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## GENERAL INFORMATION

## Surgical nutritional support today

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Glycaemia;  
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### Abstract

An abridged overview of the history, aetiology, and nature of the early challenges and controversies related to the development and clinical application of Total Parenteral Nutrition is presented, followed by abridged discussions highlighting some of the more prominent controversies and challenges which continue to prevail. Among others, these include nutritional support of patients with cancer, importance of maintenance of normal glycaemia, the primacy of Nutrition Support Teams, total parenteral nutrition vs. total enteral nutrition debate, and the utility of albumin in nutrition support. Reflections and perceptions related to nutritional support and TPN are interspersed throughout the discussions, together with a compilation of legacies of TPN to the modern practice of medicine and surgery.

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### PALABRAS CLAVE

Glucemia;  
Albúmina;  
Pacientes con cáncer;  
Equipo de soporte  
nutricional;  
Nutrición parenteral  
total

### Soporte nutricional quirúrgico en la actualidad

#### Resumen

Se presenta una panorámica de la historia, etiología, naturaleza, retos y controversias relacionados con la nutrición parenteral total, seguida de discusiones breves con énfasis en los argumentos y retos más importantes que prevalecen. Se incluye, entre otros, soporte nutricional en pacientes con cáncer, la importancia del mantenimiento de la glucemia normal, la primicia de los equipos de soporte nutricional, el debate sobre la nutrición parenteral total frente a la nutrición enteral total y la utilidad de la albúmina en el soporte nutricional. Las reflexiones y percepciones relacionadas con el soporte nutricional y la nutrición parenteral total se encuen-

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tran mezcladas a lo largo de las discusiones, junto con la compilación de legados de la nutrición parenteral total con la práctica moderna de la medicina y la cirugía.

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## Dedication

This article is dedicated to the exceptional personal and professional life and the many innovative contributions of Dr. Luis Ize Lamache over the past 40 years in his brilliant career in recognition of his collaboration and partnership and, especially, in gratitude to his precious friendship.

His kindness, skill, hospitality and generosity in sharing his knowledge and experience and his talent that achieved and maintained the highest standards of surgical and nutritional care have been an enviable example. He was a role model for generations of medical students and surgical residents and a teacher and leader for us all.

We are in deep debt to him and have had the wonderful opportunity to honour him during the International Conference on Nutrition in the Mexican Academy of Surgery in Mexico.

## Introduction and brief history

It has been nearly five decades since efforts into innovative research began at the University of Pennsylvania, Harrison Department of Surgical Research, which resulted in the first demonstration of the successful, basic and clinical development of a total parenteral nutrition technique that was practical, efficient, reproducible and reasonably safe and affordable<sup>1</sup>. The first time it was achieved in an animal species was with exclusive intravenous feeding with Beagle puppies, which had normal growth and development; thereafter the techniques, principles and practices were appropriately modified and subsequently applied to the treatment of undernourished surgical patients in order to promote positive nitrogen balance, wound healing and improvements in morbidity and mortality, among others. Shortly after being developed in laboratory animals and successfully applied to the nutrition of adults who could not use their alimentary tract properly or at all, the techniques of total parenteral nutrition were personalised to provide specific essential nutrients to sustain growth and normal long-term development to an infant who had severe and congenital small intestine syndrome, which was hitherto incompatible with life<sup>1-3</sup>. These important achievements have been subsequently redefined, modified, adapted, improved and applied in countless experimental cases by thousands of researchers to validate and optimise technical accuracy, safety and efficacy. As a result, the practice of medicine and surgery has changed forever. It is no longer justifiable, moral or ethical for severely malnourished or ill or critically injured patients to suffer or succumb because they cannot feed themselves adequately or at all.

Going back to the origins of total parenteral nutrition, in 1960 we face the prevailing dogma: "complete nutrition

through intravenous feeding was impossible; and if it were, it would be impractical and even if it were practical, it would be unaffordable"<sup>4</sup>. Total parenteral nutrition was considered the "Holy Grail" or "Gordian Knot" sought by most doctors and surgeons; our early research efforts in this area were discouraged, or even disregarded, as "a waste of valuable energy, time and resources". However, a major part of our motivation, perseverance and persistence of our constant commitment and dedication was due to that phrase which is sometimes said far too often after a heroic surgical procedure in a complex patient who is seriously ill, injured and/or extremely malnourished: "the operation was successful but the patient died". It was obvious to us that excellent surgical techniques and intraoperative procedures were not sufficient by themselves to achieve optimum results in many patients.

Nutritional and metabolic deficiencies, the inability to correct them and to meet their requirements, often resulted in complications and death, despite the exceptional technical achievements in surgery. Patients' capacity for metabolic and nutritional reserves was exhausted and their organic systems were failing, serially and collectively, given the lack of fuel and anabolic substrates. The need for effective parenteral nutrition was obvious, urgent and essential as a contributing survival measure for these patients, which prompted us to go to laboratories at the Harrison Department of Surgical Research in an attempt to resolve or minimise this serious clinical problem.

In 1960, obstacles to the development of total parenteral nutrition included the following: *a)* insistence by doctors to use peripheral venous infusion devices; *b)* restrictions on the volume of liquid in patients, usually 2-3 l/day or less; *c)* inadequate nutritive substrates commercially available for parenteral administration; *d)* formulation of solutions, quality control and inadequate storage in most hospitals.

Consequently, the challenges and fundamental principles of the total parenteral nutrition project were as follows: *a)* calculate the calories, amino acids, electrolytes, vitamins and other micronutrients required for a positive nitrogen balance, weight gain, tissue repair and/or growth and development; formulate qualitative, quantitative and compatible nutritive substrates and concentrate them into a volume of water that the patient could tolerate and metabolise safely and efficiently; *b)* infuse the resulting nutritional formula continuously at an optimal rate according the patients' use, preferably by pump in a central vein in which the high blood flow facilitates the instant dilution of hypertonic infusion to almost isotonicity; *c)* maintain aseptic and antiseptic conditions during the preparation, modification and infusion phases of the formula, maintaining long-term access to the central venous, handling and managing all components of the infusion and delivery apparatus, and

other aspects of surgical patient care that minimise the ever-present risks of infection and sepsis<sup>4</sup>.

Attention therefore focused on the development of the total parenteral nutrition components, including *a*) nutritive substrates, solubility, compatibility and stability; *b*) sterilisation techniques and antiseptics; *c*) safe techniques of insertion of central venous catheters; *d*) infusion pumps and controlled flow apparatus; *e*) principles of long-term maintenance of central venous catheters and practices to ensure safety, durability and sterility<sup>4</sup>. The successful implementation of the above resulted in the achievements mentioned in the introduction: first success in the laboratory with Beagle puppies and subsequently in paediatric patients and then adults.

Because a reliable, useful and reproducible definition of malnutrition had not yet been developed for clinical purposes and since a complete nutritional assessment had not yet been outlined, accepted and validated, it was initially proposed that the basic indications for total parenteral nutrition should include patients who *a*) cannot eat; *b*) will not eat; *c*) should not eat; *d*) cannot eat enough. We later added a fifth indication that was patients with complex metabolic problems requiring intensive and sophisticated parenteral therapy<sup>4</sup>.

As a result of the data collected from a wide variety of surgical patients, a simplified definition of malnutrition was obtained, which has survived scrutiny and resisted decades of challenges, such that it is now accepted around the world. The fundamental elements of the current definition of malnutrition are *a*) unintentional body weight loss >10%; *b*) serum albumin level concentrations of <3.5 mg/dl and/or total protein concentration serum <5.5 mg/dl; *c*) peripheral lymphocytes <20%, or total lymphocyte count <1200/ $\mu$ l; *d*) delayed skin hypersensitivity to standard antigens, or other evidence of immunity complex impairment<sup>4</sup>. In addition, this criterion can be used to assess the extent or severity of malnutrition. For example, if a patient has any one of these criteria, malnutrition is considered *mild*, if they present with two criteria it is considered *moderate*, if three criteria manifest it is considered *moderately severe*, and if they have four it is considered *severe*; total parenteral nutrition is widely indicated and is likely to be beneficial for improving moderate and moderately severe malnourished patients as demonstrated by published clinical studies. Over the past decade, the uncontrolled arrival of morbid obesity as a form of malnutrition that is the opposite to starvation, cachexia and fragility has established the current most appropriate terminology as *undernutrition*, related to a famished patient, and *overnutrition*, related to malnutrition in a patient with obesity or morbid obesity. Both are forms of malnutrition, which literally means "bad nutrition". The final axiom to treating malnutrition is that it is usually successful, accompanied by an aggregate of 10% in science, 10% experience, 10% skill, 20% patience and 50% attitude<sup>4</sup>.

One of our perceptions is that all truth passes through three stages: *first*, it is ridiculed; *second*, it is violently refuted; *third*, it is accepted as obvious. Another of our premises is that "the dumbest gastrointestinal tract is smarter than the smartest doctors, surgeons, nurses, dietitians, pharmacists, scientists and nutritionists," and that is the main advantage of oral or enteral nutrition in

total parenteral nutrition. The gastrointestinal tract is a regulator of substrates that enter our body cell mass by non-absorbent rejection actions, e.g., anorexia, nausea, vomiting, diarrhoea, cramps, pain, etc. in addition to its vital actions of digestion, absorption and assimilation. No other verification and balance system protects the patient from the potential interferences of parenteral feeding nor does it regulate intake. Therefore, once total parenteral nutrition is administered, this is the system that remains and cannot be easily removed, reversed or corrected. This imposes a huge responsibility on surgical nutrition and on the team of nutritionists to be extremely competent, capable, aware and vigilant in order to ensure that they manage patients' parenteral nutrition adequately, especially those in critical condition where the margins of error are very small. The importance of a skilled and dedicated nutritional support team cannot be overstated in this regard.

### Primary importance of nutritional support teams<sup>5</sup>

In 1980, nutritional support was given a general and specific devastating blow, mainly as a result of the establishment and relative acceptance of diagnosis-related groups that influenced and significantly changed the practice of medicine and the provision of services in the United States. Few, or no, provisions have been made for reports regarding the inadequate planning of this type of health care and the return to nutritional support. Because of these serious and harmful restrictions on medical practice, it is imperative that all health care professionals continue their efforts to restore the role of nutritional support services as essential for all patients in the future.

As an example of the vital importance of trained support teams, the use of total parenteral nutrition and other forms of oral, enteral and parenteral nutritional support has revolutionised the way in which neonatology and paediatric surgery is currently practised. Members of the American Pediatric Surgical Association (APSA), the Neonatology Society and the American Academy of Pediatrics recognise the effect its judicious and early application has on the success and care of critically ill, injured or disabled patient. At a recent meeting, the APSA reported that approximately one third of major surgical procedures in neonates and infants would be impossible or very likely fail without the successful concomitant application of parenteral nutritional support or appropriate enteral support. At the 2011 annual meeting of the Neonatology Society, its president stated that the Society had analysed data on the management of preterm neonates and concluded that there was sufficient evidence showing (conservatively) that the lives of more than 10 million preterm neonates had been saved in the United States since 1970, mainly as a result of the development and appropriate application of parenteral nutrition, and that neonatology as a speciality would not have grown as it has without the appearance of total parenteral nutrition. The vital and obvious multidisciplinary contributions made by multidisciplinary, collaborative and relevant workgroups to the great success in the improvement of patients cannot be underestimated

and should be extended and extrapolated to the management of patients of all ages<sup>5</sup>.

### The controversy between enteral and parenteral nutrition<sup>4,5</sup>

In the broadest sense, nutritional support has been defined as any method that provides nutrients through a tube to the gastrointestinal tract, consisting of an entrance to the digestive tract and through any part of the oesophagus to the rectum. However, from a practical and modern point of view, enteral nutrition is generally understood as a technique or method that provides nutrients to the patient by a feeding tube with its distal end located in the stomach, duodenum and upper jejunum. This type of support usually covers the needs of most patients (75-85%) who cannot ingest their required nutrients orally.

Modern technology has optimised technical and technological access to the stomach and small intestine, and has provided a wide variety of formulas that can be adapted to the functions, needs and/or impairments of the gastrointestinal tract. Current innovative development and improvements in technology and enteral nutritional techniques are likely to continue in the future. If the gastrointestinal tract can function normally or reasonably well and can be used safely, enteral nutritional support could be at least partially used at its maximum efficiency to provide all the critically ill patient's nutritional and metabolic requirements, especially those who cannot ingest the required nutrients normally or properly through their mouth<sup>4,5</sup>.

Below explores a personal perception of the controversy between "enteral versus parenteral" nutrition. The basic development and clinical translation of total parenteral nutrition has significantly changed medical practice. It subsequently stimulated and accelerated the widespread use of enteral nutrition. An unintended consequence of these two great advances was the imprudent advancement of both techniques as opposed to one or another. Currently, enteral and parenteral nutrition are two complementary or supplementary techniques that provide nutritional support, each with specific indications and applications and existing in symbiosis. The concept of "enteral nutrition versus parenteral nutrition" is a most disappointing, controversial and unprofessional attitude that may harm patients, interfere with providing optimal nutritional support, and discourage necessary and required clinical investigations<sup>4,5</sup>.

Below, the reflections on the controversy between "enteral versus parenteral" are exposed. Any learned party interested in providing optimal nutritional support understands that knowledge, competence, judgement and safety must prevail when choosing each part of a diet. In addition, choosing the suitable feeding technique to ensure the patient's adequate nutritional requirements are met in virtually any situation demands versatility, experience, persistence, awareness of individual care and judgement. Doctors who "always treat their patients with enteral nutrition" or "always treated them with parenteral nutrition" may be practising at levels below the highest standards of care and probably providing sub-optimal nutrition, all related to the improper use of only enteral or parenteral nutrition. Choosing the best feeding method for each situation

requires the responsible doctor or surgeon's maximum hard work, ingenuity, refinement, versatility, skill, experience, persistence, competence, judgement and wisdom. Not properly using every tool available debases our education, training, effectiveness, and professionalism, in addition to our moral and ethical standards. As an analogy: you can screw in a screw with a pair of tweezers, but obviously using a screwdriver would be more appropriate and accurate; likewise you can hammer a nail into a board with a spanner, but it is better and more appropriate to use a hammer. These principles are similar when deciding between enteral and/or parenteral nutrition. The practice of nutritional support should not allow itself to be adversely influenced by ignorance, ambition, prejudice, self-interest, financial gain, etc., it should preferably guide our efforts, talents, determination and resources towards the perfection of comprehensive nutritional support. Clinicians will thus be able to feed their patients using the most effective methods and techniques to provide substrates of sufficient quality and quantity, allowing the greatest number of cells in the body to function according to the processes that they have been designated for. It would be promising if doctors, surgeons and other nutritional specialists acquired the motivation, inspiration, training, education and resilience needed to set an example in: *a)* advancing each nutritional support method and technique to its full effectiveness and capacity; *b)* integrating the use of nutrients according to the patient's metabolism, along with other therapies, in the most rational, effective and safe way possible. We owe it to our patients<sup>4,5</sup>.

There is no longer a dispute about the axiom "if the gastrointestinal tract works, use it, but prudently." The controversy remains, however, regarding complications of total enteral nutrition, which are poorly reported compared to those related to total parenteral nutrition, which are over-reported, but are mainly: sepsis related to catheter (iatrogenic and/or technique), rather than related to parenteral nutrition itself. These complications of total parenteral nutrition can be controlled or prevented with appropriate training and education, a positive attitude and, most importantly, a competent nutritional team. Total parenteral nutrition has proven to be as safe as the best total enteral nutrition, or even better, if these rational, logical and easy to accomplish principles are complied with.

### A brief overview of the controversies and challenges facing nutritional support

The wide field of nutritional support still faces many challenges and many controversies persist, despite the countless advances in this relatively young area of scientific endeavour. The purpose of this document is to comprehensively expose the many challenges and controversies regarding it, which extend beyond the scope of this article; however, according to our perception, the following list represents the most important areas where future efforts should be applied to advance, resolve and build. They are as follows: the composition of an optimal diet; cachexia problems and their causes, appropriate therapies; early feeding for specific purposes (hyperglycaemia, insulin, hypoglycaemia); overfeeding and refeeding syndrome; avoiding obesi-

ty, prevention, suspension and reversal; nutrition for cancer patients; nutrition for geriatric patients; nutrition and management of patients with intestinal failure; nutrition for neonates, preterm and surgical infants; enteral *versus* parenteral nutrition; amino acids and vitamin formulas; lipid emulsions; role of albumin and microbial (flora) environments in the alimentary tract; role of prebiotics and probiotics in nutritional status, health and performance.

It is interesting, and sometimes frustrating that, despite extensive research, to date the optimum diet composition for parenteral, enteral, oral, diets, special conditions, nutraceutical and targeted nutritional therapies formulas have not yet been determined. Virtually all therapeutic parenteral, enteral and oral nutrient formulas differ significantly in their components, both quantitatively and qualitatively; nevertheless, they all seem to be adequate to maintaining a positive nitrogen balance, nutritional health and efficiency in a wide variety of patients. In the future a much more sophisticated technology should be perfected that will determine the daily or hourly body composition and which achieves standardised nutritional formulas. This represents a challenge for formulas that address special conditions, nutraceutical and targeted nutritional therapies.

Controversies and challenges related to the etiology, termination, reversal and successful therapies in cachexia continue to challenge explanations and resolutions. Cachexia is the common denominator of several pathophysiological conditions including cancer, sepsis, organ failure, starvation, anorexia, sarcopenia, frailty and osteoporosis. However, even though all patients with cachexia have similar characteristics and physical appearance, pathophysiology, clinical evolution and response to nutritional rehabilitation therapies are variable and inconsistent and generally result in an irreversible and inevitable development, which ends with death<sup>6-8</sup>.

### Glycaemia: controversies and surgical nutrition goals<sup>5</sup>

Early feeding for specific objectives that maintain euglycaemia and prevent hyperglycaemia, hyperinsulinemia and hypoglycaemia has precipitated controversy, mainly in patients in intensive care and neonatal units. We have always believed, defended and maintained that the values of blood sugar should be kept meticulously within a normal range by proper administration of dextrose and insulin for all patients receiving parenteral nutrition, either totally or in combination through enteral nutrition and/or orally. The innate ability of each patient to efficiently use the administered glucose, whether it be orally through enteral nutrition and/or total parenteral nutrition is variable. The diversity of its use is based on age, body weight, health status, activity, nature of the disease or disorder and presence or absence of diabetes mellitus, among many others. The constant maintenance of euglycaemia (avoiding hypo- and hyperglycaemia) is essential for optimal nutrition, through either enteral or parenteral feeding or both during changes in health, from stable and healthy to severely affected, septic and/or critically ill. The glycaemic threshold to administer insulin is debatable and controversial. It is also not comparable and cannot be standardised from

reports in the world literature. Stress-related hyperglycaemia due to trauma, surgery and/or sepsis is a different and common problem in diabetes mellitus hyperglycaemia; however, both aetiologies may be related to inflammation or infection as a cause or effect of hyperglycaemia. Depending on the complexity of the individual, the intensive care unit and/or caregiver, strict glycaemic control will vary within the range of 80-108, up to 80-180. Infusion pumps and expert nurses are essential to the safety and success of maintaining a euglycaemic state, especially in critically ill patients where the morbidity related to hypo- and hyperglycaemia is associated with unfavourable results. In nutritionally depleted patients it is much easier to achieve the goal of early feeding with total parenteral nutrition than with enteral nutrition. A delay in feeding in the intensive care unit has been associated with poor outcomes in these patients and not in those who are well nourished. Consequently, early enteral nutrition is indicated for all patients receiving this form of feeding, and enteral nutrition should be applied as soon as tolerated to achieve specific objectives.

In short, nutritional support in critically ill patients has not been resolved yet, but specific objectives should be broadened and achieved as quickly and judiciously as possible and by any means available to achieve better results. The techniques of parenteral and enteral nutrition are complementary, have clear indications and can be used individually, together or in sequence, as appropriate or required to accurately and effectively meet nutritional demands. Most of the problems that arise occur when instructions are not followed, if enteral nutrition does not start early or if it is not properly administered with parenteral nutrition.

### Overfeeding and refeeding syndrome<sup>8</sup>

Overfeeding and refeeding syndrome continue to be reported and occasionally discussed in the literature, but these problems have been identified, avoided and prevented for decades. It is no longer justifiable to cause or promote these potentially lethal complications when feeding iatrogenically, especially in severely malnourished patients where their occurrence should be abhorred and condemned. A fundamental principle in oral, enteral and/or parenteral feeding of a patient who was previously starving is that their treatment should start with a careful, slow and judicious nutritional therapy, recognising that the cell mass of malnourished patients body, organs and systems are restricted and jeopardised in their duties compared to their normal state and need to "exercise" again to fall back into their metabolic and nutritional form without damaging or altering their ability to respond to sudden, acute and excessive administration of very powerful biochemical substrates.

A general and safe guideline is that the nutritionist or doctor should administer nutritional support in approximately one third of the requirements calculated during the first 24 to 48 h and if the nutritional portions are adequately tolerated at these levels and an excessive administration of calories, amino acids and electrolytes is not indicated by the metabolic profiles in blood and urine along with vital signs and cardiopulmonary function, then the daily ration

administered may be increased to the full requirements by maintaining a strict monitoring according to the patient's response.

Another useful axiom is that nutritional rehabilitation and restoration to normality are not usually an emergency procedure that must be completed in minutes, hours or days. It is wiser to be cautious in the administration of nutritional substrates, at doses which the cell mass is able to assimilate as precisely as possible and without imposing nutritional or metabolic loads on the patient. After determining how long it took the patient to lose more than their normal weight until the time when nutritional support was initiated, it is a reasonable and safe practice to inform everyone involved that they will require about two thirds to three quarters of that time to safely return the patient to normal nutritional levels. If these ranges are exceeded when providing nutritional support, it is not usually well tolerated, mainly due to qualitative and quantitative limitations inherent in the metabolic process, and overfeeding syndromes will manifest. The main aetiologies of overfeeding and refeeding are related to the doctor, almost always as a result of *a*) ignorance related to the absence or lack of adequate knowledge or training for good nutritional support; *b*) incompetence due to an inadequate or lack of nutritional support team, and *c*) iatrogenic characteristics of the doctor related to pride and arrogance. All these unfavourable situations are preventable with education and training in awareness, competitiveness and professional behaviour, plus they are unacceptable in the modern practice of medicine and surgery. There should be no further controversy regarding this issue<sup>8</sup>. However, given human nature, it is likely to continue causing challenges in this area.

## Obesity and the poor nutrition of overnutrition

Avoiding, preventing or reversing obesity has attracted global attention and resources in many ways similar to ways an epidemic has. A discussion about the many challenges and controversies related to the massive problem of obesity is beyond the scope of this article. Suffice it to say that a rational and orderly reasoning of the problem would include at least the following: *a*) strict adherence to dietary modifications; *b*) a conscious, progressive and concomitant exercise programme; *c*) advice and psychological support; *d*) pharmacological suppression of appetite; *e*) other auxiliary, holistic, etc. therapies; *f*) bariatric surgery as a last resort; *g*) monitoring for life.

## Controversies and challenges of feeding in patients with cancer<sup>5</sup>

Feeding of cancer patients continues to generate controversy and challenges. Many believe that nutritional support is an important adjunct to antineoplastic treatments, whereas others (most oncologists) believe that nutritional intake interferes with the antineoplastic and chemotherapy regimen. Our philosophy is that greater efforts must be made to benefit these patients because *a*) most of the cell mass is nonmalignant cells and must be adequately nourished in order to maintain metabolic functions that are fun-

damental and essential to life and *b*) malignant cells operate autonomously and are fed at the expense of normal cellular mass so that deficient nutrition only damages normal cells and not neoplastic cells. Furthermore, nutritional support enhances the ability of normal cells to optimise immunity, which is the most important endogenous defence mechanism against malignant cells. Some studies have suggested that nutritional support accelerates tumour growth in rodents. However, this has never been demonstrated in humans, but rodent studies continue to be cited and applied in principle to nutritional support in humans with cancer. In addition, there are nutritional support studies that frequently report an improved quality of life and tolerance to antineoplastic treatments in cancer patients without increasing the discomfort or suffering or prolonging an inevitable death. Finally, many patients prefer to accept an inevitable death as a result of cancer and its complications rather than a death by starvation, which in many cases has a voluntary element.

When the alimentary tract cannot be used efficiently, partially or completely, to feed cancer patients, parenteral nutrition can save lives. In addition, patients who are unlikely candidates for any antineoplastic therapy, or not at all, because of weakness or cachexia can become reasonable candidates after treatment with supplemental parenteral nutrition. The morbidity and mortality of cancer patients can be significantly reduced without stimulating tumour growth when parenteral nutrition is applied consciously and competently according to established principles and techniques and when integrated with effective and specific antineoplastic therapy. The most natural and practical method to administer nutrients is voluntary through the mouth and the next most viable method is through nasogastric or nasoduodenal feeding tubes. However, in some patients minimally invasive surgery to insert a gastrostomy or jejunostomy tube is required to ensure long-term nutritional maintenance. Optimal nutritional rehabilitation through the alimentary tract sometimes requires an unusual amount of time, and specific antineoplastic therapy cannot always be delayed until the protein and energy reserves have been properly and timely restored using only this route.

A cause for the aggravating cachexia secondary to cancer still needs to be defined, and many other questions related to the metabolic abnormalities observed remain unanswered. Why is the metabolism of carbohydrates, fats and proteins in tumour cells altered?

Metabolic changes appear to place tumour cells in a predominant position –biochemically and metabolically– over nontumour cells. This is obvious from results obtained from untreated cancer patients. What is the fundamental difference in the metabolism of malignant cells compared to normal? Would a mass effect be possible or is this the result of a large tumour load? If it is, will the metabolism disorder respond to a massive tumour excision? The answer is “certainly not uniformly or obviously”. Additional questions include: Why are malignant cells seemingly inherent to inducing secretion of a large number and variety of mediating hosts that produce a chronic inflammatory state, with adverse effects on the metabolism of nutrients and the appetite? Normal host cells either do not act the same under the same conditions or do so to a lesser extent. Does the

inflammatory response associated with neoplasia indicate that tumour cells are recognised as foreign bodies or invaders? Does the tumour-induced inflammatory response have any measurable beneficial effect to contain, control or destroy the tumour? Otherwise, the inflammatory response seems hysterical and useless. How and why do tumour cells multiply and function apparently independent of the rest of the cell mass? These and other questions need answers to understand and rationally and optimally treat the tumour processes<sup>5,8,9</sup>.

### **Intestinal failure: the last nutritional challenge<sup>10</sup>**

For proper nutritional rehabilitation in patients with intestinal failure, the main controversy is safety, efficiency and convenience of total parenteral nutrition at home compared with an intestinal transplant, with its consequences and long-term durability. Currently, the former has better results than an intestinal transplantation; however, this may change in the future according to advances in transplantation techniques and immunosuppression and herein lies the challenge. In any case, attention to nutritional support remains essential for suitable management. What surgeons and their nutrition teams face regarding the complex management of intestinal failure and an extensive discussion of this and the most severe nutritional challenges that threaten life are outside the scope of this document but are available widely in the literature<sup>10</sup>.

### **Feeding of preterm or neonatal infants at risk<sup>11</sup>**

Much progress to safeguard the life of preterm infants has been made through judicious application of nutritional support. In fact, recent reports have emphasised the importance of providing amino acids from 4 h of birth along with adequate amounts of energy, electrolytes and vitamins in order to achieve growth and proper development, especially of the central nervous system (including sight). However, there are still controversies regarding very low weight preterm infants on the when, how, what, how much and for how long they should be fed by total parenteral nutrition, enteral nutrition and oral nutrition. The challenge for neonatologists, paediatric surgeons and nutritionists is to answer these complex questions that are essential to promote an optimal quality of life for frail and vulnerable infants<sup>11</sup>.

### **Challenges to perfect the components of the nutritional formulae**

Some of the controversies and challenges related to the amino acid composition in formulas include the fact that they are currently not ideal, standardised, or complete and there are no two identical commercial formulas, but they are still all used in the same way as if they were equivalent in quality and quantity and interchangeable. Mainly, by solubility and stability, some dipeptides are used that will prob-

ably be required in the composition of the "amino acid" mixtures if the formulas are improved in the future.

Finally, if the parenteral amino acid formulas were improved to provide balanced components comparable to those of oral and enteral formulas, differences in morbidity among the various techniques would virtually disappear. In fact, total parenteral nutrition is still developing and, although it has given favourable results in a wide range of patients, it has not yet been perfected nor is ideal for all situations or circumstances and should continue being worked on until such ambitious goals have been achieved. Therein lies our challenge and collective responsibility.

Perfecting vitamin formulas requires specific additional research related to the patient's age, gender, feeding method, pathophysiological conditions, comorbidities, pharmacological and/or surgical therapies, assessment of existing nutritional status and other considerations. It is very unlikely that a single formula and vitamin dose is adequate to meet all patients' requirements under all conditions and at any given moment. In addition, the relationship between the vitamin formula, disease prevention and therapy is still difficult to define and is likely to generate controversy in the immediate future. Vitamin D, folic acid, thiamine and vitamin B<sub>12</sub> have been particularly linked to pathophysiological processes, for example, related to malabsorption induced by bariatric surgical procedures. The micronutrient nature of vitamins and trace elements contributes significantly to the challenges of designing clinical studies to improve the controversies related to the quality and quantity of use of nutritional support regimes.

The three fundamental controversies related to lipid emulsions are as follows: *a*) their relationship with the development of liver disease and intestinal failure associated with liver failure; *b*) their relationship to immunocompetence, infection and sepsis, and *c*) their optimum composition<sup>12</sup>. The first two controversies are moving closer to an explanation because of results obtained from studies conducted around the world. The third, related to the appropriate composition, remains a major challenge mainly because of the reluctance of the pharmaceutical industry to incorporate recent clinical research based on data from their emulsions formulas and the approval of new emulsions for clinical use by regulatory agencies such as the U.S. Food and Drug Administration (FDA), even if they have proven to be safe and effective in humans in many other countries. So, the controversy related to emulsions based on fatty acids with omega-3 (fish oils) compared with fatty acids with omega-6 (soybean oil) compared with the combination of compounds (soybean oil, olive oil, fish, safflower, medium chain triglycerides [MCT], long-chain triglycerides [LCT]) will continue to accumulate more data, especially for nutritional support in neonates. In theory, in our opinion, structural lipids synthesised by the addition of specific fatty acids (MCT, LCT) to the glycerol backbone would be the ideal source to produce fat emulsions for total parenteral nutrition. The challenges for this development will be primarily related to the cost of synthetic production and emulsification of these complex molecules in addition to proving their stability, safety and efficacy.

## Controversies, challenges, confusion and clarification on serum albumin

Controversy persists regarding the role, utility and logic of albumin for managing malnourished patients with complex surgery or in a critical state and many conflicting, non-standardised and poorly controlled studies have been generated, leading to greater confusion more than clarification of the debates and challenges regarding the significance of serum albumin and whether, when and how it can be useful in the management of these patients. Based on our extensive clinical experience and many basic experimental studies ranging from 50 years, below we expose our reflections and action guidelines on albumin, an extremely versatile, vital and valuable molecule physiologically, metabolically and nutritionally.

The clinical utility of albumin has been generally accepted by medical nutritionists as a reliable predictor of morbidity and mortality. It is also considered a marker of stable patients' nutritional status. It functions as a colloid osmotic molecule, powerful and useful as a nutrient to treat secondary chronic and severe malnutrition in a physiopathological condition, but it is not considered economically or clinically useful as a practical source of protein or nitrogen to treat simple uncomplicated starvation because albumin can be synthesised and taken to appropriate normal values with lower cost and few or no complications through the use of total parenteral nutrition. A final belief related to this area accepts that prealbumin (transferrin) is a useful and dynamic marker of protein anabolism and catabolism. In this regard measurements of the values of serum prealbumin obtained twice a week or more frequently have been made that were very useful in the guidance, monitoring and determination of the effectiveness of total parenteral nutrition and other nutritional therapies to the extent that albumin serum values are not very useful as markers of nutritional status, mainly because of their longer half-life and the dynamics of their synthesis.

The main functions of albumin (which are not considered controversial) include the following: *a*) maintains oncotic pressure; *b*) binds toxic moieties and transports other metabolically active molecules including some pharmacological agents; *c*) collects free radicals; *d*) inhibits platelet function and contributes to antithrombotic effects; *e*) affects vascular permeability, and *f*) is a source of amino acids and sulfhydryl groups.

Personal perception of the value of albumin, based on clinical experience over the past four to five decades is that you can use it with caution as a complementary nutritional support in severe chronic starvation and that it can serve as an oncotic agent to reverse oedema, especially in critically ill patients. When serum albumin is intravenously infused judiciously and cautiously, malnourished patients with hypoalbuminemia ( $<3$  mg/dl) and hypoproteinaemia ( $<5$  mg/dl) it might improve: *a*) diuresis and restore intravascular volume; *b*) pulmonary function; *c*) decrease atelectasis; *d*) peristalsis and recover ileus *e*) gastrointestinal absorption and function; *f*) treatment of anastomosis and decreases intestinal oedema; *g*) the ambulatory force; *h*) the healing process of the wound; *i*) a decrease in morbidity and mortality rates, and *j*) a decrease in the time in intensive care units and hospitalisation. Intravenous serum

albumin, administered normally in aliquots of 12.5-25 g for 4-8 h is more effective when administered preoperatively than postoperatively. The infusion of serum albumin intravenously *is absolutely contraindicated in patients with sepsis, in unstable post-trauma patients and in the immediate 3-to-5-day postoperative period for most surgical patients*. Under these conditions the "capillary leak syndrome" occurs where infused albumin molecules migrate easily through the endothelial capillary spaces in the bloodstream, penetrating the interstitium and other extravascular spaces. The subsequent increase in the extravascular colloid osmotic pressure will aggravate the oedema rather than correct it, the result being counterproductive to the purpose of albumin infusion.

## Reflections on the legacy of total parenteral nutrition<sup>5</sup>

Considering the last 50 years dedicated to providing optimum nutritional support to all patients, we have compiled a list of significant contributions to the development and success of the clinical application of total parenteral nutrition, which could be useful for a comprehensive medical knowledge; it includes *a*) demonstration that the nutrients required for normal growth and development of any animal species (originally Beagle puppies and later in other species) could be provided intravenously in the long-term; *b*) subsequent to *a*), first demonstration that all the nutrients required for normal growth and development of human beings (originally for neonates and later preterm infants and children) could be provided completely intravenously in the long-term; *c*) first demonstration that a positive nitrogen balance, weight gain, healing of a wound, reduction of morbidity and mortality, and many other desirable clinical improvements could be achieved in critically ill patients fed completely intravenously in the long-term as required; *d*) development of a variety of parenteral substrates with micro- and macronutrients and lipid emulsions for standard critically ill patients of all ages with special nutritional metabolic support; *e*) development of safe and effective techniques of percutaneous central venous catheterisation; *f*) development of long-term nutritional support principles and practices for safe intravenous infusion; *g*) a technological revolution in the development, advancement and use of infusion pumps with alarms and other safety features, servomechanisms, miniaturisation, portability, accuracy, reliability and more; *h*) development of plastic bags for intravenous solutions, reservoirs, infusion tubes, management devices and others, all specific to the individual requirements of the patient, infusion and situation; *i*) development of a variety of central venous catheters, antimicrobial solutions and balsams, injection port reservoirs, controlled filters, infusion tubes, management devices and others; *j*) development of a technological revolution and transformation in pharmaceutical practice including automated and computerised preparation devices and laminar filter areas for air-flow, cold sterilisation by microfibrillation, nutrient-nutrient and nutrient-medication interactions and compatibilities; *k*) advancement of doctoral education and specialisation in clinical pharmacology and nutritional support programmes for pharmacists

and pharmaceutical technician programmes for the preparation of solutions; *l*) demonstration of a multidisciplinary approach to clinical nutrition and the organisation of nutritional support teams; *m*) subsequent inspiration and encouragement to establish results that are useful for professional, educational, scientific and clinical multidisciplinary societies to advance global nutritional support (e.g., American Society of Parenteral and Enteral Nutrition [ASPEN], European Society for Clinical Nutrition and Metabolism [ESPEN] Parenteral and Enteral Nutrition Society of Asia [PENZA], Latin American Federation of Parenteral and Enteral Nutrition [FELANPE], Polish Society of Parenteral and Enteral Nutrition [POLSPEN], etc.); *n*) demonstration of the utility of the induction of an intestinal rest period with total parenteral nutrition in the management of specific conditions for gastrointestinal tract disorders; *o*) establishment, with no doubt whatsoever, of the relevance of adequate nutritional support in order to achieve optimal results, reducing morbidity and mortality and improving recovery in primary or alternative therapy for critically ill patients; *p*) growing interest for the advancement of enteral nutritional support as an additional or alternative technique in patients with functional digestive tract; *q*) motivation for the study and analysis in areas of nutritional support such as its cost-effectiveness, risk-benefits, results, policies and procedures, standards, legislation and monitoring, permits, refunds, medicolegal and ethical aspects; *r*) development of nutritional solutions for specific metabolic requirements such as kidney failure, liver failure with encephalopathy, pulmonary failure and immunomodulation; *s*) concept of nutrients either individually or in various combinations such as a medical food for therapeutic use in a disorder, disease or condition (e.g., nutraceuticals and functional foods). *t*) development and advancement of the concept that nutritional support clinical practice is not only to provide "food" but also involves the integration and/or modulation of cell biochemistry, molecular biology, immunology, genetics and function. *u*) development of concepts, devices, experience and nutritional outpatient support systems leading to the explosive growth of the home care and therapy industry for outpatient services as well as development and advancement of the concept, management and biology of intestinal failure and the development of experiences and services in this area of gastrointestinal management as vital, complex and sophisticated. *v*) support for rehabilitating patients requiring parenteral and/or enteral nutritional support in the long-term including psychological, emotional, spiritual, social, economic, legal, custodial, occupational, educational and psychotherapeutic support. *w*) development of standards of care, principles and practices, auxiliary medications, valuation and other guidelines relating to the safety, efficacy and optimal supply of nutrients to all patients under all conditions. *x*) demonstration of the importance of ongoing nutritional education in medical schools, post-graduate programmes and lifelong learning<sup>5</sup>.

## Conclusion

As with most technological advances, proposals or hypotheses made in the course of the introduction and development

of new or existing areas of medical endeavours and achievements, the development of total parenteral nutrition has not only been accompanied but also preceded and followed by challenges and controversies over the past 50 years since its inception in 1960 until today. The tedious process of advancing this novel and controversial technique over the next 20 years to ensure it becomes cutting-edge and the science of sick or critically ill patients' nutritional support under a variety of circumstances has been widely described in other studies<sup>13</sup>. Without the support of valid and representative data, arguments and disputes would be based solely on opinions and prejudices of the disease instead of on data or facts that ensure that the truth is found. However, healthy controversy through the acquisition and/or production of reliable data, experience and/or information (and based on measurable scepticism that does not destroy creativity) can admirably and effectively serve to argue for the best scientific method in the search for truth. It is imperative that the principles and practices established for surgical nutritional support are efficiently and accurately applied to each patient at all times and under all circumstances if optimum results are sought. This is exactly what Dr. Ize Lamache did during his distinguished life and which we should all continue to do, imitate and carry out according to his teachings, practices and philosophy.

## Conflict of interest

The authors declare no conflict of interest.  
In memory of Dr. Luis Ize Lamache.

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