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''Enteral Versus Parenteral Nutrition: Effects on Gastrointestinal Function and Metabolism'': Background

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ABSTRACT

Nutrition therapy for the critically ill patient is today an integral part of the treatment concept in intensive care medicine. Parenteral and enteral artificial nutrition are expensive, cost-intensive treatment procedures that are certainly not risk-free. For both ethical and economic reasons, the indications and principles of artificial nutrition must always be adapted to the latest knowledge. *Nutrition* 1998;14:76–81. ©Elsevier Science Inc. 1998

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ENTERAL VERSUS PARENTERAL NUTRITION: WHICH ARGUMENTS SHOULD BE TAKEN INTO ACCOUNT?

Given that the range of parenteral substrates is only putatively complete, the guaranteed absorption of the substrate is always quoted as being an advantage of parenteral nutrition, as this can be guaranteed even in the case of limited intestinal resorptive capacity. The side effects of the parenteral method of administration have long since been regarded as not particularly serious and as controllable. This view was based on the premise that, provided that there is good knowledge of the substrate utilization and that intensive metabolic monitoring is carried out, the parenteral substrate administration can be easily modified and adapted to the patient's individual needs. In addition, the intensive care doctor is familiar with the intravenous access that is necessary for the administration of parenteral nutrition. This access is well protected, and nutrition therapy is administered by trained specialist staff. Equally important is the fact that parenteral nutrition, compared with enteral nutrition, has had a ''sophisticated image,'' and this has had a detrimental effect on the reputation of the enteral method of administration.

What then are the advantages of enteral nutrition? It has been claimed that tube feeding is technically more easily carried out and that the complications are less dangerous than those associated with parenteral nutrition. In practice, however, experience has shown that the administration of enteral nutrition can be considerably impeded by high reflux levels in the case of epigastric atonia or by diarrhea in the case of limited resorptive capacity. Protracted constipation, for example, in the case of an acute pseudoobstruction of the colon, or aspirations in the case of ineffective protective reflexes or side effects caused by the tubes, constitute a serious risk when administering early enteral nutrition to the critically ill patient.

All of these factors may have contributed to the frequent use of parenteral nutrition in the past, even when there were no contraindications against enteral nutrition.[1] This was particularly the case in Europe: even at the end of the 1980s, the ratio of enteral nutrition therapy to parenteral nutrition therapy was 1:3 in Europe and the Federal Republic of Germany, whereas the ratio in the United States was already 1:1.[1]

Since the beginning of the 1990s, there has also been a renaissance in enteral nutrition in Europe. This cannot be exclusively attributed to the costs, which are lower than those associated with parenteral nutrition, or to the development of new tube techniques and diets. A decisive factor was the recollection of the fact that artificial enteral nutrition corresponds most closely to the physiologic conditions of normal oral nutrition. The principle behind this recollection led to a series of more recent experimental and clinical studies that focused on the following two main viewpoints.

First, it is suspected today that there is a causal connection between a disturbed intestinal function, the development and persistence of systemic inflammatory response syndrome (SIRS)

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and the subsequent development of multiorgan dysfunction syndrome (MODS).[2] There are increasing indications that the intestinal mucosa barrier function can be ensured more effectively against translocating bacteria and toxins during artificial tube feeding than during parenteral feeding. If the intestine is understood to be the primary or secondary cause of SIRS, enteral nutrition therapy could, in the future, be accorded a certain value with regard to the prophylaxis and treatment of systemic inflammatory responses. Cerra et al.,[3] in their clinical study on hypermetabolic patients with sepsis, were unable to establish any reduction in the development of MODS or in mortality during enteral nutrition when an isocaloric and isonitrogenous enteral nutrient solution was compared with the parenteral substrate administration. A reduced incidence of septic complications during early enteral nutrition therapy, however, has certainly been proved when compared with parenteral nutrition therapy.[4–7] New experimental and clinical studies are also indicating that special substrates such as pyrimidine and purine nucleotides, arginine, glutamine, and n-3-fatty acids offer certain advantages in terms of mucosal barrier protection during both enteral and parenteral administration.[8] It would be interesting to determine whether the possible advantage of enteral nutrition is simply an expression of a more complete range of substrates—and, therefore, whether enteral nutrition merely appears so advantageous because our current range of parenteral nutrients is too unbalanced and incomplete.

The second viewpoint has been common knowledge for a long time; all that has changed is the assessment of its clinical relevance. This involves the publication of the more recent literature, which provides experimental indications that the substrate homeostasis is more favorable during enteral nutrition than it is during parenteral substrate administration.[9,10] In our study, ''Enteral versus parenteral nutrition: effects on gastrointestinal function and metabolism,'' we dealt almost exclusively with this second aspect of early enteral nutrition. The lessening in stress response during early enteral nutrition, which has already been proved in animal experiments, can lead to a reduced energy consumption because of the diminished release of stress hormones[9] and, consequently, to a catabolic reduction.[10] As we were able to demonstrate clinically, this is connected with an increase in carbohydrate utilization and with an improvement of the synthesis of visceral functional proteins and, consequently, of nutritional status. Equally important, an improved tolerance of the substrates also appears to be connected with the enteral method of administration. In our study, this could be seen in terms of a reduced increase in the integrity parameters of the liver and the pancreas and an increased intestinal resorptive capacity.

Both of these aspects—the improved intestinal barrier function and the ameliorated substrate homeostasis—advocate an early enteral substrate administration for critically ill patients and are connected with the luminal and more complete range of substrates for enteral nutrition.

WHAT PROMPTED US TO RESEARCH CLINICAL NUTRITION?

Nutrition of the critically ill has been my interest for the last 15 years, starting with a postdoctoral fellowship in physiology at the University of Munich. After medical qualification in 1981 and after military service, during which I had the opportunity to start my career as a resident in anesthesiology and critical care medicine, I successfully gained a position in the Munich Department of Physiology directed by Professor Eckehart Gerlach. At that time, I had the good fortune to join Professor Heinz-G. Zimmer's laboratory, where I became involved in the intervention of ribose in the cardiac pentose phosphate pathway, enhancing nucleotide synthesis and, subsequently, the cardiac function of the energy-depleted rat heart. During that time, much was learned about the pathophysiology of the heart function, particularly in circumstances when there is a lack of high-energy phosphates. In 1984, I returned to the field of human medicine as a resident in anesthesiology. Once again, I had the good fortune to join Professor Klaus Peter's Department of Anesthesiology at the University Hospital of Munich, where I had the opportunity to continue my career in anesthesiology. In addition to my clinical education, I continued research at Professor Zimmer's laboratories, investigating the stimulatory action of β-adrenergic agonists on the oxidative pentose phosphate pathway in the rat heart. Thanks to the ongoing guidance and generous support that I gratefully received and continue to receive from Professor Peter, I was offered a research fellowship in anesthesiology (critical care) at the Montefiore Medical Center in the Bronx, New York. It was in this way that I joined the laboratory of Professor David H. Elwyn[a] and Professor Jeffrey Askanazi from 1987 to 1988. During that time, I received strong inspiration both in personal and scientific terms. As a clinical research fellow. I was the practical arm of a clinical research project, dealing with the metabolic effects of recombinant human growth hormone in chronic obstructive pulmonary disease (COPD) patients receiving parenteral nutrition. Much was learned about protein and energy metabolism in the critically ill patient. In addition, I became experienced in planning and managing clinical trials. Guided also by Dr. Michael M. Rothkopf, I received extensive training and experience in clinical nutritional support therapy through joining the nutritional services of the Veterans Administration Medical Center, East Orange, New Jersey. In 1988, I returned to Professor Klaus Peter's Department of Anesthesiology at the University Hospital of Munich, where I became a staff member of the intensive care unit (ICU) for the next 5 years. In addition to my clinical duties, I formed a local research group in the field of clinical nutrition. My first coworker was Dr. Klaus Beck, and we were subsequently joined by Dr. Thomas Eckart and Dr. Uwe Senftleben. As I involuntarily transferred the inspiration that I had received during my fellowship in New York, we, together, built up a small but powerful working group. In our scientific activities, we continued to elucidate the effects of recombinant human growth hormone on malnourished critically ill patients while they were weaned from respirator therapy. In addition, we focused on the effects of alimentary lipids on prostaglandin metabolism, immunologic status, lung function, and hemodynamics in the critically ill patient. Our third but equally important scientific focus was defined as the effects of clinical nutrition on gastrointestinal function and metabolism.

During clinical work in the ICU, it was evident that the possibilities for early artificial enteral nutrition all too often were ignored and that preference was given in many cases to parenteral nutrition, even when this was not necessary. The reasons for this appeared to be those already detailed here, combined with a lack of up-to-date evidence concerning the clinically relevant advantages of enteral nutrition therapy. Inspired by the clinical studies carried out by Moore and Jones,[4] Moore et al.,[5] and Kudsk et al.,[7] our working group therefore set itself the goal of collecting data from our own patient population to provide further evidence of the importance of early enteral nutrition. We decided to carry out the study as part of a prospective clinical investigation of postoperative neurosurgical patients with spontaneous or traumatic head trauma. We chose this patient population, because there was

[a] As a footnote, I would like to pay tribute to Professor David Elwyn, who recently passed away. His mentorship and support provided the impetus to the continuance of my studies in this field. He will be sorely missed.

minimal contraindication against the use of enteral nutrition support and, because early enteral nutrition for neurosurgical patients was still a subject of much controversial discussion in the literature.[11–17] We quickly gained the full support of the medical superintendents of the Department of Neuroanaesthesia, Professor Robert Enzenbach, and Dr. Reinhard Murr. To realize the project, however, we still required a sponsor who would be prepared to promote the project. Once again, it was Professor Peter who had faith in our project and who was instrumental in securing the financial support for our project from Abbott, Wiesbaden. In addition to the financial support, Dr. Monika Scholz (Abbott, Wiesbaden) was also made available to us as a contact and her assistance was invaluable in helping us to surmount numerous problems.

WHICH QUESTION DID WE WANT TO ANSWER?

When drawing up the design for the study, it was decided that our trial should help to clarify the question concerning the ways in which the administration method used for nutrition therapy can affect the substrate homeostasis and organ function. It was therefore necessary to compare a group of patients fed enterally with a group of patients fed parenterally under optimal conditions. The list of exclusion criteria was deliberately very strict, and patients were excluded from the study if there were preoperative signs of malnutrition, a resorptive disturbance, or a nutritionally relevant organ dysfunction. Equally, patients with a developing SIRS unrelated to the operation trauma were excluded from this study if there were any indications pointing to an above-average disturbance of substrate utilization or to restricted resorption. The study was not designed to generate comparative data in regard to the ''outcome.'' Instead, the aim of the investigation was to investigate two nutrition regimens carried out under optimal conditions with regard to their effects on gastrointestinal function and on the patient's metabolism. The authors are convinced that outcome parameters such as mortality or morbidity and the length of the stay in the ICU depend on a large number of factors that are not related to the nutrition regimen used. To investigate the effect of the selected nutrition regime on these parameters, much higher numbers of patients would have been required and this would have been beyond the team's organizational scope.

WHY SUCH A HIGH DROP-OUT RATE?

Of the 49 patients included in the study, 15 patients (that is, approximately 30%) subsequently had to be excluded. This was grist to the mill to all of us skeptics who were carefully observing the situation and a high degree of patience was required from all members of staff, given the frustration involved. What then was the cause of this high number of patients who had to be excluded? Six patients dropped out of study because of early recovery and a decision to desist providing further nutritional therapy. The very selective study design applied resulted in the relatively high nutrition of nine patients who had to be withdrawn from the study owing to hemodynamic and metabolic instability accompanied by symptoms of SIRS. It was only in these patients that decreased substrate utilization and enteral incompatibilities were evident and caloric intake had to be reduced below 75% resting energy expenditure (REE) during a period of 2 consecutive days.

When patients with head injury do not die from the head trauma itself, the most common cause of death is sepsis and multisystem organ failure.[11,18,19] The high propensity for infection as a cause of death in this patient group raises the question of gut-origin septic states, as in other trauma and bowel-rest patients who are similarly stressed.[5] A major issue that relates gut-origin septic states to neurotrauma patients suffering from enhanced intracerebral pressure could be the high vasopressure loads that are frequently applied in this patient population. In all neurosurgical patients, the mean arterial blood pressure was kept above 70 mmHg. If intracerebral pressure was obtainable, cranial-perfusion pressure was kept above 70 mmHg. In cases of subarachnoidal bleeding, transcranial Doppler measurements were performed to assess the flow velocity of the vessels maintaining cerebral blood flow. If flow velocity was found to be increased, it was sometimes appropriate to enhance mean arterial blood pressure, to levels above 110 mmHg, relating to a systolic blood pressure close to 200 mmHg. In addition to an appropriate volume replacement therapy these goals could only be met by supplying dopamine in quantities of up to 30 mg/h and, if necessary, noradrenaline in quantities of up to 2 mg/h intravenously. In our trial, this exogenous supply of stress hormones might have been responsible for the severe impairments of substrate elimination and utilization, as well as for the failure of resorption, which, in turn, led to withdrawal from the study. It can be assumed that visceral perfusion became reduced during extended therapy with catecholamines. Reduced enteral nutrient compatibility might be related to this regimen of vasopressor therapy. In our opinion, the four excluded enterally fed patients were unable to withstand the appropriate enteral volumes, even if they had been administered through the jejunal route. Supported by other published data,[20–22] we have good reason to believe—but based on our single data we can only hypothesize—that catecholamine-induced alterations of the mucosal barrier were most extensive in this small group of nine patients and that bacterial translocation, and finally the risk of systemic inflammation, were thereby enhanced.

MEASUREMENTS OF RESTING ENERGY EXPENDITURE DURING THE EARLY FLOW PHASE: CLINICAL OR SCIENTIFIC SIGNIFICANCE?

Temperature, catecholamine levels, severity of injury, resting muscle tone, spontaneous muscle activity, and the use of drugs are major determinants of REE in neurosurgical patients.[23] Resting energy expenditure has already been measured by indirect calorimetry and was generally found to be elevated to 135–165% of the level predicted by the Harris-Benedict equation.[24] The range of 70–280% of the predicted level was quite broad. Similar trials calculated energy needs on the basis of anthropometric data.[11–13,16,25] Occasionally, this may have caused an overestimation of energy needs which subsequently lead to disturbances of substrate elimination as well as utilization due to hyperalimentation. In addition, disturbances in gastrointestinal function, such as regurgitation, diarrhea, or abdominal distention may have been augmented. In our trial, these problems were probably reduced by supplying energy loads equal to each patient's REE, as measured daily by means of indirect calorimetry.

At present, we are concerned that even this procedure may overestimate the energy needs during the flow phase. Neurohumoral effects on the metabolic regulation lead to changes in metabolism of energy carriers, which are characterized by the mobilization of endogenic substrate reserves together with the simultaneous restriction of the utilization of these. The restrictions of substrate utilization cannot be overcome through nutrition therapy measures while the underlying neurohumoral changes of the metabolic regulation and the causes of these continue to exist. The loss in lean body mass can only be lessened, but it cannot be halted by nutritional support. The attempt to maintain or to restore lean body mass in malnourished individuals subjected to stress metabolism has little chance of success and can even be related to a worsening of the outcome.[26–28] The aim of the nutrition therapy during the flow phase should be restricted to maintaining the function of the organs that are essential for survival. In the case of neurosurgical patients, priority has to be given to the central nervous system. Based on the measured REE, the orientation of the nutrition therapy to the individual elimination and utilization

possibilities can even make a hypoenergetic substrate administration necessary. This form of nutrition remains adapted to need, however, as it includes the neurohumorally induced endogenic supply of substrates in the requirement plan. During the flow phase, the control of the substrate administration should take place exclusively through diagnostic monitoring of the serum urea, urea production rate in urine, serum triglycerides, and blood sugar. This monitoring can only be supplemented by the use of indirect calorimetry.

Orienting substrate administration to the basal metabolic rate alone means, however, that there is no possibility of effectively controlling nutrition therapy under the conditions of stress metabolism. Under SIRS conditions, even the measured energy consumption values are often higher than the substrate quantities at which sufficient elimination and utilization can be guaranteed in the case of exogenic administration. Even exact knowledge of the resting metabolic rate cannot be an instrument for controlling the energy administration during flow phase because an increased thermogenesis may be induced by a potentially possible hyperalimentation. Nutrition-dependent increases of the plasma levels of noradrenaline lead to an increase in oxygen consumption, as well as an increase in the resting metabolic rate.[29] An increased ''futile cycling'' of the substrates is regarded as a significant biochemical correlative of the alimentarily induced thermogenesis and is subject to β-adrenergic control. Thermogenesis would be increased further still if the energy administration were adapted once again to the consumption values.

During the flow phase, the attempt must be made to control the disturbances of the intermediary metabolism that are caused by the illness and to avoid any side effects of the nutrition therapy on the organ function through hyperalimentation, and yet without giving up in the attempt to have a positive influence on the cellular energy status. Only once the stress-triggering causes have been successfully treated and the neurohumoral regulatory mechanisms have normalized, can any priority be given to restoring the lean body mass.

WHAT WAS LEARNED IN TERMS OF CARBOHYDRATE METABOLISM?

Patients subjected to stress metabolism often reveal a carbohydrate homeostasis disturbance with, in some cases, strongly increased blood sugar levels. The gluconeogenesis is increased,[30,32] whereas the glucose oxidation is limited[33] and shows a decrease in relation to the availability. This leads to hyperglycemia, hyperosmolarity, immunosuppression,[34,35] respiratory insufficiency,[36,37] and adipose infiltration of the liver.[38] The carbohydrate administration for these patients must be controlled and limited. A glucose administration in excess of $3.5\ g \cdot kg^{-1} \cdot d^{-1}$ is no longer recommended because the possibilities of oxidative utilization are exceeded and the dangers of metabolic complications that arise as a result of the administration of glucose increase. If plasma glucose levels in excess of 180 mg/dL occur during current glucose administration and if there is no knowledge of any insulin-dependent diabetes mellitus, this must then be interpreted as a utilization disturbance and the glucose administration must be reduced. Based on the results of our studies, early enteral nutrition, in addition to allowing adaptation to the individual utilization capacities, offers the clinically relevant possibility of deciding on the amount of carbohydrate administration with greater certainty. Humoral feedback mechanisms that are induced after the enteral substrate administration appear to respond in a more intensive manner than during parenteral nutrition. The endogenic release of insulin appears to function more effectively. Besides it can be assumed that enteral nutrition measures lead to a reduction in the intensity of systemic inflammation because of the improved mucosal barrier function of the intestine. This in turn may lead to an improved substrate homeostasis of carbohydrates.

An improvement in the substrate homeostasis is of great significance for patients with recent craniocerebral trauma, as it is known that there is a correlation between increased plasma glucose levels and a worsening of the cerebral outcome.[39] The most likely mechanism for poor brain recovery in the case of hyperglycemia is metabolic acidosis. In areas of poorly oxygenated brain tissue, glucose is metabolized anaerobically to lactate, which decreases the local pH and causes cell damage.[40,41] Without overemphasizing the results of this study, we consider the tangentially better Glasgow Coma Scores of the enterally fed patients to be an important indication, the results of which should be substantiated by further studies. The data already collected on our wards have helped to combat a carbohydrate-induced hyperalimentation in order to be able to monitor our patients' serum glucose levels more carefully. Patients with severe head injury must overcome central as well as systemic peripheral insults. Even in the light of extreme caloric requirements, limitation of caloric intake can apparently be condoned for a limited period and may favor the neurologic outcome.

WHAT WAS LEARNED IN TERMS OF PROTEIN METABOLISM?

Patients with severe brain injury exhibit marked catabolism of body protein stores in response to a hormonal pattern that is similar to that seen in multitrauma patients without head injury.[42,43] Although protein synthesis is increased, the simultaneous increase in proteolysis is predominant, resulting in a net protein loss. The clinical correlative of this phenomenon is the rapid loss of skeletal muscles, together with an increased nitrogen secretion in the urine. The protein synthesis in the liver and the intestine increases to the same extent as the occurrence of a flux of amino acids that takes place from the periphery to the central visceral organs.[44,45] This metabolic centralization toward the intestine is connected with an increased energy and substrate consumption within the visceral organs. A changeover of this kind is caused by neurohumoral reaction patterns that have developed phylogenetically and which facilitated our survival in times before clinical nutrition therapy was introduced.[46]

The peripheral protein loss is an expression of these stress-induced changes. This was also demonstrated in our investigation. A mean value of about 45–60 g of urea was produced daily after day 6 in both the enterally and parenterally fed study groups, indicating comparable catabolic states. This is in accordance with other data reported.[47] The assumption seems likely that during the early flow phase, peripheral protein catabolism cannot be prevented by nutritional support. It is understood that, as in other highly stressed populations, the increased protein intake may improve protein synthesis but does not decrease protein catabolism. Given the current level of knowledge, it is unwise—if not downright dangerous—to combat the high nitrogen losses with a particularly high administration of amino acids. Doses of 1.5 g/kg or, in exceptional circumstances, up to 2 g/kg should not be exceeded.

In addition, the value of the nitrogen balance in predicting the efficacy of nutritional efforts in this patient population is probably limited. There are well-justified doubts about the plan to reverse the catabolic substrate flow to visceral organs from skeletal muscles in order to favor a positive nitrogen balance, as is the case with the administration of insulin. The principle of intestinal metabolic centralization with a locally increased energy and oxygen consumption and the subsequent increase in visceral protein synthesis is important for the survival of the organism. There are indications that the lack of increases of the visceral amino acid clearance, combined with reduced visceral protein synthesis rates in critically ill patients, are connected with high mortality.[48–50] It

should be a major goal of nutritional support to provide substrates in order to sustain visceral protein levels and immunologic competence. In our clinical trial, it could be shown that after only 12 days of total enteral nutrition, these goals could be met, as indicated by significant enhancements of visceral protein synthesis and predominant increases in thrombocyte and lymphocyte counts in the enterally fed patient group.

IS ''NIL BY MOUTH'' THE RIGHT ANSWER TO VISCERAL ORGAN DYSFUNCTION?

Cholestasis, pancreatitis, and gut atrophy are most common abnormalities seen in patients on total parenteral nutrition (TPN).[51,52] The persistence of significant TPN-induced visceral organ dysfunction despite decades of research suggests a multifactor etiology.

As recognized complications of TPN, cholestasis as well as pancreatitis usually tend to occur after a prolonged period of parenteral feeding.[53] Our findings reveal enhanced plasma levels of bilirubin, β-glutamyl-transferase, alkaline phosphatase, amylase, and lipase even after a period of 6–12 days of TPN. These side effects seem to be related to an abnormal pattern of gut hormones. Without succus entericus, there is no impetus for the secretion of gut-derived hormones such as cholecystokinin, the lack of which can contribute to cholestasis.[53]

Before this study was performed, we, as did most clinicians, believed in therapeutic approaches that promote pancreatic rest for the treatment of acute pancreatitis.[54,55] As we saw from our own data, however, TPN might be related to a higher risk of cholestasis and, possibly, pancreatitis than is the case with enteral nutrition. Feeding patients with pancreatitis without stimulating pancreatic exocrine secretion has become an objective despite the absence of any clinical or scientific evidence to support this approach.[56,57] Although gastric infusion of an enteral diet may not be tolerated in case of gastric atonia, we today would recommend enteral feeding into the jejunum even under circumstances of pancreatitis. Close monitoring of enteral incompatibilities is, however, still indispensable.

In the stressed or infected patient,[58] intestinal mucosal atrophy is favored by the absence of luminal nutrients, the lack of mechanical stimulation, an abnormal hormone pattern, and an insufficient supply of primary enterocyte fuel sources. This atrophy develops after only a few days of enteral starvation. Animal data strongly suggest that this may contribute to the translocation of gut bacterial factors, which may contribute to the development of remote infection, fueling systemic inflammatory response syndrome. In addition to the barrier function, the intestinal mucosa also attain basal significance as a digestive and resorptive organ. Under normal conditions, the intestinal mucosa can ensure these functions as a result of a large surface, an appropriate microcirculation, and a high metabolic activity of the cells. This finely tuned system would nevertheless appear to be very adversely affected by a disuse atrophy of the tissues involved. The restrictions of lipophagia shown by our working group after 12 days' TPN confirm this assumption.

For many years, nothing by mouth and TPN were the clinician's answer to visceral organ dysfunction. Recent experimental and clinical trials provided enlightenment about the overzealous use of this therapeutic approach. Contrary to earlier popular belief, bowel rest has not made any positive impact on clinical outcome, but rather the opposite. Yet, it became evident that early enteral nutrition is not easy to put into practice. It would appear that the importance of adjusting support to meet needs, avoiding deficiency states, and maintaining bowel mucosal[59] integrity from the start of nutrition therapy are central to the issue. Any of these demands are in accordance with the recommendation to use the gut whenever possible, even if total support by the enteral route is not attainable.

CONCLUSION

The nutritional and metabolic management of the patient with brain injury will continue to challenge clinicians. Optimizing provision of nutrients while minimizing the complications of nutritional support are the mainstays of quality care.[24] The data of our trial clearly favor the enteral route to meet these goals. Although we believe that the current rise in status of early enteral nutrition is to be welcomed, there is nevertheless a lack of long-term clinical studies that provide evidence that enteral tube feeding is superior. How should this future evidence be provided?

The monitoring of the effectiveness of tube feeding has hitherto been carried out in the chemistry laboratory, particularly through the evaluation of the nitrogen balance, and by using anthropometric methods. The significance of anthropometrically obtained data is the subject of fierce controversy. As explained earlier here, determining nitrogen balance would not appear to be of prime importance, and this process is also beset with considerable difficulties of method. Because the therapeutic aim cannot be to correct raised laboratory parameters to within the standard range, but instead must be oriented toward improving endogenic organ and system functions, the maintenance of these functions should be used in the future to monitor the effectiveness of nutrition therapy. The parameters observed in this study, namely intestinal resorption, substrate tolerance, and the synthesis of functional visceral proteins would seem to provide a useful starting point. A positive nitrogen balance is not necessarily synonymous with improved synthesis or the improved functioning of vital organs. Indeed, determining the number of leukocytes is only the first step in the right direction in the assessment of cellular immunity. Here, again, relevant functional parameters must in future be checked in relation to nutrition therapy.

The value of a therapeutic strategy cannot always be measured solely against outcome parameters such as mortality, morbidity, and the length of hospital stay. There are too many factors involved in the effects in intensive care medicine, the differences that can be expected are too fine, and in order to satisfy this claim in terms of statistical significance, many studies would subsequently have to be carried out that would be too expensive. Very often the significance of the type II or β-error is underestimated, as this frequently suggests that two treatment procedures are of equal value, whereas in fact there is a difference between them. The investigation into organ and system functions in the future remains a relevant, if not a particularly advanced, method for comparing different therapeutic strategies.

REFERENCES

1. Dietze GJ. Prinzipien der künstlichen parenteralen und enteralen Ernährung. In: Peter K, Dietze GE, Hartig W, Steinhardt HJ, eds. *Differenzierte klinische Ernährung. Workshop Grainau-Eibsee Juni 1986; Klinische Ernährung 25.* 25th ed. Munich: W. Zuckschwerdt Verlag, 1987:1
2. Wilmore DW, Smith RJ, O'Dwyer ST, Jacobs DO, Ziegler TR, Wang X-D. The gut: a central organ after surgical stress. Surgery 1988;104:917
3. Cerra FB, McPherson JP, Konstantinides FN, Konstantinides NN, Teasley KM. Enteral nutrition does not prevent multiple organ failure syndrome (MOFS) after sepsis. Surgery 1988;104:727
4. Moore EE, Jones TN. Benefits of immediate jejunostomy feeding after major abdominal trauma: a prospective, randomized study. J Trauma 1986;26:874
5. Moore FA, Moore EE, Jones TN, McCroskey BL, Peterson VM. TEN

versus TPN following major abdominal trauma: reduced septic morbidity. J Trauma 1989;29:916
6. Moore FA, Feliciano DV, Andrassy RJ, et al. Early enteral feeding, compared with parenteral, reduces postoperative septic complications: the results of a meta-analysis. Ann Surg 1992;216:172
7. Kudsk KA, Croce MA, Fabian TC, et al. Enteral versus parenteral feeding. Effects on septic morbidity after blunt and penetrating abdominal trauma. Ann Surg 1992;215:503
8. Suchner U, Senftleben U, Felbinger T. Nichtenergetische Aspekte der Ernährung. In: Lawin P, Peter K, Prien T, eds. *Intensivmedizin 1995, praxis der intensivbehandlung; 16. Internationales Symposium über aktuelle Probleme der Notfallmedizin und intensivtherapie, Münster*. Stuttgart: Georg Thieme Verlag, 1995:178
9. Saito H, Trocki O, Alexander JW, Kopcha R, Heyd T, Joffe SN. The effect of route of nutrient administration on the nutritional state, catabolic hormone secretion, and gut mucosal integrity after burn injury. J Parenter Enter Nutr 1987;11:1
10. Mochizuki H, Trocki O, Dominioni L, Brackett KA, Joffe S, Alexander JW. Mechanism of prevention of postburn hypermetabolism and catabolism by early enteral feeding. Ann Surg 1984;200:297
11. Rapp RP, Young B, Twyman D, et al. The favorable effect of early parenteral feeding on survival in head-injured patients. J Neurosurg 1983;58:906
12. Hayashi JT, Wolfe BM, Calvert CC. Limited efficacy of early postoperative jejunal feeding. Am J Surg 1985;150:52
13. Muggia-Sullam M, Bower RH, Murphy RF, Joffe SN. Postoperative enteral versus parenteral nutritional support in gastrointestinal surgery. Am J Surg 1985;149:106
14. Hausmann D, Mosebach KO, Caspari R, Rommelsheim K. Combined enteral-parenteral nutriton versus total parenteral nutrition in brain-injured patients. Intensive Care Med 1985;11:80
15. Clifton GL, Robertson CS, Contant CF. Enteral hyperalimentation in head injury. J Neurosurg 1985;62:186
16. Ott L, Young B, Phillips R. Altered gastric emptying in the head-injured patients: relationship to feeding intolerance. J Neurosurg 1991; 74:738
17. Young B, Ott L, Haack D, et al. Effect of total parenteral nutrition upon intracranial pressure in severe head injury. J Neurosurg 1987;67:76
18. Young B, Ott L. The neurosurgical patient. In: Rombeau JL, Caldwell MD, eds. *Clinical nutrition, parenteral nutrition.* 2nd ed. Philadelphia: Saunders, 1993:585
19. Waters D, Dechert R, Bartlett R. Metabolic studies in head-injury patients: a preliminary report. Surgery 1986;100:531
20. Border JR, Hassett J, LaDuca J, et al. The gut origin septic states in blunt multiple trauma (ISS-40) in the ICU. Ann Surg 1987;206:427
21. Deitch EA, Bridges RM. Effect of stress and trauma on bacterial translocation from the gut. J Surg Res 1987;42:673
22. Deitch EA. The role of intestinal barrier failure and bacterial translocation in the development of systemic infection and multiple organ failure. Arch Surg 1990;125:403
23. Robertson CS, Clifton GL, Grossman RG. Oxygen utilization and cardiovascular function in head-injured patients. Neurosurgery 1984; 15:307
24. Evans NJ, Compher CW. Nutrition and the neurologically impaired patient. In: Torosian MH, ed. *Nutrition for the hospitalized patient: basic science and principles of practice.* New York: Marcel Dekker, Inc., 1995:567
25. Young B, Ott L, Twyman D, et al. The effect of nutritional support on outcome from severe head injury. J Neurosurg 1987;67:668
26. Alexander JW, Gonce SJ, Miskell PW, Peck MD, Sax H. A new model for studying nutrition in peritonitis. The adverse effect of overfeeding. Ann Surg 1989;209:334
27. Yamazaki K, Maiz A, Moldawer LL, Bistrian BR, Blackburn GL. Complications associated with the overfeeding of infected animals. J Surg Res 1986;40:152
28. Vo NM, Waycaster M, Acuff RV, Lefemine AA. Effects of postoperative carbohydrate overfeeding. Am Surg 1987;53:632
29. Askanazi J, Carpentier YA, Elwyn DH, et al. Influence of total parenteral nutrition on fuel utilization in injury and sepsis. Ann Surg 1980;191:40
30. Weissman C. The metabolic response to stress: an overview and update. Anesthesiology 1990;73:308
31. Lowe DK, Jacobs DO, Wilmore DW. Metabolic background. In: Fischer JE, ed. *Total parenteral nutrition.* London: Little Brown, 1991:165
32. Unger RH. Glucagon and the insulin: glucagon ratio in diabetes and other catabolic illnesses. Diabetes 1971;20:834
33. Wolfe RR, O'Donnell TFJ, Stone MD, Richmand DA, Burke JF. Investigation of factors determining the optimal glucose infusion rate in total parenteral nutrition. Metabolism 1980;29:892
34. Bagdade JD, Root RK, Bulger RJ. Impaired leukocyte function in patients with poorly controlled diabetes. Diabetes 1974;23:9
35. Baxter JK, Babineau TJ, Apovian CM. Perioperative glucose control predicts increased nosocomial infection in diabetics. Abstr Crit Care Med 1990;18:S207.
36. Askanazi J, Rosenbaum SH, Hyman AI, Silverberg PA, Milic Emili J, Kinney JM. Respiratory changes induced by the large glucose loads of total parenteral nutrition. JAMA 1980;243:1444
37. Askanazi J, Nordenstrom J, Rosenbaum SH, et al. Nutrition for the patient with respiratory failure: glucose vs. fat. Anesthesiology 1981; 54:373
38. Burke JF, Wolfe RR, Mullany CJ, Mathews DE, Bier DM. Glucose requirements following burn injury: parameters of optimal glucose infusion and possible hepatic and respiratory abnormalities following excessive glucose intake. Ann Surg 1979;190:274
39. Young B, Ott L, Dempsey R. Relationship between admission hyperglycemia and neurologic outcome of severely brain-injured patients. Ann Surg 1989;210:466
40. De Salles A, Kontos H, Becker D. Prognostic significance of ventricular CSF lactic acidosis in severe head injury. J Neurosurg 1986;65:615
41. Robertson C, Goodman J, Narayan R. The effect of glucose administration on carbohydrate metabolism after head injury. J Neurosurg 1991;74:43
42. Chiolero R, Schutz Y, Lemarchand T. Hormonal and metabolic changes following severe head injury or noncranial injury. J Parenter Enter Nutr 1989;13:5
43. Elwyn DH. Protein metabolism and requirements in the critically ill patient. Crit Care Clin 1987;3:57
44. Cerra FB, Siegel JH, Coleman B, Border JR, McMenamy RR. Septic autocannibalism. A failure of exogenous nutritional support. Ann Surg 1980;192:570
45. Cuthbertson DP. Post-traumatic metabolism: a multidisciplinary challenge. Surg Clin North Am 1978;58:1045
46. Jahoor F, Desai M, Herndon DN, Wolfe RR. Dynamics of the protein metabolic response to burn injury. Metabolism 1988;37:330
47. Ott L, Young B, McClain C. The metabolic response to brain injury. J Parenter Enter Nutr 1987;11:488
48. Cerra FB. Hypermetabolism, organ failure, and metabolic support. Surgery 1987;101:1
49. Dahn MS, Lange P, Lobdell K, Hans B, Jacobs LA, Mitchell RA. Splanchnic and total body oxygen consumption differences in septic and injured patients. Surgery 1987;101:69
50. Clowes GH, Hirsch E, George BC, Bigatello LM, Mazuski JE, Villee CAJR. Survival from sepsis: the significance of altered protein metabolism regulated by proteolysis inducing factor, the circulating cleavage product of interleukin-1. Ann Surg 1985;202:446
51. Clark PJ, Ball MJ, Kettlewell MGW. Liver function tests in patients receiving parenteral nutrition. J Parenter Enter Nutr 1991;15:54
52. Baker AL, Rosenberg EH. Hepatic complications of total parenteral nutrition. Am J Med 1987;82:489
53. Doty JE, Pitt HA, Porter-Fink V, DenBesten L. Cholecystokinin prophylaxis or parenteral nutrition-induced gallbladder disease. Ann Surg 1985;201:76
54. Ettien JT, Webster PD. The management of acute pancreatitis. Adv Intern Med 1980;25:169
55. Ranson JHC, Spencer FC. Prevention, diagnosis and treatment of pancreatic abscess. Surgery 1977;82:99
56. Ranson JHC. Acute pancreatitis: pathogenesis, outcome and treatment. Clin Gastroenterol 1984;13:843
57. Kirby DF, Craig RM. The value of intensive nutritional support in pancreatitis. J Parenter Enter Nutr 1985;9:353
58. Rombeau JL, Kripke SA. Enteral nutrition. In: Fischer JF, ed. *Total parenteral nutrition.* 2nd ed. Boston: Little, Brown, 1991:423
59. Sax HC. Complications of total parenteral nutrition and their prevention. In: Rombeau JL, Caldwell MD, eds. *Clinical nutrition, parenteral nutrition.* 2nd ed. Philadelphia: W.B. Saunders, 1993:367

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