

Jonathan Rhoads Symposium Papers

History of Parenteral Nutrition

Erik Vinnars, MD, PhD* and Douglas Wilmore, MD†

From the *Karolinska Institute, Stockholm, Sweden; and †Harvard Medical School, Boston, Massachusetts

ABSTRACT. A survey is given of the development of parenteral nutrition with the beginning of William Harvey's fantastic discovery of the circulation to today's discussion of what is an optimal regime of parenteral nutrition. The important and different steps of development during the 17th and 19th centuries are discussed. The modern steps during the last century leading to the con-

cept we have today of parenteral nutrition is mentioned, with reference to all pioneers all over the world. Glucose, protein hydrolysates and crystalline amino acids, development of safe fat emulsions, and the current concepts of parenteral nutrition and future considerations are discussed. (*Journal of Parenteral and Enteral Nutrition* 27:225–232, 2003)

Jonathan Evans Rhoads, MD, Surgical Nutritionist, towered above his peers in intellect, energy, and vision. He was a dedicated surgeon who hated to lose any patient to the ravages of malnutrition, and he was absolutely determined to find a safe and effective method of feeding patients with fistulas and limited intestinal function. Rhoads' vision of the potential value of intravenous feeding was not always shared by his peers in the Harrison Department of Surgery at the University of Pennsylvania, and some even felt that he was using departmental resources unwisely. However, his dedication to the issue inspired many young investigators to push the research process forward. Rhoads' continued interest in research until his death last year at age 94 was the inspiration behind the current research program at A.S.P.E.N.

This special series in JPEN is dedicated to the memory of Jonathan Evans Rhoads, and strives to describe the development of parenteral nutrition. Of course, Dr Rhoads was not working alone in the quest for IV feeding, and his accomplishments were dependent on the successes of many investigators in other laboratories and other countries. The first paper in this series, by Drs Vinnars and Wilmore, describes a long series of clinical and experimental developments that were in many ways building blocks for the experiments in Rhoads' laboratory. The impressive laboratory and clinical experiences of Stanley Dudrick, MD, Henry Vars, PhD, Douglas Wilmore, MD, and others at the University of Pennsylvania, will be described in a future article by Dr Dudrick. The full development of parenteral nutrition, as we know it today, was dependent on endless hours of effort by dedicated nurses, pharmacists, and dietitians, that will also be described in future articles in this series. The professional support

systems developed for the safe use of parenteral nutrition varied in different regions of the world, and will also be addressed in this series.

No series of papers can adequately pay homage to the vital contributions of Jonathan Evans Rhoads, MD. These contributions range from research and programmatic guidance at ASPEN, to the many physicians and other professionals trained by him and his protégés, to current and future patients with intestinal failure whose survival and quality of life have been radically improved by the availability of parenteral nutrition. His personal value for mentoring the efforts of others that underpinned the contributions from his laboratory, should be emulated by other investigators and clinicians in order to move nutritional management, including parenteral nutrition, to the next level of quality and usefulness. Jonathan Rhoads would expect nothing less.

*Charlene Compher, PhD, RD, FADA, CNSD
University of Pennsylvania School of Nursing
Clinical Nutrition Support Service*

Complete parenteral or IV nutrition is a therapeutic method that has been available for approximately 50 years. The successful development of this mode of therapy, in a modern sense, was initiated in the late 1930s, but its practical clinical use did not emerge until the 1960s. However, the history of this field dates back >350 years. The discovery of the circulation of the blood by William Harvey in 1628¹ formed the basis for the rationale for IV injections and infusions. Several decades later, in 1665, Sir Christopher Wren published his studies on IV infusions of wine, ale, and opiates in a dog.² He noted that alcohol given IV had the same inebriating effect as alcohol given orally to humans. Wren was a physiologist and physician, and at the age of 27, was appointed Professor in Astronomy in London, and later in Oxford. He was later appointed Surveyor General (chief architect) of England by Charles II. He was responsible for building many parish

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Correspondence: Dr Douglas Wilmore, Department of Surgery, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02445. Electronic mail may be sent to dwilmore@partners.org.

churches, libraries, hospitals, and royal residences throughout the country and is probably best remembered as the main architect of St Paul's Cathedral in London.³

In 1662, Lower presented a paper before the Royal Society on IV feeding and blood transfusion in the dog.⁴ A blood transfusion from a sheep into a young man in London some years later was reported as being successful, probably meaning that the patient survived.⁵

Other pioneers were William Courten, who in 1712 infused olive oil in a dog, given at a dose of about 1 g/kg body weight.⁶ The dog died with symptoms of severe respiratory distress, most likely caused by fat embolism in the lungs. Hence, it was recognized at that time that fat or oil could only be supplied by IV in some special or modified form.

In 1818, Blundell in London questioned the value of bleeding critically ill septic patients and suggested the possibilities of blood transfusion in selected patients.⁷ A decade later, an important contribution to the development of IV infusions was made during the severe cholera epidemic of 1831 to 1832 by the Scottish physician Latta.⁸ He was the first to infuse water and salts (saline) into a patient, who quickly recovered and survived. This case demonstrated that the diarrhea associated with cholera led to severe dehydration and salt deficiency that must be compensated for by providing the appropriate replacement solutions.

Edward Hodder, in Canada in 1873, infused fat in the form of milk into 3 cholera patients.⁹ Two of the patients recovered completely, an effect that was "magical," but the third cholera patient did not survive despite the milk infusion. According to Hodder, this patient was infused with insufficient amounts of milk. After some criticism of his work, Hodder did not continue his studies, but several others found that milk infusions caused several adverse reactions, and this therapeutical method was abandoned by the end of the last century. These studies confirmed the earlier observations of Courten that unmodified fats could not be given IV.

Menzel and Perco in Vienna in 1869 gave fat subcutaneously to dogs and showed that relatively large amounts of this substance could be supplied without detrimental effects.¹⁰ In 1904, Paul Friedrich performed further studies by using subcutaneous administration of nutrients.¹¹ He supplied parenteral nutrition in humans by giving subcutaneous infusions of peptone, fat, glucose, and electrolytes. However, these infusions were so painful that the method could not be used clinically.

STUDIES WITH GLUCOSE

It seems obvious in retrospect that the field of parenteral nutrition could not progress successfully before much more was known in the basic sciences. Such an important contribution was made by Claude Bernard, who introduced the term *Le milieu intérieur*, and in 1859, demonstrated the importance of glucose for metabolism.¹²

Arthur Beidl and Rudely Krauts, in 1896, were the first to infuse glucose IV in humans.¹³ They adminis-

tered 200 to 300 mL of a 10% glucose solution without observing glucosuria, but severe fever resulted. Such febrile reactions were often reported after infusions of both glucose and salt solutions in these early studies. It was believed that these bodily reactions were caused by the administration of fluid, glucose, or salt by the IV route, which was thought to be very unphysiological. The terms "glucose fever" and "salt fever" were often used as explanations of these adverse reactions. Nothing was known about pyrogens at that time.

In 1915, Woodyatt and co-workers reported studies on IV administration of glucose in humans.¹⁴ They used an infusion pump to insure constant infusions, varied the infusion rate to establish a dose-response relationship, and monitored urinary glucose excretion. They reported that about 0.85 g of glucose/kg per hour could be supplied by IV without ensuing glucosuria. This classic early study predated glucose clamp investigations by more than 50 years. They stated: "IV nutrition with glucose is thus proved to be a feasible clinical proposition, and the way is opened for experiments with amino acids, polypeptides, etc."

Matas, in 1924, was the first to use a continuous drip infusion of glucose,¹⁵ and some years later, Zimmerman, in 1945, described the infusion of IV solutions through an IV catheter placed in the superior vena cava.¹⁶ This approach was used by Dennis and Dennis and Karlson, who reported the support of surgical patients with the continuous infusion of a solution of 20% glucose along with some vitamins, electrolytes, and 300 to 400 mL of plasma.^{17,18} Malnourished patients with inflammatory bowel disease requiring a surgical procedure were some of the individuals who received this supportive treatment.

The next major contribution was the infusion of hypertonic glucose and all necessary nutrients by Dudrick et al,¹⁹ and these studies will be discussed later.

The Use of Plasma as a Protein Source

In the 1930s, Whipple, Holman, Madden, and associates demonstrated that the protein requirements of the adult dog could be provided by infusing plasma protein by vein while the animals received a protein-free diet.²⁰ (Whipple shared the Nobel Prize in Physiology and Medicine in 1934 for discoveries concerning liver therapy in cases of anemia.) Whipple noted that hemoglobin did not readily contribute to the protein pool and that the body was highly protective of this protein during periods of starvation.^{21,22} Albright and his research team at the Massachusetts General Hospital in Boston investigated the metabolic fate of infused plasma protein in humans and demonstrated that such infusions contributed to positive nitrogen balance.²³ Later, Yuilie et al²⁴ infused labeled plasma protein into dogs and found that there was a gradual increase in tissue radioactivity over time and a simultaneous fall off of ¹⁴CO₂.

These studies were all brought to a dramatic conclusion with the demonstration by Allen et al²⁵ that growth in puppies could be achieved by the provision of IV plasma protein in animals receiving a protein-free diet.

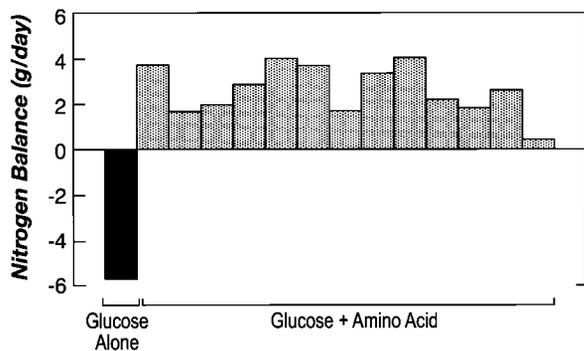


FIG. 1. Positive nitrogen balance was achieved in a depleted cancer patient with the addition of an acid hydrolysate of casein to an infusion of glucose. Data derived from Elman R, ed: *Parenteral Alimentation in Surgery*. Hoeber, New York, 1947.

PROTEIN HYDROLYSATES AND CRYSTALLINE AMINO ACIDS

In the beginning of the 20th century, it was known that dietary proteins were hydrolyzed in the intestinal tract before absorption occurred. It was then logical to investigate the effect of IV administration of amino acids and hydrolysates. The first successful study in this field was reported in 1913 by the 2 Danes, Henriques and Andersen, who infused a beef hydrolysate into a goat and achieved a positive nitrogen balance.²⁶ At the same time, Van Slyke and Meyer reported their studies on the metabolism of amino acids obtained from the hydrolysis of casein or beef protein infused into dogs.²⁷

The field of protein metabolism made major progress with the classic studies of Rose in the 1930s, who determined the essential amino acids in humans and proposed the ideal mixture of amino acids that could support protein synthesis in healthy adults.²⁸ One of his students was Robert Elman, a surgeon who worked in St Louis. In 1937, he published the first successful studies evaluating the IV infusion of amino acids in the form of a fibrinogen hydrolysate in man.^{29,30} This was an indisputable landmark in the development of IV nutrition (Fig. 1). Undoubtedly, Elman deserves the complement given to him by Arvid Wretlind, who referred to him as the "father of IV nutrition."³¹

In Europe, the first protein hydrolysate to be marketed was developed by Wretlind and was introduced in 1944 in Sweden.³² In contrast to Elman's preparation, which was a hydrolysis of whole proteins by strong acids, Wretlind hydrolyzed casein enzymatically and then dialyzed the product to take away large polypeptides. The solution was given the name Aminosol. The most important step in producing Aminosol was use of the dialysis technique. Later, Abbott Co (Chicago, IL) produced another hydrolysate of casein, which was also given the name Aminosol. Abbott and Vitrum, the company which produced Wretlind's product, didn't know that they had used the same name Aminosol, but they came to an agreement so that both companies could continue using the same name, because they believed they were not going to compete in the same markets. Abbott's Aminosol was incomplete, because the essential amino acid, tryptophan,

was destroyed in the hydrolysis process and this amino acid was supplemented to the hydrolysate.

The protein hydrolysates had the disadvantage that the amino acid pattern could not be changed. On the other hand, these solutions contained all amino acids necessary for protein synthesis. More recently, it has been shown that many of the small polypeptides, which were included in the hydrolysates, contained abundant amounts of glutamine; therefore, the impact of these solutions on the nitrogen balance was very effective.³³ It took many years of adjusting formulations before crystalline amino acid solutions with similar biologic activity could be produced.

The first to introduce a crystalline L-amino acid solution was Bansi in 1964 in Germany.³⁴ Bansi used the proposed formula from the classical work by Rose found in his 1949 publication "Amino Acid Requirement of Man."²⁸ In Bansi's product, the nonessential nitrogen content was primarily glycine, which soon was shown to be highly ineffective. In the late 1960s, Wretlind therefore introduced a more complete crystalline amino acid solution, named Vamin, which was shown to be much more effective on the postoperative nitrogen balance than solutions with a high content of glycine. In the 1970s, the hydrolysates disappeared from the market.

In the early development of crystalline amino acid solutions, it was difficult to include tyrosine, cysteine-cystine, and glutamine because of technical reasons. Earlier it was believed that glutamine was an indispensable amino acid. However, the study by Bergström et al³⁵ showed that glutamine was the most abundant intracellular free amino acid in skeletal muscle, and in 1976, the same group demonstrated that after trauma or operations, the glutamine content in muscle tissue dropped approximately 50%.³⁶ The significance of these findings was unclear at this time, but glutamine could not be included in balanced amino acid solutions because of its low solubility and lack of a stable shelf life. These problems were solved by Fürst et al in the 1980s by introducing dipeptides, which enhanced solubility and stability and made it possible to develop solutions containing both glutamine and tyrosine.³⁷ The only existing problem with the amino acid solutions used today is to supply cysteine-cystine, which is unstable even as dipeptide if the solutions undergo heat sterilization.

DEVELOPMENT OF SAFE FAT EMULSIONS

It was realized early on that optimal use of the amino acids in solutions could only be achieved by simultaneously providing adequate amounts of necessary energy. In those days, glucose was the only available nonprotein source that could be given IV.

Between 1920 and 1960, scientists in both the United States and Japan developed and tested hundreds of fat emulsions of varying composition. Leaders in this field included Yamakawa and Nomura in Japan³⁸; Stare and Geyer, working at the Harvard School of Public Health³⁹⁻⁴¹; Meng, located at Vanderbilt University⁴²; and later Canham, who directed clinical investigations from the US Army Research and Development Command.⁴³ From these studies, a fat

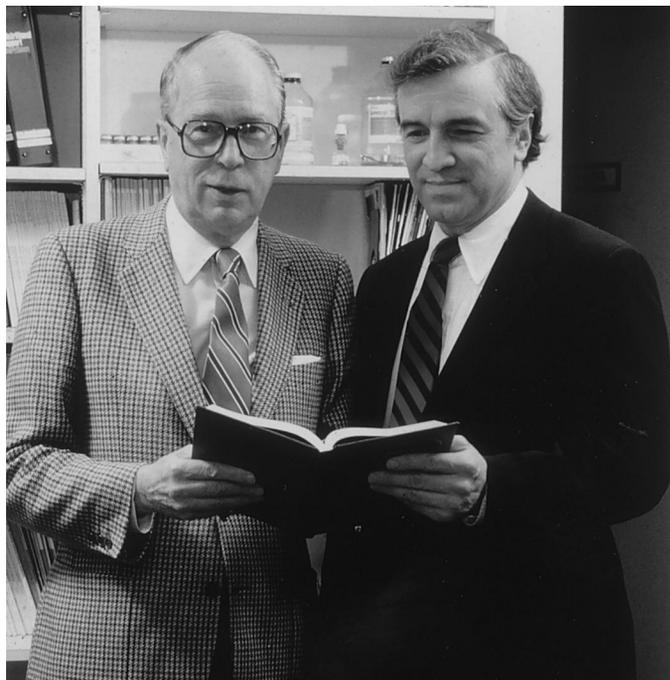


FIG. 2. Two major contributors to contemporary parenteral nutrition: Arvid Wretlind (left) and Stanley J. Dudrick (right).

emulsion named Lipomul was produced by the Upjohn Co (Kalamazoo, MI). However, the adverse effects were quite serious (including chills, fever, nausea, vomiting, and at times dyspnea, hypoxia, and hypotension), and the product was withdrawn from the market after some years. These negative experiences in the United States greatly dampened the interest in fat emulsions also in other parts of the world. As a result, investigators had only glucose to use as an energy source.

The first to develop a nontoxic readily available fat emulsion was the Swedish scientist Arvid Wretlind, who in 1961, introduced Intralipid together with O. Schubert.⁴⁴ After many years of trial and error, Wretlind found that an emulsion prepared from soybean oil and egg yolk phospholipids, used as an emulsifier, could be safely infused.⁴⁵ Commercialization was possible by working cooperatively with the Vitrum Co in Stockholm, a family-owned enterprise committed to the concept of total parenteral nutrition (TPN). After the initial success of Intralipid, this lipid emulsion was copied by many other companies throughout the world.

In 1962, one of the first symposiums on parenteral nutrition was held in Kungälv, Sweden. This was the first time details of a TPN program were presented. All presentations from the symposium were published in *Acta Chirurgica Scandinavica* as a supplement in 1964.⁴⁶ For his many developmental contributions, it seems appropriate to call Arvid Wretlind the "father of complete parenteral nutrition" (Fig. 2).

In 1968, a new landmark in the history of parenteral nutrition was passed by Dudrick et al,¹⁹ who demonstrated that a catheter placed in the superior vena cava could be used over extended periods of time to administer a solution of concentrated glucose, along with all other essential nutrients (although, initially essential fatty acids were lacking because lipid emulsions were

unavailable in the United States). This system provided a means of delivering long-term parenteral support, which resulted for the first time in growth in infants and weight gain, wound healing, and fistula closure in adults. Because fat emulsion was not available in the United States at that time, Dudrick et al's regimen was based on administering high doses of glucose, amino acids, and other essential nutrients—the so-called glucose system. In contrast, the Swedish regimen, which provided approximately one-half of the calories as lipid emulsion and the remainder as glucose, was referred to as the fat system. With the manufacture and increasing availability of all the necessary substrates for parenteral nutrition throughout the world, these 2 approaches have merged. Most providers use a mixed fuel source of both fat and glucose, but rely on a central catheter for long-term solution administration.

Professor Rhoads also introduced the term "hyperalimentation," which implied that depleted or hypermetabolic patients should receive more than their normal nutrient requirements, thus contributing to the anabolic responses observed in many of the initial patients. Caloric prescriptions have become more precise over the years, and the problems associated with overfeeding are now well recognized. Many units now measure oxygen consumption to calculate more exact metabolic requirements and tend not to give excessive calories.

OTHER CONTRIBUTIONS

Studley, in 1936, demonstrated that a body weight loss of >20% before an operation for chronic peptic ulcer resulted in a postoperative mortality rate of 33%.⁴⁷ The importance of IV nutrition support to these patients was therefore clear.

However, in the early half of this century, most IV infusions of electrolytes and glucose were followed by febrile reactions, which sometimes were quite alarming. These reactions were believed by many to be an unavoidable complication of IV infusions, but it was later realized that these responses originated from contamination with certain organic substances, termed pyrogens. These pyrogens had been discovered by Francis Siebert in 1923.⁴⁸ Later, it was shown that pyrogens consisted of endotoxins derived from the bacterial cell wall. Without the knowledge of pyrogens, it would have been impossible to develop and produce in large volume safe solutions for parenteral use.

With the provision of nonpyrogenic IV solutions, other technical developments followed. An entire science emerged around fluid and electrolyte balance, perioperative metabolism, changes associated with the catabolic state, and the metabolism of starvation. Contributions were likewise made in the field of infant nutrition and child growth and development.

During the last 20 years, the development of IV feeding has been enormous. New fat emulsions and amino acid solutions have been introduced to the market and proven to be effective. Pumps and catheters are more fail-safe and are available throughout the world. Parenteral nutrition is being delivered to patients at

home who have conditions that require this type of long-term support. Methodologies are in place to insure safe home infusions, and patients are cared for by highly trained support teams. One classical case of long-term home nutrition, and probably the first to be published, concerns a woman who was treated by Jeejeebhoy et al⁴⁹ in 1973. The patient was treated for 23 months at home without complications.

The opinion today is that indications for nutrition support exist when a patient has lost $\geq 10\%$ of their body weight or cannot start to eat within 10 days after an operation or trauma. There is essentially no major difference between enteral and parenteral nutrition if delivery is practiced correctly. If the gut can be used, enteral support should be given. But in many clinical situations, the patient cannot eat or is not permitted to use the gut, and parenteral nutrition should be used. In catabolic conditions such as a major operation, trauma, or sepsis, the protein breakdown is accelerated, and it takes approximately 4 times longer to regain body cell mass than it takes to lose. If nutrition support is not provided for weeks, the injured patient will quickly become malnourished, especially when compared with a starvation situation in an otherwise healthy person.

The complication rate is significantly increased in the malnourished individual. The most common complications are infections related to a decreased immune response. It is mainly the muscle mass that is lost, leading to muscular weakness. This loss has consequences for ventilatory efforts, ambulation and self-care, wound healing, and gut integrity. When the patient has lost $>20\%$ of its body weight, mortality is dramatically increased.

A contemporary parenteral feeding program consists of water, energy (carbohydrates and fat), amino acids, vitamins, and trace elements. It is extremely important that these nutrients are administered together. An improvement, aimed to simplify the infusions, was the introduction of the "All-in-One" system, where all nutrients are mixed in 1 bag at the local pharmacy or at a pharmaceutical company. The method was introduced by Solassol et al in 1972.⁵⁰ At first, many were skeptical of this method, because they believed that the other components of the nutrient mix would influence the stability of the lipid emulsion. However, since that time, many laboratories have confirmed the stability of the variety of nutrient components contained in such triple-mixed solutions.

CURRENT CONCEPTS AND FUTURE CONSIDERATIONS

Carbohydrate Metabolism

The nitrogen-sparing effect of infused glucose stems both from the suppression of endogenous glucose production (thereby sparing gluconeogenic amino acids) and from the direct oxidation of the infused glucose (thereby competing with the oxidation of amino acids). These 2 processes can minimize changes in plasma glucose concentration during a glucose infusion by reducing glucose production and enhancing the ability to clear glucose from the bloodstream. During the first few hours of glucose infusion, the primary operative

mechanism is the suppression of glucose production. After several hours of glucose infusion, the insulin becomes effective in stimulating glucose clearance. It is important to realize that the rate of gluconeogenesis cannot be suppressed below 0. Insulin is commonly given during a high-dose glucose infusion to minimize the resulting hyperglycemia. A recent randomized trial in critically ill patients demonstrated the importance of maintaining euglycemia.⁵¹ Although insulin may have a direct action to inhibit protein breakdown, extra insulin has little effect on the oxidation of infused glucose. During high glucose loads, the respiratory quotient (RQ) will be >1 , reflecting a conversion of infused glucose to fat. There is a maximal rate of glucose infusions beyond which beneficial effect cannot be expected. This amount is roughly about 5 mg/kg body weight per minute.⁵²

When the optimal rate for glucose infusion is exceeded, detrimental side effects occur, including fat deposition. The high rate of fat synthesis is associated with fatty liver. The increased energy required for triglyceride (TG) synthesis from carbohydrate contributes to an increased metabolic rate, and because of the high RQ of TG synthesis, CO_2 production increases to a much greater extent than the VO_2 . This process of glucose conversion to fat before oxidation is accompanied by a greater production of CO_2 and water and a higher consumption of O_2 compared with the direct oxidation of glucose. The result may be a significant ventilatory load to a patient with pre-existent respiratory impairment. The water load imposed on the subject may also contribute to pulmonary edema.

Another problem for the patient is post-traumatic insulin resistance. This means that insulin-dependent tissues will decrease the glucose oxidation and prefer fatty acids for oxidative processes. A further problem is the acquired growth hormone resistance that occurs after injury and also has consequences as it attenuates protein synthesis.

Despite the physiologic changes, glucose is the major carbohydrate used in parenteral nutrition and will remain so in the future.

Lipid Metabolism

After injury, fat oxidation is increased. Thus, infused triglycerides are well oxidized. Intralipid, the first safe fat emulsion of high quality on the market, contains long-chained essential fatty acids (LCT), mainly linoleic acid (52%), linolenic acid (8%), and oleic acid (22%). Linoleic acid belongs to the ω -6 family, and linolenic acid belongs to the ω -3 family. The ratio between them in Intralipid is 6 to 1. Intralipid is available as 10%, 20%, and 30% solutions, but the 20% emulsion definitely has advantages over Intralipid 10%. The lower ratio of phospholipid to TG in Intralipid 20% and 30% compared with Intralipid 10% minimizes the increase in plasma levels of lipoprotein X. Lipid infusions prevent and reverse fatty infiltration of the liver, minimize respiratory and metabolic stress, prevent essential fatty acid deficiency, and allow peripheral infusion of nutrients in some clinical situations. Lipid emulsions have been used in patients with liver diseases, renal failure, and pancreatitis.

During the last few years, middle-chained triglycerides (MCT) and ω -3 fatty acids have been discussed, and they will probably be used in more specific situations as liver diseases and acute septic conditions.^{53,54}

MCT is probably oxidized easier than LCT, and a mixture of LCT and MCT is presently on the market.⁵⁵ In the near future, a structured LCT-MCT fat emulsion will come on the market. This solution has many advantages. If unmodified MCT is infused too rapidly, a metabolic acidosis will occur. Also ATP in the cells will be depleted. A modified MCT contains the ω -3 fatty acids eicosapentaenoic acid and docosahexaenoic acid, which are also produced from linolenic acid. ω -3 fatty acids shift the balance in eicosanoid synthesis toward mediators with vasodilatory and antiaggregatory effects.⁵⁶ Linoleic acid is precursor to arachidonic acid (AA), which is an ω -6 fatty acid and competes with EPA on the 2 enzymes, cyclo-oxygenase and 5-lipoxygenase. From arachidonic acid is produced prostacyclin 2 with vasodilatory effects and thromboxane 2 with vasoconstrictive effects. EPA produces both prostacyclin 3 and thromboxane 3, which promote vasodilation and platelet aggregation. Also, the 2 leukotrienes, 4 (LTB 4) and 5 (LTB 5), have opposite effects on the vasculature and platelet aggregation. LTB 4 is produced by AA and LTB 5 from EPA. From a practical point of view, we do not know which is the optimal ratio between ω -6 and ω -3 fatty acids. An overproduction of ω -3 eicosanoids led to a bleeding tendency, because the coagulation factors are decreased. An overproduction of ω -6 eicosanoids, on the other hand, led to an increased tendency to thrombosis.

There exist some investigations indicating that the ideal ratio ω -3/ ω -6 would be 50/50 in acute catabolic situations.⁵⁷ From clinical experiences, it is clear that an LCT emulsion is useful in >95% of patients. It is only in very specific situations that MCT/LCT and ω -3 have advantages, but this has not been proved in clinical experiments. On the other hand, there are animal studies indicating that the specialized emulsions probably have advantages in liver diseases and sepsis.

Protein Metabolism

Normally, the adult human synthesizes about 300 g of protein per day. All proteins have different turnover times, from seconds to months. The balance between synthesis and breakdown is highly regulated and very sensitive. When the 2 processes are the same, the patient is in nitrogen balance, which is the normal situation. In trauma or sepsis, the protein synthesis in skeletal muscle is decreased up to 50%, but if the trauma is not large, the breakdown processes are unchanged. In severe trauma, the protein breakdown is also increased, thereby furthering the negative nitrogen balance. Synthesis of some proteins, such as the acute phase proteins, is increased. The breakdown processes can be minimized by good analgesia, keeping the patient warm, using β -blockade, and sometimes by blocking prostaglandin synthesis. To stimulate protein synthesis, traditional TPN is not enough. Glutamine must be included in the solution.⁵⁸ The branched-chain amino acids have no special stimulatory effect.⁵⁹ Thus,

nitrogen balance can optimally be achieved by administering an amino acid solution with high biologic value that contains all necessary amino acids in the appropriate concentrations.

This poses some practical problems. Tyrosine and cystine are both very insoluble in solution. Cysteine and glutamine are relatively unstable in water. This problem has been solved by giving tyrosine and glutamine as dipeptides. Cysteine is still difficult to add to solutions but can be administered as the tripeptide glutathionine, which acts as a cysteine precursor.

Vitamins, Electrolytes, and Trace Elements

These substances must all be included in a nutritional program. Tocopherol, or vitamin E, is especially important to give with fat emulsions, thus minimizing oxidative changes. Many preparations on the market contain recommended amounts to satisfy specific requirements, but additional quantities may be necessary for antioxidant defense.

The history of parenteral nutrition is extensive, and contributions have been made by many investigators over the centuries. As a result, we have today the tools to support a patient IV for years without developing nutrient deficiencies. Many of the new products that have been introduced on the market are still undergoing clinical trials to determine if they have proven advantages over our present day regimens. Very special conditions, such as sepsis and organ failure, are situations where specific nutritional regimens will probably optimize recovery.

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