

2006 marked the 40th year of publication for *The Annals*. Throughout its history, *The Annals* has provided important contributions to the development of clinical pharmacy. In 2007, we are continuing to publish articles reflecting on the history of clinical pharmacy through the eyes of practitioners, including those pioneering clinical pharmacy, as well as those who have more recently entered the profession and a well-established specialty. In addition, we are presenting articles and editorials from the early history of *The Annals* that have given direction and shape to the practice of clinical pharmacy (see page 873).

Advancement of Nutrition Support in Clinical Pharmacy

Jay M Mirtallo

Malnutrition occurs frequently in patients with diseases and as a consequence of their disease process. Ever since Butterworth¹ reported the high prevalence of malnutrition in hospitalized patients (referred to as skeletons in the closet), nutrition support has been of interest to clinicians. Pharmacists' early endeavors in nutrition support were limited to sales of vitamins and, on occasion, enteral supplements. There was also an interest in assessing the effect of food on drug absorption and utilization. Early literature suggested a role of malnutrition in altered drug metabolism. Hence, investigation of drug–nutrient interactions was initiated. Currently, one considers nutrition support and pharmacy practice in the context of parenteral nutrition (PN) and/or enteral tube feedings or enteral liquid supplements. How this came about is, in my mind, somewhat short of a miracle.

Physicians had long been interested in methods of feeding individuals by either oral or parenteral means when the patient could not voluntarily ingest enough food to prevent malnutrition. It was not until the mid to late 1960s that techniques of central venous access were developed for safe administration of medications or fluids. The rate of blood flow in the superior vena cava was sufficient for the

vein to tolerate infusion of hyperosmolar fluids, such as a solution of presterilized nutrients. In 1968, Dudrick et al.,² of the Hospital of the University of Pennsylvania, described the use of central venous access to infuse nutrients into and successfully nourish beagle puppies into full-grown dogs. Shortly after this discovery, the therapy was applied to infants with catastrophic gastrointestinal tract deformities or diseases and was then initiated in adults.

This was a very exciting era for nutrition support. However, none of this would have happened had it not been for a pharmacist who solved the problem of making nutrients in a form that could be infused intravenously. Stanley Serlick was this pioneer in pharmacy nutrition support. He was able to prepare and ensure sterile, stable, and compatible mixtures of nutrients that could be infused intravenously. When one considers the number of chemical entities in a parenteral nutrition solution and the complexity of the admixture process, it is amazing that one individual had the genius to make the number of discoveries required to prepare a nutrition product for intravenous use. This is what I refer to as being just a little short of a miracle.

By 1971, commercial parenteral nutrition products were available, and clinicians throughout the nation were using the therapy.³ It became apparent that a sophisticated system for ordering, preparing, and administering parenteral nutrition was necessary. This coincided with the implementation of intravenous admixture programs in hospital pharmacies. Safety issues occurred frequently. Since central ve-

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nous catheters (CVC) were used almost exclusively for administration of PN, there was a great deal of interest in catheter-related complications in these patients. Studies on catheter-related infections and microbial growth characteristics of PN solutions were published. Procedures for catheter care, including antiseptics used for catheter dressings, were modified. New catheters and catheter types (single-, double-, and triple-lumen CVC catheters for short- and long-term use) became available and were used for PN. Since the proper dose of nutrients was not fully elucidated, overfeeding complications, especially glucose intolerance, occurred with sometimes lethal outcomes. This was identified by Nehme⁴ in 1980 when he published data on PN outcomes related to whether PN was prescribed by individual clinicians or by a team dedicated to managing PN and its complications. He reported improved outcomes with the team approach and solidified what many believed to be the best method of delivering PN: a nutrition support team (or service). The interdisciplinary involvement of a physician, nurse, dietitian, and pharmacist became the preferred method of providing parenteral nutrition.

Pharmacists' positions on nutrition support services were justified by various means. My position was justified in 1978 by documenting the pharmacist's ability to improve the ordering process for PN and to communicate changes to other pharmacy staff, such that the wastage of PN solutions was reduced. This process was estimated to save the hospital \$100 000 per year. Since the early 1970s, pharmacists have expanded their knowledge of and contributions to nutrition support. This has gone beyond the sterile, stable, and compatible admixture of PN to the clinical management of PN patients, PN research, and continual involvement with improving the safety of PN use.

By 1978, PN and advances in enteral nutrition allowed nutrition support to be used in a variety of patients who earlier would have been left to starve while enduring their disease treatments. That same year, the American Society for Parenteral and Enteral Nutrition (ASPEN) was established. This interdisciplinary society of physicians, nurses, dietitians, pharmacists, and nonclinical researchers is dedicated to optimal nutrition support of patients during hospitalization and throughout convalescence. The founders of ASPEN recognized the importance of research, clinical practice, advocacy, and education, as well as the interdisciplinary approach to nutrition support. These have become the Society's pillars, on which it strives to support its membership and the patients who are served.

Over the next 2 decades, nutrition support evolved, not with what I would consider major breakthroughs but more with an improved sophistication as to how the therapy could be applied safely in a variety of clinical settings. During the 1980s, there was active research into amino acid injection products. With this study came elucidation

of nutrient metabolism in renal and hepatic disease, as well as in stress and sepsis. New amino acid products were developed specifically for use in patients with renal and hepatic failure and in those with stress. Another aspect of these investigations was the finding that exogenous nutrients were not as efficiently used by patients with conditions that significantly altered nutrient metabolism. As such, a part of the success of nutrition support was the medical management of the disease process so that the individual would be in a better condition to respond to nutrition. This influence of disease on the success of nutrition support may explain the poor results of studies attempting to identify the efficacy of PN.

During that time, summary of the data for use of PN during the perioperative period and as an adjunct to chemotherapy was disappointing. Few or no beneficial effects could be found, while a significant increase in infectious complications was reported. Routine use of PN in these conditions was discouraged, and PN was to be used only when gastrointestinal function was severely diminished for a prolonged period (>5–7 days). In patients with short bowel syndrome, PN is a lifesaving therapy and has successfully nourished patients from months to several years.

Also, during this decade, intravenous fat emulsions (IVFE) became commercially available. Initially, these products were used to prevent essential fatty acid deficiency; however, complications of glucose administration stimulated the investigation of IVFE as an energy source to replace a portion of glucose calories. This concept of a mixed fuel system stimulated most of the research demonstrating the favorable effects of IVFE when used as a calorie source. Reduction in carbon dioxide production, with improvements in pulmonary function, was reported by Askanazi et al.⁵ with the use of a mixed fuel system. The consequences of overfeeding on carbohydrate metabolism, hepatic function, and patient stress were observed and led to continual scrutiny of the safest and most useful caloric dose. With the use of IVFE as a calorie source, admixture of IVFE in the same final container as the other PN nutrients became an issue. This form of PN, known as total nutrient admixtures, imparts complicated physicochemical variables that influence the compatibility and stability of PN and remains a system that some pharmacists still avoid. As these issues were being addressed, automated compounding technology became available for PN admixture. This technology improved the accuracy of and reduced the time needed to compound PN. Also, it simplified the clinician's ability to tailor PN formulas to individual patients.

As the role of the nutrition support pharmacist evolved, it became important to formalize the practice. ASPEN published standards for nutrition support pharmacists in 1987, and in 1988, the Board of Pharmaceutical Special-

ties recognized nutrition support pharmacists as specialists. As a result, the scope of practice and the criteria for clinical competence for a pharmacist practicing in nutrition support were defined. Interestingly, in addition to the pharmaceutical aspects of PN and clinical management of nutrition support patients, management, quality improvement, education, and research were included as key components of the role of a nutrition support pharmacist (Board Certified Nutrition Support Pharmacist, BCNSP).

Early on in therapy, it was recognized that it was cost prohibitive and, in some sense, cruel to keep a patient in the hospital just to provide PN. Financially, it was the only means by which the therapy would be reimbursed, but this was only after educating and lobbying payers on the benefits of this new therapy. Once reimbursement for the hospitalized patient was accomplished, consideration of payment for patients receiving therapy in the home was sought and finally achieved. As such, the birth of this therapy was not only the result of scientific and clinical endeavors but also of public policy. Soon, home PN programs were developed. From this, the home infusion therapy industry developed and expanded into intravenous antibiotics, chemotherapy, and pain therapy. Initial home infusion programs were hospital based; private, for-profit, and pharmaceutical companies soon became involved.

The type and quality of service being provided in home-based PN varied. This led to publication of standards of practice for home nutrition support by ASPEN, as well as guidelines on the pharmacist's role in home care by the American Society of Health-Systems Pharmacists (ASHP). Home care accreditation by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) followed. The home care accreditation program was the first to use pharmacists as surveyors, educators, and consultants. Clinical management of patients by pharmacists was a component of the JCAHO's home care standards. Pharmacy surveyors were educated on the concepts of Hepler and Strand,⁶ which included the identification of drug-related problems and development of a plan to resolve the problems, including a method to monitor the success of the plan. Throughout the accreditation process, pharmacists became educated and involved with the quality improvement efforts of their organizations.

As nutrition support moved into the 1990s, investigators continued to elucidate the most effective caloric dose to provide to patients. In addition, the shortage of parenteral multivitamins demonstrated again the extent to which patients who are not able to eat depend on the clinician to provide complete, balanced PN. When vitamins were not available, many serious complications of vitamin deficiencies were reported, including deaths due to thiamin deficiency. Studies of nutrition support efficacy suggested the enteral route to be the preferred route for nutrition support,

especially for critically ill patients. Work by Kudsk et al.⁷ and others pointed to the importance of maintaining gastrointestinal tract function to achieve better patient outcomes (reduced frequency of infections, shortened length of stay in intensive care units and the hospital, improved glucose homeostasis, lower mortality rates). This led to the investigation of glutamine as well as parenteral versus enteral nutrition as it relates to outcomes. It was found that enteral nutrition was better than PN alone or PN with glutamine in improving patient outcomes. As we currently consider the gastrointestinal tract not only as an organ for nutrient processing and absorption, but also as an organ that contributes substantially to the proper immunologic functions of the body, it makes sense that outcomes are better when a patient can be nourished by the oral route. Advances in the techniques for enteral nutrient access and enteral nutrition products are a current focus of the nutrition support community.

Concurrently, the system of nutrition support was taking on new importance. Continual efforts by ASPEN, ASHP, the American Dietetic Association, and other organizations came to fruition with the JCAHO's development of Nutrition Care Standards. These standards were approved and started to be surveyed in 1995. A nutrition care process flow diagram was developed and standards were established for many of the functions required to provide quality nutrition support. Emphasis was placed on an interdisciplinary care process whereby organizations needed to provide evidence that nutrition care was being coordinated among the various healthcare professionals involved with the patient. During that time, a lethal event caused by precipitation of calcium phosphate in a PN formulation resulted in close Food and Drug Administration scrutiny that resulted in the release of a safety alert. As a result, ASPEN, in partnership with ASHP, created a task force to develop Safe Practices for Parenteral Nutrition, which was first published in 1998 and revised in 2004.⁸ These guidelines provide recommendations for safe practices for PN ordering, labeling, compounding, and administration.

Currently, nutrition support is provided in a variety of healthcare environments, with pharmacists having an integral role in the systems needed to provide this therapy, as well as in the clinical management of the patient. Very few, if any, new products are available for PN, but we continue to learn better methods of delivering nutrients intravenously. Once the complications of overfeeding became known, there has been a gradual trend toward decreasing patients' caloric intakes; at the same time, protein doses have increased. Information correlating the rate of infusion to adverse events of IVFE has resulted in recommendations to provide this as a continuous infusion. New concepts in glucose control in intensive care and routine hospital units have resulted in attempts to maintain tighter glucose con-

trol than is generally applied to the patient receiving nutrition support. There is continued pressure to improve the safety of the nutrition support system. Recently, the JCAHO has stimulated interest in PN safety by determining that the National Patient Safety Goal 3b (Improve medication safety: standardize and limit the number of drug concentrations) applies to PN. How this is to be implemented for a complicated product such as PN remains to be determined.

The following issues will impact the future of nutrition support clinicians:

1. The alarming increase and prevalence of obesity. Usual caloric doses are not well tolerated. Hypocaloric feedings have improved the tolerance of nutrition support in obese patients, but more information is needed to determine whether the initial nutritional benefits of this approach can be maintained for long-term PN.
2. Outcomes related to enteral versus parenteral nutrition in various patient types, but particularly in critically ill patients. Evidence supports the concept that those who are able to tolerate use of the gastrointestinal tract for nutrition support will have improved outcomes (survival, length of stay in intensive care and the hospital). This concept needs to be more consistently implemented in critical care settings.
3. Measuring and improving PN outcomes. Why does an episode of PN, having an average duration of 10–14 days, not favorably impact a patient's outcome? Perhaps it is too simplistic to look at one episode of PN; rather, it is more important to evaluate the patient's nutrition as he or she moves through the treatment of a disease process. In this manner, PN is considered a component of a larger nutrition care plan evaluated continually over the period of treatment for the disease.

Even though nutrition support pharmacy practice has matured over the past 40 years, there is still more to be learned and there should be better methods to provide PN safely. Is there a way that PN outcomes can be improved? Will maintaining glucose levels less than 150 mg/dL reduce PN complications such that the benefit of this form of nutrition can be realized? Will a new IVFE having a lower amount of long-chain triglycerides result in improved patient outcomes? Do standard formulas or a standardized process of PN ordering, labeling, compounding, and administration benefit PN patients? What training does a pharmacist need to be competent to participate in PN therapy? Since PN was discovered, its complexity has led to adverse events. An interdisciplinary approach has been shown to minimize complications. How will pharmacists participate in the team approach if there is no formal nutrition support service in their organizations? Can the challenges in care coordination that this represents be overcome?

Patients deserve to have nutrition support prescribed and administered in the safest manner possible, with systems created to minimize error. Evidence suggests that improvements can be made in the nutrition support process. The nutrition support pharmacist will be a key participant in the maintenance and improvement of the nutrition care process. What problems will there be in achieving this goal? First, education and training in nutrition support are not consistent and, in most cases, are not adequate. There are a number of patients receiving specialized nutrition support (enteral and parenteral). Are there enough trained pharmacists to participate in their nutrition care? Nutrition support and, in particular, PN need to be managed as a system of care rather than just something practitioners provide when they have time. It is purely interdisciplinary—the success of the process is attributed to a number of clinicians and how well they coordinate their efforts on behalf of the patient. Every healthcare setting that provides nutrition support should have an individual (or group) who oversees the nutrition support process, with the major focus on improving or repairing nutrition support systems or educating individuals about nutrition support when knowledge deficits are identified.

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References

1. Butterworth CE Jr. The skeleton in the hospital closet. *Nutrition Today* 1974;9:4-8.
2. Dudrick S, Wilmore DW, Vars HM, Rhoads JE. Long-term total parenteral nutrition with growth, development, and positive nitrogen balance. *Surgery* 1968;64:134-42.
3. Flack HL, Gans JA, Serlick SE, Dudrick SJ. The current status of parenteral hyperalimentation. *Am J Hosp Pharm* 1971;28:326-35.
4. Nehme AE. Nutritional support of the hospitalized patient. *JAMA* 1980; 243:1906-8.
5. Askanazi J, Rosenbaum SH, Hyman AL, et al. Respiratory changes induced by large glucose loads of total parenteral nutrition. *JAMA* 1980; 243:1444-7.
6. Hepler CD, Strand LM. Opportunities and responsibilities in pharmaceutical care. *Am J Hosp Pharm* 1992;45:1045-51.
7. Kudsk KA, Carpenter G, Petersen S, Sheldon GF. Effect of enteral and parenteral feeding in malnourished rats with *E. coli*-hemoglobin adjuvant peritonitis. *J Surg Res* 1981;31:105-10.
8. Task Force for the Revision of Safe Practices for Parenteral Nutrition and the A.S.P.E.N. Board of Directors. Safe practices for parenteral nutrition. *JPEN J Parenter Enter Nutr* 2004;28(suppl):S39-70.