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Developing Research Programs in Clinical and Translational Nutrition

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Abstract

Most clinicians believe that nutrition support therapy improves outcome in hospitalized patients. Unfortunately, few patients receive optimal nutrition management. A lack of strong, well-designed research studies may prevent the medical/surgical community from fully embracing the practice. More quality research is needed. This article discusses 3 potential strategies to improve research activity in clinical nutrition: increase funding of nutrition research, foster young physician training in nutrition and research, and attract nutrition researchers to our national nutrition society meetings. The best chance for this process to succeed is for the national nutrition societies to partner with medical and surgical subspecialty societies to develop larger scale clinical and translational research programs.

Keywords

nutrition research; randomized trials; data registry; research consortium

The American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) was established in 1976 and grew from <1000 members to nearly 8000 by 1990.¹ This rapid growth reflected the tremendous interest in nutrition support of hospitalized patients during this time and paralleled the development and growth of nutrition support teams (NSTs). Well-attended poster and oral abstract presentation sessions of cutting-edge research combined with excellent networking opportunities made the annual A.S.P.E.N. meeting an event not to be missed.

This was an exciting time. Intensive care units (ICUs) had been developed that allowed critically ill patients to survive previously lethal insults. Research had increased the basic understanding of how the metabolic response to stressful insults could induce acute protein malnutrition and impair the immune response, thus setting the stage for postoperative complications, nosocomial infections, multiple organ failure (MOF), and late ICU deaths.^{2,3} Moreover, parenteral nutrition (PN) had become widely available, and new stress formulas

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of PN appeared to have potential to prevent the MOF cascade to death.⁴ NSTs, using a novel, multidisciplinary model of physician, nurse specialist, pharmacist, and dietitian, were developed to safely administer PN and to study its effectiveness. From its inception, A.S.P.E.N. has been a multidisciplinary society and has emphasized the concept of NSTs. Subspecialty certifications in specialized nutrition support were developed for physicians, nurse specialists, pharmacists, and dietitians who cared for patients requiring specialized enteral nutrition (EN) and PN, which continue to exist in various formats. Such certified, multidisciplinary health professionals played key roles as co-investigators in clinical trials on the clinical and metabolic efficacy of EN and PN support. Of note, the U.S. National Institutes of Health (NIH) through the new Clinical and Translational Science Award (CTSA) program has recently emphasized the need to increase such multidisciplinary research teams in clinical research, a practice that has been routine in the clinical nutrition support research arena since the 1970s.

Several developments in the 1990s changed the tempo of this dynamic field. First and foremost, the environment over the past 20 years has become steadily more and foremost, the environment over the past 20 years has become steadily more adverse. Changes in payment by insurance companies and government began to put extreme cost constraints on hospital finances. This often resulted in limited financial support for NSTs, particularly the physician and nurse specialist members. As concern for the nutrition status of patients spread to other specialties, such physicians as critical care physicians, trauma/burn surgeons, gastroenterologists, endocrinologists, and nephrologists often took responsibility for nutrition support, with a focus on patients in their area of expertise. This has increasingly replaced the model of an internist or general surgeon with special skills and interest in specialized nutrition support playing the key MD-nutritionist role across the specialties and serving as a key academic role model in this area. Finally, enthusiasm for PN waned. In the 1980s and early 1990s numerous randomized clinical trials (RCTs), testing PN yielded unexpected and disappointing results PN could not reverse cancer-induced cachexia, and its use in the perioperative period was found to be associated with increased infections.^{5–7} The alternative was to use EN, which were shown by RCTs to be consistently more effective than PN.^{8,9} Research efforts related to PN largely disappeared except for small descriptive studies. RCTs related to optimizing EN continued through the 1990s, but there was a paradigm shift. In the 1980s, the goal of nutrition support was to place the patient in early positive caloric and nitrogen balance with PN and thereby prevent stress-induced acute protein malnutrition. In the early 1990s, based on ongoing studies from recognized experts, new immune-enhancing diets (IEDs) were being developed and introduced into clinical practice.^{10–12} These special enteral formulas were to be started early (within 24–48 hours) and delivered at modest dosing (14–8 kcal/kg/d) and for a limited duration (7–10 days). The clinical goals were to deliver low-dose EN to maintain vital gut functions while minimizing gastrointestinal (GI) intolerance and to favorably modulate the immune response with a variety of nutraceutical supplements including arginine, glutamine, ω -3 fatty acids, and nucleotides. Because these IED formulas are considered to be foods (not drugs), the clinical trials testing them were neither scrutinized by the U.S. Food and Drug Administration (FDA) nor adequately funded by industry. As a result, the overall quality of trials was suboptimal for reasons such as inappropriate blinding strategies, varying inclusion/exclusion criteria, small study group sizes, and lack of an intent-to-treat design. Meta-analysis became a popular tool to combine these studies to get adequate statistical power and consistently showed that IEDs reduced nosocomial infections and length of hospital stays.^{13–15} However, given the low quality of the individual studies, conclusions of the meta-analyses were easily challenged by naysayers. By the early 2000s, funding from industry began to disappear. The annual meeting of A.S.P.E.N. became less research oriented, physician involvement notably dwindled, and the meeting's primary focus has largely shifted to ongoing education of dietician and pharmacy members.

Although multidisciplinary education has always been a strong core value of A.S.P.E.N., physician involvement in nutrition research is necessary to advance the field. Our clinical decision-making and evidence-based guidelines are largely based on outdated information.^{16–18} Although we are improving the quantity and quality of nutrition trials, we badly need high-quality phase 2 RCTs testing a number of fundamental questions related to nutrition interventions, including optimal route, timing, and dosing of macro- and micronutrients.^{19–22} Additionally, a network of physician-led multidisciplinary research teams are needed to rapidly perform adequately powered phase III prospective RCTs. If the field of clinical nutrition in hospitalized patients is to be advanced, the number of appropriately trained physicians leading or participating in nutrition research needs to increase substantially. For A.S.P.E.N. to achieve this goal and remain a vibrant organization, it needs to collaborate with other interested professional organizations to (a) develop strategies to increase federal, foundation, and industry funding of high-quality nutrition research; (b) foster training in clinical and research nutrition; and (c) entice nutrition researchers, including more physicians, to participate in the annual meeting. The purpose of this article is to review options to achieve these strategies.

Increase Funding of Nutrition Research

Facilitate Clinical Trials

Extramural funding avenues are available (<http://www.nutrition.org/education-and-professional-development/funding-opportunities/>), but academic physician-scientists interested in hospital-based nutrition are few and are not successfully competing for those funding opportunities. Our nutrition community is in dire need of high-quality research concerning optimal clinical nutrition support for hospitalized patients. As described above, the quality of data upon which we base clinical decisions is poor, and definitive RCTs are badly needed.^{19–22} NIH appears interested in funding high-quality clinical trials and is currently funding several RCTs related to nutrition support in critically ill patients. Critically ill patients appear to be the appropriate cohort to study because it is well accepted that they are at high risk for developing healthcare-associated (ie, iatrogenic) malnutrition and associated complications including nosocomial infections, poor wound healing, prolonged ICU stays, late deaths, and prolonged rehabilitation.²³ Furthermore, evidence shows that attempts to improve the amount of nutrition provided to critically ill patients can improve their outcomes.²⁴ Yet current international audits consistently document substandard performance in North American hospitals.²⁵ The available data support early EN (within 24–48 hours),^{16–18} yet this does not seem realistic for many patients in many ICUs worldwide. However, a combination of early PN and EN could provide more nutrition earlier in many critically ill patients and may be an important strategy to reduce the caloric and nitrogen debt experienced by critically ill patients.²⁶ In the negative RCTs related to PN in the 1980s, patients were given excessive calories with PN, a practice which we now know increases infectious morbidity. In the modern era of nutrition support practice, it is reasonable to hypothesize that earlier positive caloric and nitrogen balance using combined PN and EN combined with intensive insulin therapy would improve outcomes compared with the present standard of early underfeeding with EN. Designing and completing a definitive RCT to test this hypothesis or other relevant hypotheses could have a tremendous impact on changing care and generating more funding opportunities of research in clinical nutrition of hospitalized patients. There are several ways this could be done. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) supports investigator-initiated, multicenter clinical studies through a 2-part process. Part 1 is an implementation planning (U34) grant. The U34 planning grant is designed to (1) permit early peer review of the rationale for the proposed clinical study, (2) permit assessment of the design/protocol of the proposed study, (3) provide support for the development of a complete study protocol and associated documents including a manual of operations, and (4)

support the development of other essential elements required for the conduct of a clinical study. Part 2 is a U01 grant. NIDDK considers applications from U34 awardees only and provides the funding to complete patient enrollment over a 5-year period. The funding permits studies that can be done at 3 or 4 sites. Another approach is to develop a more comprehensive research network of expert physician nutrition scientists with more sites that could complete RCTs over a shorter time period. NIH appears to be interested in helping to fund these research networks to perform high-quality clinical prospective RCTs. Three notable examples are the Transplantation Research Consortium, the ARDS (Acute Respiratory Distress Syndrome) Clinical Network, and the Resuscitation Outcomes Consortium (ROC). With either approach, A.S.P.E.N., in collaboration with other professional organizations, could organize meetings with the NIH and other funding agencies to help identify appropriate study questions, prioritize the most important to be tested, and identify the centers that can (a) provide high-quality nutrition care, (b) enroll a high volume of potential study patients, and (c) provide appropriate research infrastructure to conduct the study. This is how ROC was developed and is the origin of the Resuscitation Science Symposium, which is now held just prior to the American Heart Association annual meeting. This year >1000 researchers from around the world meet for 2 days to discuss cutting-edge research developments in cardiopulmonary and trauma resuscitation.

Develop Centers of Excellence

A.S.P.E.N. and other organizations have developed evidence-based clinical practice guidelines (CPGs) to be used in developing optimal processes of care and performance improvement (PI) programs to identify best practices. A.S.P.E.N. could make prevention of hospital-associated malnutrition a key quality issue with the payers of healthcare and external organizations that monitor healthcare quality. A.S.P.E.N. could partner with other nutrition professional organizations to develop the indicators of quality of care consistent with published CPGs. Processes of care could be implemented by NSTs or existing multidisciplinary ICU teams to meet these standards, and A.S.P.E.N. could serve as professional group to identify and certify “centers of excellence” that provide high-quality nutrition care.²⁷ This strategy has proven to be quite effective in the trauma community over the past 30 years: the Committee of Trauma of the American College of Surgeons developed and serially amended the standards for trauma center designation and conducts the verification site visits by which trauma centers are designated. More recently, the same approach has been used by bariatric surgeons to develop bariatric centers of excellence. This approach can be quite effective in leveraging hospitals to provide the appropriate resources to ensure high-quality care. Quality of care implementation research could become a focus of our annual meeting and an area of ongoing research on how we can best translate new knowledge into the routine bedside care. The Agency for Healthcare Research and Quality (AHRQ) and Canadian Institutes of Health Research (CIHR) might fund this program.

Foster Young Physician Training in Nutrition and Research

Create Mentoring Programs

The first challenge is to spark interest in nutrition in medical students and young physicians. This can be done by expanding or creating new mentoring programs. Following are some examples.

Nestlé Nutrition Institute Enteral Nutrition Fellowship—This program was developed for medical or surgical subspecialty fellows to foster knowledge, experience, and enthusiasm for EN therapy in the care of acute and chronically ill patients. With the specialized education provided through the fellowship program, participants have the opportunity to advance both their clinical and professional development under the

mentorship of recognized leaders in nutrition therapy. Fellows develop specialized nutrition skills and knowledge through both didactic and clinical experiences. Participants receive training in general nutrition principles as well as factors specific to the nutrition management of the stressed and critically ill patient. In a 4-week clinical rotation hosted by program faculty, participants spend 2 weeks on site with each of 2 faculty members. This one-on-one mentoring opportunity provides intense immersion into the science and practice of specialized nutrition support. The fellows work with their faculty mentors to select a primary nutrition topic that will be developed into a clinical review paper and submitted for publication. The fellows are, also eligible to attend and participate in the A.S.P.E.N. Clinical Nutrition Week (January 2011, Vancouver, Canada). Opportunities will be available to participate in an international nutrition congress such as the Nestlé Clinical Nutrition Course or the European Society for Parenteral and Enteral Nutrition.

American Society of Nutrition (ASN) Clinical Nutrition Internship Program—

ASN offers nutrition internships for medical students via its Clinical Nutrition Internship Program. This program is designed to increase the role of nutrition in the practice of medicine, medical research, health promotion, and disease prevention by providing a unique combination of educational experiences to medical students. Each selected student works under a recognized authority in clinical nutrition in a U.S. medical school or hospital. All are members of ASN. The internships last 8 weeks and usually are scheduled in the summer, but other times can be arranged. The students are exposed to both clinical and academic aspects of nutrition. Each student receives a \$2500 stipend for the 8-week internship. Interns must (a) visit at least 1 nutrition clinic (ie, outpatient, eating disorders, obesity, pediatric nutrition clinics) each week; (b) participate in at least 8 nutrition support rounds; (c) attend at least 1 research conference each week (ie, lab meeting, research seminar, or journal club meeting), followed by discussion between mentor and student; (d) spend half a day with a dietitian on 4 or more occasions; (e) write a 3- to 5-page research paper on a clinical or research nutrition topic of the student's choice, to be completed and presented to the mentor at the end of the 8-week program and also sent to the ASN office; and (f) complete an evaluation form at the end of the internship and mail it to the ASN office.

Develop Nutrition Research Centers

The second challenge is to train interested young physicians to conduct high-quality research, and this can be accomplished by fostering the development of nutrition research centers (NRCs) that are capable of performing high-quality translational research. These can serve as training sites for the next generation of clinical nutrition scientists who will be capable of successfully competing for extramural funding. The first step in developing NRCs is to identify nutrition researchers who have R01 grants and set up a meeting at which these researchers are educated by senior A.S.P.E.N. members on the concept of NRCs and how to fund them. We could identify young physicians who have the drive and talent to obtain an R01 grant and mentor/fund them so that they can obtain preliminary data for starter grants (K01, K08, and K-23) as a step in the process of obtaining an R01 grant. Examples of successful NRCs should be described. The following are several examples.

Training Program at the New England Deaconess Hospital and now the Beth Israel Deaconess Medical Center—

This program can be used to illustrate certain aspects of a successful program. For 30 years beginning in 1976, 3–5 fellows per year from medicine, surgery, and several subspecialties, particularly gastroenterology, endocrinology, and critical care, would spend from 6 to 12 months learning the basics of PN and EN in critical care and surgery. Fellows usually completed 2–3 years of surgical training, completed all of their internal medicine training, or went on to further subspecialty training subsequent to their nutrition training. Each fellow was expected to complete a clinical

research project under the direction of the 2 co-directors, a surgeon, and a critical care internist. These fellows were paid via hospital funds, industrial research funds, or NIH training grants. Other fellows would spend 2 years with a greater research component through training grants or NIH R01 support. This will be the stumbling block in attempts to reproduce this kind of program, because hospital funds and NIH training and individual grant support are now more difficult to obtain. We may be able to find other sources of financial support, such as funds from a department of surgery or medicine to establish a nutrition support service containing all these elements of improved clinical care and training surgical, gastroenterology, endocrinology, and critical care residents in nutrition support. Certainly a number of hospital centers that recognize the importance of nutrition in improving clinical care already provide some level of support. Here is where the need for definitive clinical trials demonstrating the effectiveness of PN and EN in improving hospital morbidity and mortality becomes most pressing, for with this evidence, financial support in academic medical centers for nutrition training programs and nutrition support services would likely be forthcoming.

National Institute of General Medical Sciences (NIGMS) Trauma Research

Center—NIGMS earmarks money to fund trauma research centers (TRCs) as P-50 program project grants, and critical care nutrition would be an appropriate topic. Each TRC receives roughly \$10,000,000 over 5 years. Generally there are 4–5 basic laboratory projects that are focused on a specific research theme with several cores (eg, administrative, molecular, and clinical) and a mandate to perform translational research. There are currently 8 NIGMS-sponsored TRCs. Once these TRCs are established, complementary T-32 training grants can be pursued to fund training for fellows to conduct high-quality research. Additionally, young faculty work in the TRC laboratories/clinical core to obtain preliminary data necessary to successfully compete for KO-8/R23 grants.

NIDDK Nutrition Obesity Research Center (NORCs)—NORCs are funded as P30 grants, and their objective is to bring together basic science and clinical investigators from relevant disciplines to enhance and extend the effectiveness of research related to nutrition sciences, obesity, and related disorders, with clinical and/or translational applications in these areas. The NORCs are based on the core concept. Four to 6 cores are usually included in a center. Cores are defined as shared resources that enhance productivity or in other ways benefit a group of investigators working in nutrition sciences and obesity and related disorders research to accomplish the stated goals of the center. Examples of such resources include biostatistics, imaging, biotechnology, and instrumentation facilities. It is appropriate and may be beneficial to have 1 or more central themes around which core center research investigations are focused. Centers are encouraged to include a clinical component or core that deals with patients. This clinical component can exist as a stand-alone core or part of another core such as the administrative core. Besides leading to a better understanding of disease etiology and natural history of disease, such cores might provide biostatistical support, enhance clinical study design, enhance collaboration among researchers and recruitment of subjects for clinical studies, support epidemiological studies, or provide modest funding for tissue, DNA, or serum storage. A clinical or epidemiology core may more effectively address NIH policies concerning participation of children, women, and ethnic minorities in clinical studies. Two other types of activities should be supported with center funding: a pilot and feasibility (P/F) program and an enrichment program. The P/F program provides modest support for new initiatives or feasibility research studies. This program is directed at new investigators, at investigators established in other research disciplines with expertise that may be applied to obesity or nutrition sciences research, and at established investigators who wish to substantially change the direction of their nutrition sciences or obesity research. It is expected that the majority of P/F project investigators will

fall into the first category, and only in exceptional circumstances will investigators in the third category be supported. Temporary salary support for 1 “named new investigator” in a specified area of research with a defined P/F study may be requested for up to 24 months, with subsequent individuals to be named by the center director and approved by the center’s external advisory board and the NIDDK. The core center grant may include limited funds for program enrichment such as seminars, visiting scientists, consultants, and workshops.

Expand the A.S.P.E.N. Rhoads Research Foundation

Expansion of the A.S.P.E.N. Rhoads Research Foundation is in progress. The hope is to expand the foundation’s resources from \$1 million to \$3 million. This would make it possible to give more substantial research awards and/or partner with the NIH to provide matching funds for K08, K23, or equivalent grants. Vascular and trauma research communities have successfully conducted matching fund programs in recent years. The NIH has an annual meeting in which K08/R23 grant awardees visit NIH for a 2-day symposium to learn about the NIH and how to write a successful grant. The NIH will invite A.S.P.E.N. Rhoads Foundation grant awardees to this meeting if A.S.P.E.N. pays the travel expenses.

Develop an Annual Clinical and Translational Research Course

Collaborate with other organizations to develop a 1-day course that teaches the basics of nutrition-oriented research. For example, the Association of Academic Surgery offers a course on basic research that is held each fall just prior to the annual meeting of the American College of Surgeons, and new laboratory fellows are encouraged to attend. We would not duplicate that course but could focus more on translational research and clinical trials.

Attract Nutrition Researchers to the Annual Meeting

Restructure How the Annual Program Is Developed

The annual meeting needs to be viewed as the core product of A.S.P.E.N. If we produce a good meeting, people will want to attend the meeting, join the organization, read our journals, and become actively engaged in organizational activities. We propose that the process of creating the annual program be restructured. More up-front work should be done to ensure a well-balanced and exciting meeting. In September and October the program committee would work with the president to identify key topics that should be presented at our annual meeting. These topics would be reviewed by the A.S.P.E.N. Board in November. These would be listed as “topics of interest” in the December mailing requesting proposals for planning the meeting for the following year. The program committee members would then reach out to individuals who are the “best athletes” in these topics and encourage them to submit proposals for these topics of interest. “Best athletes” are those who are recognized to be experts in their field and who are capable of preparing and delivering enticing presentations. At the April meeting, the program committee would review submissions and discuss how to best round out the meeting and to identify more such experts. The monitoring committee would monitor the sessions at the annual meeting to identify speakers and topics that were effective and those that were not. As the process matures, recurring topics of interest will be identified and a curriculum will be developed that will rotate these topics over a 3-year cycle; “best athletes” will be brought back if they continue to be thought leaders in their respective fields, and we will encourage them to join the organization.

Attracting experts in various topic areas will require more financial support, because some of these individuals may not be A.S.P.E.N. members and we need to provide more financial support for them to attend our meeting. Industry is the obvious source. Industry spends a lot of money on speakers bureaus to fund educational programs that promote knowledge of

their products. Unfortunately, faculties at major universities are experiencing increasing scrutiny concerning their relationship with industry, and participation in speakers bureaus will not be allowed in the near future. Industry knows this and is beginning to use commercial continuing medical education organizations to run independent symposiums. Professional organizations such as A.S.P.E.N. need to seize this opportunity. We are in a much better position to provide these educational programs. Not only do we have more credibility, but we can provide large numbers of active clinicians who will participate in these sessions. The program committee needs to work with the president to plan symposiums that the president can present to industry leaders with a funding request; industry leaders can provide even more support by creating symposiums that are valuable to their mission. These funds, or at least some that involve the more basic science, could be administered by the A.S.P.E.N. Rhoads Research Foundation with the idea funding a certain type of educational activity.

Another strategy is to have a late-breaking session that focuses on clinical research. Time should be reserved during the annual meeting that will not be filled with topics and speakers until fall prior to the meeting. The program committee will “scan the horizon” over the summer to find the important clinical research that will be published in the near future and arrange for the responsible researchers to present their findings at this special session. We could get an ongoing dedicated educational grant from industry to fund this session. A \$5000–\$10,000 educational grant would fund 3 respected researchers to attend each year to give three 25-minute talks. This could be announced in the fall to promote the upcoming annual meeting.

Attract Research Community

We must continue the NIH-sponsored research meeting held prior to the annual meeting and focus on basic and translational research related to a specific area that will attract high-quality researchers to our annual meeting. The schedule of the annual meeting should have a research or disease-specific track that would encourage participants in the research meeting to stay for the annual meeting.

Highlight Young Investigators

A.S.P.E.N. needs to highlight young investigators at the annual meeting. This can be done through a variety of mechanisms. Travel awards have been very successful for the Shock Society. Top-ranking young investigator abstracts are identified by the abstract review committee, and several young investigators are awarded a small stipend (eg, \$500) to partially defray travel expenses. These individuals would be introduced at the plenary session and their abstract presentations highlighted in the program. Travel awards can also be cited in their CVs. Additionally, research abstracts should be published in a *JPEN* supplement. Hard copies of abstracts should be available at the annual meeting so attendees can review the abstracts and decide which presentations to attend. Top abstracts should receive a citation (eg, “Abstract of Distinction”). These would be presented at the Young Investigator Session, during appropriate symposiums, or in a special poster session moderated by senior members of A.S.P.E.N. A well-moderated and advertised research poster session is a good way for young investigators to get exposure and interact with the more senior and accomplished researchers at no cost. Finally, the young investigators session and the breakfast awards should be continued and possibly expanded to enhance networking opportunities.

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