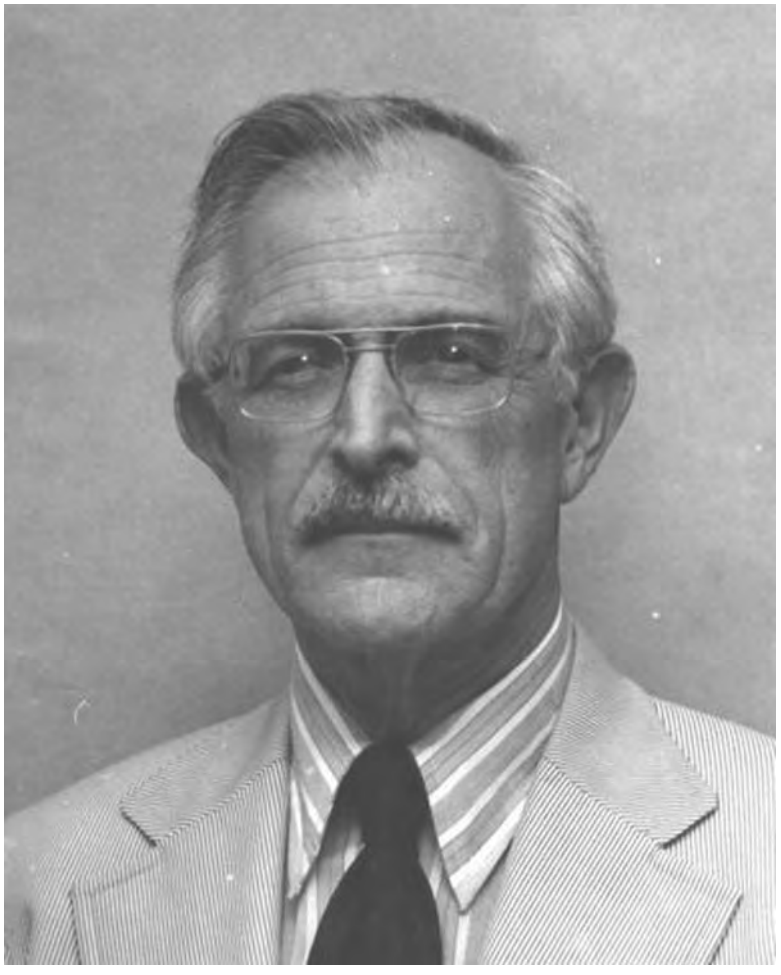

Maurice E. Shils

The Advent of Home Parenteral Nutrition Support

Maurice E. Shils

Professor Emeritus of Medicine, Cornell University Medical College, Attending Physician and Director of Clinical Nutrition (Retired), Memorial Sloan-Kettering Cancer Center, New York, New York 10065; email: mshils@triad.rr.com

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Abstract

I review here some key developments of personal and professional interest, with special reference to total parenteral nutrition (TPN), an area in which I have been involved from 1937 until recently. As a result of basic and biomedical science advances achieved in university and industrial laboratories in numerous countries, many essential nutrients were identified, synthesized, produced, and provided to patients in safe and effective forms both enterally and parenterally. This period also saw important developments in analytic instrumentation. I have had the privilege of seeing major advances in nutrition during my lifetime, and it is my belief and my hope for the future that with the advent of bowel transplants and tissue growth from cells, TPN will be a temporary measure rather than a lifetime regimen.

Contents

PREFATORY NOTE

The purpose of this article is to present my recollections of the history and advances made in the field of nutrition during my lifetime. I was privileged to have worked with many outstanding scientists, both as a student and as a physician. The discovery of vitamins, minerals, macronutrients, and micronutrients, and the determination of nutrient requirements through the studies of others, led to better nutrition for all and extended the lives of many who have relied on enteral or parenteral nutrition. This experience, as well as my affiliation with the New York Academy of Medicine, made my career as a biochemist and physician very meaningful and satisfying.

IDENTIFICATION AND PRODUCTION OF MICRONUTRIENTS

I was very interested in the observations recorded by doctoral candidate N. Lunin, a student of von Bunge, in his experiments in 1882, that "mice can live as well . . . when receiving suitable foods (e.g., milk) but since they cannot subsist on proteins, fats, carbohydrates, salts and water, it follows that other substances indispensable for nutrition must be present in milk besides casein, fat, lactose and salts" (15). The search for these essential substances first produced supporting evidence for this view in 1907, with the identification of the existence of an antiscorbutic factor by Axel Holst and Theodor Frolich, and in 1913, the identification of fat-soluble vitamin A by Elmer V. McCollum and Marguerite Davis. Dr. McCollum was involved in research in nutrition and eventually became professor and chairman of the Biochemistry Department at the School of Hygiene and Public Health at the Johns Hopkins University. In fact, my interest in nutrition began when I was in high school and read a chapter in Paul de Kruif's 1928 book, *Hunger Fighters*, which described the achievements of a Kansas farm boy, E. V. McCollum.

At the time that I was finishing high school, the country was in the Great Depression, and it was uncertain if I would be able to attend college. Times were so bad that, as treasurer of my high school class, I doubted that we could have our prom because all except one of the banks in town had closed. Thanks to the generosity of our high school principal, we were able to have the prom.

One day, one of my teachers informed me that someone representing the Johns Hopkins University wanted to see me. This resulted in my receiving a scholarship at Johns Hopkins and was the beginning of my long and pleasant career in nutrition and medicine.

I became one of Dr. McCollum's graduate students in one of the most interesting periods of advances in experimental nutrition: the isolation, structural identification, and

synthesis of vitamins A, E, and K, ascorbic acid, biotin, riboflavin, vitamin B_6, pantothenate, and nicotinic acid (niacin). During this period, the discovery that thiamin, riboflavin, and nicotinic acid existed in phosphorylated form as coenzymes for key enzymes in intermediary metabolism provided the biochemical evidence for their essentiality. Vitamin K, thiamin, riboflavin, niacin, and ascorbic acid in synthetic forms were being used therapeutically in the early 1940s (27). Folate was isolated in 1943 and synthesized in 1945; vitamin B_{12} was isolated in 1948.

The essential roles for magnesium and the trace elements copper, zinc, and manganese had been demonstrated in acute and chronic depletion studies in laboratory animals in the late 1920s and early 1930s (25). The needs for the trace elements, iron, and iodide were already well established. In a relatively brief period, basic experimental diets changed from those utilizing crystalline vitamins to those meeting total individual needs, including highly purified macronutrients and micronutrients.

I earned my degree of Doctor of Science in biochemistry in 1940 in Dr. McCollum's department and became a junior faculty member in the department. There, my interests were directed to small animal research, primarily on the effects of thiamin and manganese and trace element deficiencies, but I also became involved in human nutrition. Between 1938 and 1942, I attended various medical school grand rounds with some of my medical student friends and became aware of clinical interest and studies in fluid, electrolytes, and acid-base balance as well as the use of intravenous glucose and some electrolytes in the treatment of acidosis and dehydration in diarrheal states (8) and in connection with ongoing studies on adrenocorticoids.

STIMULUS OF WORLD WAR II TO CLINICAL NUTRITION RESEARCH

When the United States entered World War II, I spent nearly five years as a civilian scientist with the Army. During the time that I was in Washington, D.C., I was involved in a new unit in the Military Planning Division of the Quartermaster General that helped develop more palatable, safe, and nutritionally adequate food, including new combat rations. With troops involved in stressful, prolonged mobile combat, a major concern became the ration supply, stability, nutritive value, and acceptability in varying climatic circumstances in distant places. Multiple biomedical problems led to intensive research on the physiologic, nutritional, and therapeutic needs of soldiers. The work of Cuthbertson (4) in 1932 had indicated that traumas such as bone fractures increased nitrogen and mineral losses. This work was expanded by others in the fields of endocrinology and biochemistry. Numerous studies were conducted on energy and nutrient modifications and needs induced by work, stress, trauma, infection, and partial starvation, including testing and short-term use of parenteral nutrition in patients who were unable to eat (6, 14). The military studies were supported by the expertise and equipment at our biochemical laboratory in Chicago, with consultants from industry and academia in food technology and basic medical sciences. These studies led to more specific information on energy and other nutrient requirements under differing conditions.

For a period after the war, the military and various private foundations (the National Institutes of Health did not yet exist) contributed to the advancement of clinical nutrition research by assisting bioscientists returning to academic institutions. This also was a period of important advances in analytic instrumentation, such as micromethods for measuring blood constituents, ion-specific electrodes, the flame photometer, and precise colorimetric and other analytic methods including (eventually) automation, which replaced the laborious gravimetric and titrimetric methods. Knowledge of intermediary metabolism was markedly accelerated by the major contributions of Schoenheimer (16) in the use of stable isotopes to mark and follow organic compounds. Other major analytic advances were increasingly sophisticated: chromatography, electrophoresis,

and the radioimmunoassay technique (30). Kinney's computerized closed canopy for assessing the respiratory exchange and energy expenditure of ill patients (2, 12) and the Beckman metabolic measurement cart and its successors (2) would play an important role in providing bedside data on the energy requirements of patients needing nutrition support.

At one point, I received a request from Robert Goodhart, MD, who was technical advisor of the nutrition division of the Office of Defense Health and Welfare Services, to conduct a survey of the nutritional adequacy and quality of food served to industrial workers in the cafeterias of factories engaged in the production of military equipment. I spent a few months traveling around the country, interviewing food service department heads, and was pleased to find that serious attention was being paid to meet the nutritional needs of employees of all three shifts.

Near the end of the war, Dr. Goodhart contacted me and inquired if I would be interested in a faculty position in the School of Public Health at Columbia University. I learned that Dr. Goodhart was to be in charge of a new granting institution that was interested in enticing scientists into the fields of both teaching and research in clinical nutrition. This resulted in my becoming a member of the Columbia University faculty in the new Department of Industrial Medicine.

COLUMBIA UNIVERSITY SCHOOL OF PUBLIC HEALTH

When I joined the faculty at the Columbia University School of Public Health, I had to move to the New York area from outside Washington, D.C. Rather than live in the city, I elected to live in Shanks Village with my wife and two small children in government-constructed buildings with other postwar scientists and physicians who were returning from service. I and other new residents converted this area into a small town, established food stores and shops, and brought in doctors and dentists for our community. Schools for the children were located nearby. This was an experience that my children remember well. The scientists, physicians, and graduate students, including me, commuted daily into the city for work and/or additional education.

At the Columbia University School of Public Health, I had the opportunity to teach aspects of nutrition to physicians on their return from military life, as they entered the field of public health. I obtained funding from various groups to do nutrition research in experimental animals and organized a laboratory in the school for nutritional studies, including the toxic effects of various drugs on the nutritional status of small animals. During this time, it pleased me that one of my laboratory technicians became so interested in research that she obtained her PhD and became a professor. In the last two years I spent at Columbia, I became interested in the effect of nutrients, or the lack thereof, on the development of fatty livers. My interest in these studies was stimulated by reports of fatty livers developing in South African humans in the disease known as kwashiorkor. My studies with rats with fatty livers indicated that the cause of fatty livers was the lack of certain amino acids. I was also involved in establishing a clinical nutrition laboratory for major public nutrition clinics in New York City. It was at this time that I again met Dr. Goodhart, who was a very important person in my life. Dr. Goodhart and Dr. Michael Wohl recognized the need for a major textbook in clinical nutrition, and I was invited to contribute to the textbook *Modern Nutrition in Health and Disease*. In 1950, I became an editor of the textbook and eventually became the senior editor. The tenth edition (and fiftieth anniversary edition) was published in 2005.

I was later offered research support by a funding organization that was interested in having nutritionists enter the field of medicine. I applied to New York University for a faculty position because I was aware of some of the faculty's interest in human nutrition.

MEMORIAL SLOAN-KETTERING CANCER CENTER

In 1958, I earned my MD from New York University, and with some uncertainty as to my future activities, I entered a medical internship that was organized by a combination of the Cornell University Division at Bellevue Hospital and of Memorial Hospital. As I listened to my fellow interns from various medical schools discussing their future plans in a variety of established practices, I realized that this was not what I wanted. Accordingly, I approached the professor from Cornell who was in charge of the internship and discussed with him my desire to proceed to a medical school or hospital where I could do research, teach, and administer clinical care in nutrition areas. As I look back now, I realize how fortunate I was in choosing this professor.

He listened carefully, agreed that I had a valid concern, and arranged for me to speak to the Chief of Medicine at Memorial Hospital in New York, where there were opportunities to participate in research in various areas as well as in clinical practice.

I was well aware of the functions and organization that combined Memorial Hospital and the Sloan-Kettering Cancer Center since I had spent some weeks as a New York University student in several of their teaching programs and clinics.

It was clear at my meeting with the Memorial professor that he had been well briefed on my background because he quickly suggested that if I were willing to enter and successfully serve in a three-month internship on the newly developed chemotherapy service, then I would be invited to join, as a new member, the physiology service, which was composed of medical and surgical doctors who were involved in overseeing patients with significant metabolic problems. I agreed and transferred to Memorial Hospital. After a short period on the chemotherapy service, I was made the head of a special laboratory and trained the staff to analyze nutrients in food, blood, and urine of patients after the existing chief was promoted to head of the hospital laboratory.

INCREASED INTEREST IN PARENTERAL NUTRITION

I was aware that Robert Elman, a pioneer in parenteral nutrition, had repeated as late as 1947 his belief that parenteral nutrition was only for short-term use (6). However, advances in nutritional knowledge, medicine, and surgery, along with the availability of antibacterial and then bacteriostatic drugs and safe blood transfusions, improved survival time for patients with extensive burns, trauma, and radical intestinal transections. These situations increased the number of patients who required long-term nutritionally complete intravenous feedings in order to maintain life.

During the postwar period, glucose was depended on as the primary energy source for parenteral nutrition; however, a major difficulty was patients' rapid development of phlebitis and thrombosis of peripheral veins, which often occurred with infusion in glucose concentrations of 10% or more. This led to the acceptance in the United States of a sterile stable lipid emulsion, Lipomul IV (Upjohn, Kalamazoo, MI), consisting of cottonseed oil, 4% glucose, egg phosphatides, and a synthetic emulsifier. Providing 1500 Kcal/L (equivalent to a glucose concentration of about 45%) did not damage peripheral vessels; it was oxidized in vivo and allowed nitrogen retention and weight gain when given with other nutrients to laboratory animals and human subjects (3). Because of early and late infusion-related side reactions, Upjohn recommended restricted use of Lipomul IV in the early 1960s (19) and shortly thereafter discontinued production.

It was obvious from the patients that I had seen during my chemotherapy service that serious malnutrition commonly resulted from cancer and from the its various treatments. Some patients had to be fed enterally and others parenterally.

Without a suitable lipid source in the United States, long-term parenteral nutrition by peripheral vein was problematic. For critically ill patients, I (and presumably others) adopted the procedure of slow direct infusion of solutions containing hypertonic glucose solutions

into small-bore tubing threaded from peripheral veins directly into the vena cava. This technique was associated with problems in maintaining patency of veins and infusion tubes and with infections.

ADVANCES IN LIPID EMULSIONS

O. Schuberth and A. Wretlind in Sweden had by 1961 succeeded in developing an intravenous fat emulsion, Intralipid, consisting of soybean oil, egg phosphatides, and glycerol (17). This proved to be well tolerated with prolonged use. With this emulsion or others produced in Germany and France and with various carbohydrates and essential nutrients, total parenteral nutrition by peripheral vein was successfully used in Europe (17).

Although Intralipid was not approved by the Food and Drug Administration (FDA) for use in the United States until 1977, it became available in about 1974 for experimental purposes in a number of U.S. research hospitals, thus meeting an urgent need for nonglucose calories and essential fatty acids. It was composed of soybean-based emulsions of 10%, 20%, and 30% fat, with their contents of essential fatty acids, phosphorus, and vitamins E and K (24). Admixtures of lipid with amino acids, glucose, and other nutrients (total nutrient admixture or triple mix) proved stable with proper ionic concentrations (24). Newer intravenous lipids have been developed with medium-chain triglycerides or mixtures of medium-chain and long-chain fats that may be more effective nutritionally and metabolically than are vegetable oil emulsions (24).

ADVANCES IN AMINO ACID FORMULATIONS

Hydrolysates of casein and of beef-blood fibrin were the primary sources of amino acids in parenteral nutrition into the early 1970s. Japanese successes in large-scale production of crystalline amino acids resulted in their becoming commercially available in the United States (14, 29). These crystalline amino acids proved superior to the hydrolysates in terms of better utilization of nitrogen, fewer side reactions, more adaptability to special needs, and very much less aluminum and other contaminants. These amino acid solutions have since been modified to better meet needs, e.g., with the addition of cysteine and taurine in pediatric formulations (10, 29) and the addition of nonessential amino acids such as glutamine.

IMPROVED FEEDING METHODS FOR CHILDREN AND ADULTS

The enteral tube feeding methods used were unpleasant because of the large tubes placed through the nose and the uncertain duration of administration. In addition, this was often done without knowledge of the actual dietary requirements for the individual patients. In the metabolic laboratory, we established methods for analyzing the patient's ability to absorb nutrients using the blood and urine levels of essential nutrients in order to determine the most beneficial formulas and the proper rate and duration of feedings.

The physiology team (see **Figure 1**) at Memorial Hospital was fortunate in obtaining the first hemodialysis unit in the New York City area, and as a member of the team I became aware of the very thin tubes used in dialysis. I found that these small tubes could be used for both enteral and parenteral feeding. As a result of the availability of these small, more comfortable tubes for patients and through work with the dietitians in our research kitchen, I developed nutritionally complete formulas that would go through the tubes. With very close nutritional monitoring of the patients, we were able to modify the formulas as often as every four to six hours as needed to meet the individual nutritional requirements of new patients.

Since no adequate intravenous vitamin or micromineral formulations were commercially available at that time, I obtained permission from the federal government to prepare our own. It also became apparent that a significant number of patients required weeks or months of enteral tube feeding.

Figure 1

The author's team. Includes physicians, nurses, dieticians, and pharmacists who worked with the clinical staff at the time as well as some former members and the research kitchen personnel.

The University of Pennsylvania surgical team reported on its successful long-term studies of parenteral nutrition support in dogs and later in adult and infant humans using catheters inserted percutaneously into the subclavian or jugular veins and then into the superior vena cave (5). When it was found that these catheters could easily and safely be placed into larger veins near the atrium, surgeons in the United States and elsewhere began to request parenteral feeding.

Our team demonstrated the success of long-term intravenous feeding when a young man with major intestinal resection with resultant malnutrition was admitted to our service from another hospital in the early 1960s. He was unable to absorb enteral tube formulas because of persistent infection of his remaining bowel, so we started him on total parenteral nutrition (TPN). The thin-bore sterile tube was inserted into either a peripheral vein or a subclavian vein, and by using an automatic pump, we were able, over a period of eight months, to give him a complete parenteral formula based on all minerals, micronutrients, vitamins, absorbable amino acids, essential fatty acids, and carbohydrates until his infections were finally controlled. TPN, between repeated intestinal surgical interventions, finally enabled him to absorb the necessary enteral nutrition formulas again.

The enthusiastic adoption of this support modality, although generally successful, was also accompanied by several sets of problems. One problem was related to the sizeable number of initiates—physicians, pharmacists, and nurses, with little or no experience in this area—who often applied the nutrition, physiologic, and patient-care aspects in a cookbook fashion to their patients. For example, when fibrin hydrolysate, which had been developed as a competitor of casein hydrolysate and had much less calcium, phosphorus, and zinc than did casein hydrolysate (21), was used as the amino acid source, failure to add adequate amounts of these nutrients to the formula in the presence of a large amount of glucose led in a matter of days to severe symptomatic hypophosphatemia (26, 28). Commercial intravenous trace-element solutions (other than iron and iodide) were not available; hence, unless plasma was added as a source of these elements or unless hospital personnel prepared sterile solutions of trace elements, the result was the occurrence of deficiencies. When fibrin hydrolysate was used, some deficiencies, especially zinc, occurred in weeks, particularly in previously malnourished individuals or those with intestinal or other losses (21). In the first days of parenteral infusions, especially in malnourished or traumatized patients, plasma levels of macronutrients (vitamin K, phosphorus, and magnesium) and microminerals could decline fairly rapidly if plasma levels were not carefully followed. Intravenous replacements had to be given to prevent these declines. Hospital personnel had to be advised that certain vitamins (e.g., retinol) could be absorbed on the surfaces of plastic tubes or bags or that thiamin and ascorbic acid were destroyed if allowed to stand overnight in a complete formula.

The approaches to these problems progressively improved with intensive education programs initiated within hospitals and pharmacies and by various journals and organizations.

Other problems were caused by the lack of adequate commercially available vitamin solutions for children and adults and of any essential trace-element solutions other than iron and iodide. The only available multivitamin preparation commercially available in the United States for intravenous use in the 1960s and most of the 1970s was MVI (USV Pharmaceutical) (21). This formulation was inadequate because it lacked folate, vitamins B_{12} and K, and biotin and had very high levels of vitamins A and D and thiamin. Some physicians and pharmacists injected or infused some or all of the missing vitamins available as individual solutions; unfortunately, others did not. Reports also appeared of excessive use of MVI, with the potential for toxicity by vitamins A and D and of deficiencies of certain vitamins (21).

Because no safe and adequate vitamin and mineral solutions were available in the United States, I recommended that the American

Medical Association (AMA) establish a committee composed of physicians and pharmacists knowledgeable in parenteral feeding. In 1975, I made suggestions to the committee for formulations, based on my work, and these became the basis for the committee's recommendations for the optimum adult and pediatric formulations. The Nutrition Advisory Group of the AMA defined the formulations, and on January 16, 1976, the 27-page guideline, titled *Multivitamin Preparation for Parenteral Use*, was transmitted to the director of the Bureau of Drugs of the FDA by the AMA executive vice-president. The FDA readily accepted this report and its recommendations without change. This enabled the adult and pediatric formulations to become the required ones for commercial production and these remained unchanged until the FDA made some minor modifications, which were accepted in 1978. The formulations then became the standard ones in the United States and were later produced commercially. The U.S. adult formulation was given to stable patients using TPN at home for long periods, and the blood levels of prothrombin and of 12 vitamins were found to be in acceptable ranges (23). The pediatric formulation was found to be adequate for full-term infants and children; however, modification of dosages was needed for premature and very-low-birth-weight infants (9, 10).

Later, the *Guidelines and Standards for Essential Trace Element Preparations for Parenteral Use*, proposed by our committee, was sent to the FDA. These guidelines were published in the *Journal of the American Medical Association* (*JAMA*) in 1979 (1). The formulations and suggested daily intravenous intakes for zinc, copper, chromium, and magnesium for pediatric and adult patients were proposed, and they were again accepted, with the exception of our request that each micromineral solution be made in a separate solution. The FDA permitted both individual and mixed-mineral solutions to be produced commercially. This resulted in some problems with nutrient overdoses or deficiencies in some patients. In any case, it was essential that the physician responsible for the patient insist that periodic nutrition evaluation of blood and urine be done. As TPN further developed, it was determined, for long-term use, that selenium and molybdenum should be added to children's formulations and selenium to adult formulas.

HOME PARENTERAL NUTRITION

The ability of long-term TPN to prolong life in those with severe chronic inability to absorb food adequately, but with no other persistent disease, led us to suggest hospital discharge of such patients to a home environment. Of course, proper training and support by hospital personnel were necessary to continue this lifesaving technique in a safe fashion. The first reported home-discharge case, in December 1969 (25), was accompanied by or followed by similar reports (13, 18). To accomplish this goal, it was necessary to have a multiprofessional clinical nutrition team able to perform each step of a complex program including patient selection and training in solution preparation and infusion and in catheter care. Another requirement was a close liaison between the patient at home and the nutrition team members (20).

Under my direction, the first Home Parenteral Nutrition (HPN) Registry for the United States and Canada was established at the New York Academy of Medicine between 1975 and 1983. The data from this registry were published in part by the Academy (11). On my retirement from the Academy, the Registry was transferred as a joint activity to the Oley Foundation and the American Society of Parenteral and Enteral Nutrition (ASPEN) and then solely to the Oley Foundation. It was later discontinued. ASPEN is now in the process of reinstituting an HPN Registry.

As always, advances in knowledge and therapies create new problems. Nutrition support does not cure nonnutritional diseases; thus, survival of HPN patients depends on the success of treatment of underlying disease. Some

Figure 2

The author, Maurice Shils, with his Sheltie, Berry.

problems encountered fairly early persist, including infection control, multifactorial bone disease, gallstones, and most worrisome, liver cirrhosis and failure, especially in those having major loss of intestines (24). The latter type of patient is now considered a candidate for intestinal transplant as indicated in a recent review in the *New England Journal of Medicine* (7). Increased knowledge of the molecular biology of disease may result in the ability to diminish or even avoid some of the consequences of the underlying diseases. It is my hope that with bowel transplants and the promise of growing tissue from cells that TPN will become a temporary rather than a permanent means of maintaining life.

THE NEW YORK ACADEMY OF MEDICINE

In addition to my interests in research and patient care, in 1976 I had the privilege of an additional career by becoming the executive secretary of the Committee on Public Health of the New York Academy of Medicine. It was there that I helped to develop the Subcommittee on Nutrition of the Committee on Public Health and the Section on Clinical Nutrition of the Academy and organized and served as principal investigator of the New York–New Jersey Regional Center for Clinical Nutrition Education. I was honored by and received a plaque from the Academy of Medicine in 1989, and more recently, a tribute in 2009.

THE PRESENT DAY

After the death of my first wife, I married Betty, who was the chief clinical dietitian at Wake Forest University Baptist Hospital in Winston-Salem. We elected to live in Winston-Salem, and I became an adjunct professor at the medical school until I retired from teaching. I continued to be the senior editor of *Modern Nutrition in Health and Disease* through the tenth edition, but now, at the age of 95, I am totally retired and am enjoying my wife, children, grandchildren, great-grandchildren, and last but not least, our special little Sheltie, Berry (**Figure 2**).

DISCLOSURE STATEMENT

The author is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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Errata

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