G.M. Homer, J.P.F. Murphy, C.A. Linder, and V.R. Must (Department of Research, Miami Valley Hospital, Dayton, OH). The Effect of a Liquid Food Diet on Human Subjects in a Life Support Systems Evaluator. Final Report: April-May 1965. Report No. NASA-CR-116253, AMRL-TR-67-76. Joint NASA/USAF Study. Contract No. AF 33(657)-11716; NASA R-85. Wright Patterson Air Force Base, OH: Aerospace Medical Research Laboratories, 1970.

Kien, C.L. and H.E. Ganther. Manifestations of chronic selenium deficiency in a child receiving total parenteral nutrition. American Journal of Clinical Nutrition 37:319-328, 1983.

Kien, C.L., A. Cordano, D.A. Cook, and V.R. Young. Fecal characteristics in healthy young adults consuming defined liquid diets or a free-choice diet. American Journal of Clinical Nutrition 34:357-361, 1981.

Koretz, R.L. and J.H Meyer. Elemental diets--facts and fantasies. Gastroenterology 78:393-410, 1980.

Kurtz, T.W. and R. Morris, Jr. Dietary chloride as a determinant of "sodium-dependent" hypertension. Science 222(4628):1139-1141, 1983.

Levenson, J.L. Biotin-responsive depression during hyperalimentation. Journal of Parenteral and Enteral Nutrition 7(2):181-183, 1983.

Levine, G.M., J.J. Deren, E. Steiger, and R. Zinno. Role of oral intake in maintenance of gut mass and disaccharide activity. Gastroenterology 67(5):975-982, 1974.

LyphoMed, Inc. (Chicago, IL). Product literature. Personal communication. September 1983.

MacFie, J., J.H.M. Holmfield, R.F.G. King, and G.L. Hill. Effect of the energy source on changes in energy expenditure and respiratory quotient during total parenteral nutrition. Journal of Parenteral and Enteral Nutrition 7(1):1-5, 1983.

Malcolm, R. et al. Psychosocial aspects of total parenteral nutrition. Psychosomatics 21(2):115-125, 1980.

Martin, D.W., Jr., P.A. Mayes, and V.W. Rodwell. Harper's Review of Biochemistry. 19th Ed. Los Altos, CA: Lange Medical Publications, 1983.

McCamman, S., P.L. Beyer, and J.B. Rhodes. A comparison of three defined formula diets in normal volunteers. American Journal of Clinical Nutrition 30:1655-1660, 1977.

McCarron, D.A., C.D. Morris, and C. Cole. Dietary calcium in human hypertension. Science 217:267-269, 1982.

Mead Johnson & Company. The Enteral Nutritional Management System: Product Handbook. Evansville, IN: Mead Johnson & Company, 1984.

Mertz, W. The essential trace elements. Science 213:1332-1338, 1981.

Monsen, E.R., L. Hallberg, M. Layrisse, D.M. Hegsted, J.D. Cook, W. Mertz, and C.A. Finch. Estimation of available dietary iron. American Journal of Clinical Nutrition 31:134-141, 1978.

National Research Council. Recommended Dietary Allowances. 9th Ed. Washington, DC: National Academy of Sciences, 1980.

Nicogossian, A.E. and J.F. Parker, Jr. Space Physiology and Medicine. NASA SP-447. Washington, DC: National Aeronautics and Space Administration, 1982.

NUTRISOURCE Technical Information Manual. Minneapolis, MN: Sandoz Nutrition [formerly Doyle Pharmaceutical Company], 1982.

Perrault, J., G. Devroede, and G. Bounous. Effects of an elemental diet in healthy volunteers. Gastroenterology 64 (4):569-576, 1973.

Phillips, G.D. and C.L. Odgers. Parenteral nutrition: current status and concepts. Drugs 23:276-323, 1982.

Physician's Desk Reference. 37th Ed. Oradell, NJ: Medical Economics Company, Inc., 1983.

Physician's Desk Reference. 38th Ed. Oradell, NJ: Medical Economics Company, Inc., 1984.

Physician's Desk Reference for Nonprescription Drugs. 3rd Ed. Oradell, NJ: Medical Economics Company, Inc., 1982.

Popov, I.G. Food and water supply. pages 22-55. In: Calvin, M. and O.G. Gazenko (eds.). Foundations of Space Biology and Medicine. Volume III. Space Medicine and Biotechnology. Joint USA/USSR Publication. Washington, DC: National Aeronautics and Space Administration, 1975.

Rambaut, P.C. Nutritional criteria for closed-loop space food systems. pages 113-131. In: Cheston, T.S. and D.L. Winter (eds.). Human Factors of Outer Space Production. AAAS Selected Symposium 50. Boulder, CO: Westview Press, 1980.

Randall, H.T. Enteral nutrition: tube feeding in acute and chronic illness. Journal of Parenteral and Enteral Nutrition 8(2):113-136, 1984.

Riley, H.K., J.L. White, P.A. Jarrett, J.A. Maylan, Jr., and J.P. Grant et al. Immediate postoperative enteral nutrition. Surgical Forum 31:103-105, 1980.

Rudman, D. and P.J. Williams. Megadose vitamins: use and misuse. Letter. New England Journal of Medicine 309:488-490, 1983.

Russell, R.I. Elemental diets. Gut 16:68-79, 1975.

Sandoz Nutrition (Minneapolis, MN). Precision Isotonic Diet (product literature). Personal communication. 1984.

Schaumburg, H., J. Kaplan, A. Windebank, N. Vick, S. Rasmus, D. Pleasure, and M.J. Brown. Sensory neuropathy from pyridoxine abuse: a new megavitamin syndrome. New England Journal of Medicine 309:445-448, 1983.

Schwarz, K. Essentiality versus toxicity of metals. pages 3-22. In: Brown, S.S. (ed.). Clinical Chemistry and Chemical Toxicology of Metals. New York: Elsevier/North Holland, 1977.

Seltzer, M.H. Components of trace mineral package administered to patients. Journal of Parenteral and Enteral Nutrition 7(1):69-70, 1983.

Shenkin, A. and A. Wretlind. Complete parenteral nutrition and its use in diseases of the alimentary tract. Progress in Food and Nutrition Science 3(5/6):141-202, 1979.

Shils, M.E. Parenteral nutrition. pages 1125-1152. In: Goodhart, R.S. and M.E. Shils (eds.). Modern Nutrition in Health and Disease. 6th Ed. Philadelphia: Lea & Febiger, 1980.

Smith, J.L. and S.B. Heymsfield. Enteral nutrition support: formula preparation from modular ingredients. Journal of Parenteral and Enteral Nutrition 7(3):280-288, 1983.

Solomons, N.W., F. Viteri, T.R. Shuler, and F.H. Nielsen. Bioavailability of nickel in man: effects of foods and chemically-defined dietary constituents on the absorption of inorganic nickel. Journal of Nutrition 112:39-50, 1982.

Thompson, J.S. and R.E. Hodges. Preventing hypophosphatemia during total parenteral nutrition. Journal of Parenteral and Enteral Nutrition 8(2):137-139, 1984.

Vander, A.J., J.H. Sherman, and D.S. Luciano. Human Physiology. 2nd Ed. New York: McGraw-Hill, 1975.

Vital High Nitrogen. Columbus, OH: Ross Laboratories, Division of Abbott Laboratories, 1981.

Voitk, A.J. The place of elemental diet in clinical nutrition. British Journal of Clinical Practice 29(3):55-62, 1975.

Welch, B.E. Dietary regimes in space cabin simulator studies. pages 181-190. In: Helvey, T.C. (ed.). Conference on Nutrition in Space and Related Waste Problems. NASA-SP-70. Washington, DC: National Aeronautics and Space Administration, 1964.

Winitz, M. Individualized Chemically-Defined Diets in Life-Support Systems During Space Flight. Semi-Annual Status Report: January 1-November 30, 1962. NASA Grant No. NsG-285-63. Duarte, CA: City of Hope Medical Center, 1962.

Winitz, M., S.M. Birnbaum, and J.P. Greenstein. Quantitative nutritional studies with water-soluble, chemically defined diets. IV. Influence of various carbohydrates on growth, with special reference to D-glucosamine. Archives of Biochemistry and Biophysics 72:437-447, 1957.

Winitz, M., J.P. Greenstein, and S.M. Birnbaum. Quantitative nutritional studies with water-soluble, chemically defined diets. V. Role of the isomeric arginines in growth. Archives of Biochemistry and Biophysics 72:448-456, 1957.

Winitz, M., J. Graff, N. Gallagher, A. Narkin, and D.A. Seedman. Evaluation of chemical diets as nutrition for man-in-space. Nature 205(4973):741-743, 1965.

Winitz, M. et al. Studies in metabolic nutrition employing chemically defined diets. I. Extended feeding of normal human adult males. American Journal of Clinical Nutrition 23:525-545, 1970a.

Winitz, M. et al. Studies in metabolic nutrition employing chemically defined diets. II. Effects on gut microflora population. American Journal of Clinical Nutrition 23:546-559, 1970b.

Young, E.A., and E. Weser. The metabolism of infused maltose and other sugars. pages 73-99. In: Physiological Effects of Food Carbohydrates. ACS Symposium Series, No. 15. Washington, DC: American Chemical Society, 1975.

Young, E.A., L.A. Cioletti, J.B. Traylor, and V. Balderas. Gastrointestinal response to oral versus gastric feeding of defined formula diets. American Journal of Clinical Nutrition 35(4):715-726, 1982.

Young, E.A., N. Hueler, P. Russell, and E. Weser. Comparative nutritional analysis of chemically defined diets. Gastroenterology 69(6):1338-1345, 1975.

Young, E.A., L.A. Cioletti, W.B. Winborn, J.B. Traylor, and E. Weser. Comparative study of nutritional adaptation to defined formula diets in rats. American Journal of Clinical Nutrition 33:2106-2118, 1980.

1. Report No.	2. Government Accession No.	3. Recipient's Catalog No.
NASA CR-3850		

4. Title and Subtitle	5. Report Date
NUTRITIONAL MODELS FOR SPACE TRAVEL FROM CHEMICALLY DEFINED DIETS	November 1984
	6. Performing Organization Code
7. Author(s)	8. Performing Organization Report No.
Patricia A. Dufour	
	10. Work Unit No.
9. Performing Organization Name and Address	11. Contract or Grant No.
Science Communication Studies, DCE&SS The George Washington University Washington, D.C. 20052	NASW-3165
	13. Type of Report and Period Covered
12. Sponsoring Agency Name and Address	Contractor Report
Life Sciences Division, Office of Space Science & Applications, NASA Headquarters Washington, D.C. 20546	14. Sponsoring Agency Code EBM

15. Supplementary Notes

Prepared at the request of James H. Bredt, Life Sciences Division, NASA Headquarters, for the CELSS Program

16. Abstract

Human nutritional requirements are summarized, including recommended daily intake and maximum safe chronic intake of nutrients. The biomedical literature on various types of chemically defined diets (CDD's), which are liquid, formulated diets for enteral and total parenteral nutrition, is reviewed. The chemical forms of the nutrients in CDD's are detailed, and the compositions and sources of representative commercial CDD's are tabulated. Reported effects of CDD's in medical patients, healthy volunteers, and laboratory animals are discussed. The effects include gastrointestinal side effects, metabolic imbalances, nutrient deficiencies and excesses, and psychological problems. Dietary factors contributing to the side effects are examined. Certain human nutrient requirements have been specified more precisely as a result of long-term use of CDD's, and related studies are included. CDD's are the most restricted yet nutritionally complete diets available. Very long space missions may have severe limitations on the number and types of food sources. Data on CDD's may be useful to the CELSS (Controlled Ecological Life Support Systems) Program in the design of diets for future space missions of long duration.

17. Key Words (Suggested by Author(s))	18. Distribution Statement
Chemically Defined Diets; Nutrient Requirements; Nutrient Toxicity; Gastrointestinal Side Effects; Total Parenteral Nutrition; Enteral Nutrition; CELSS Food	Unclassified - Unlimited Subject Category 54

19. Security Classif. (of this report)	20. Security Classif. (of this page)	21. No. of Pages	22. Price*
Unclassified	Unclassified	139	A07

* For sale by the National Technical Information Service, Springfield, Virginia 22161

NASA-Langley, 1984

National Aeronautics and
Space Administration

Washington, D.C.
20546

Official Business
Penalty for Private Use, $300

THIRD-CLASS BULK RATE

Postage and Fees Paid
National Aeronautics and
Space Administration
NASA-451

NASA

POSTMASTER: If Undeliverable (Section 158
Postal Manual) Do Not Return