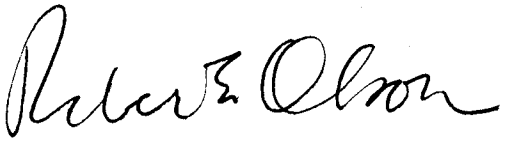

Annu. Rev. Nutr. 1996. 16:1–32

ON THE MAKING OF A CLINICAL NUTRITIONIST

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KEY WORDS: glutamate, vitamin K, ubiquinone, protein-calorie malnutrition, atherosclerosis

ABSTRACT

Clinical nutrition may be defined as the application of the principles of nutrition science and medical practice to the diagnosis, treatment, and prevention of human disease caused by the deficiency, excess, or metabolic imbalance of nutrients. At present, many physicans do not appreciate the great traditions established by their forebears in this field (Hippocrates, Lind, Eijkman, Glisson, Casal, Livingstone, Hopkins, and Goldberger). They have tended to avoid nutritional problems, plead ignorance of nutrition principles, and delegate the nutritional care of their patients to paramedical personnel. Only by changing this situation can members of the medical profession offer adequate care to their patients. In this chapter, I have attempted to present the duties and responsiblites of a clinical nutritionist in an academic environment. A well-trained academician in such a position can improve the education of medical students in nutrition, attract well-motivated graduates into nutrition training programs, and establish clinical nutrition as a bona fide subspecialty of medicine.

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0199-9885/96/0715-0001$08.00

Ah, but a man's reach should exceed his grasp,
Or what's a heaven for?
Robert Browning, 1855

Of the twenty-six *Annual Review*'s published yearly, eighteen currently publish prefatory chapters. These are generally autobiographical accounts of significant advances made in the authors' respective sciences. One of the first prefatory chapters appeared in the 1953 volume of the *Annual Review of Biochemistry* (which was founded in 1931) and featured Elmer McCollum's reminiscences of his experience as a student, teacher, and investigator of nutritional biochemistry (42).

During my tenure as Associate Editor and Editor of the *Annual Review of Nutrition*, I participated in the selection of authors for prefatory chapters. Over the past fifteen years, five of these chapters have been devoted to nutritional policy, two have addressed important global nutritional problems, and the remaining eight have been autobiographical accounts of investigations in nutritional science. I am honored to join the scientists in this group, although I must confess that I harbor some doubts as to my worthiness.

In the account that follows, I have tried to reconstruct the events that led me from physics to clinical nutrition, a career characterized by many serendipitous events, one that nonetheless has convinced me of the need for the continuing entry of physicians into the field of clinical nutrition. Not only does it provide exciting research opportunities, it is a field that I believe should be, and ultimately will be, a subspecialty of medicine.

PROLOGUE

My ancestors were Swedish farmers who lived in the provinces of Värmland and Småland. In the middle of the nineteenth century, my grandparents immigrated to the United States and settled in Minnesota, where my father, Ralph W. Olson, was born. As a high-school graduate, my father moved from his father's farm in Waverly to Minneapolis, to enter a carpet business, which was later affiliated with the Armstrong Company. My mother, née Minnie A. Holtin, was born in Minneapolis. Educated through business college, she became a secretary to Professor Storm at the College of Agriculture at the University of Minnesota. She met my father in Minneapolis and in 1917 they were married. In 1919, I was born and subsequently they had two additional sons: William G. in 1921 and James A. in 1924. William graduated from the

Minneapolis Art Institute and became a commercial artist. James, after attending college and graduate school, elected an academic career and currently is a Professor of Biochemistry at the State University of Iowa in Ames.

As a student in South High School in Minneapolis, I was intrigued by physics as it pertained to electricity and electronic devices. This led me to take up amateur radio as a hobby and I became a "ham" radio operator. During my senior year, I decided that pursuing electrical engineering at the University of Minnesota would be an exciting challenge. My father, however, insisted I consider Gustavus Adolphus College, a Lutheran School in St. Peter, Minnesota. After considerable argument, I yielded and applied for a scholarship at Gustavus, entering the college in the fall of 1935. In the absence of an electrical engineering program, I registered for courses in physics and chemistry and, to my delight, encountered an excellent teacher and amiable mentor in the person of Peter Skartvedt, who chaired the Chemistry Department. At the end of my freshman year I decided to major in chemistry, which turned out to be a pivotal decision.

In the middle of my junior year I discovered that I had earned enough credits to graduate in 1938, a year early. With the support of the Dean of the College and Professor Skartvedt, I applied to graduate schools for continuation of my studies in chemistry, which I hoped would lead to a PhD degree, and in the spring of 1938 was offered a fellowship in organic chemistry from Purdue University. About that same time, Professor Skartvedt came to me with a letter from a former graduate of Gustavus, Dr. Alrick Hertzman (AB 1919), who was then a Professor of Physiology at St. Louis University School of Medicine. He told Professor Skartvedt that Dr. Edward Doisy, Professor and Chairman of the Department of Biochemistry at St. Louis University School of Medicine, was interested in recruiting graduate students in biochemistry and wanted suggestions from him. Skartvedt told me he had a high regard for Hertzman and knew about Doisy as a leading investigator of steroid hormones. He thought my going to St. Louis would be a good idea. I didn't know much about biochemistry at that time, but I knew it involved the study of the metabolism of organic compounds. I applied and was granted a fellowship of $450.00 per year, slightly more than I was offered by Purdue. After graduation from Gustavus in the spring of 1938, I decided to become a biochemist.

GRADUATE STUDY AT ST. LOUIS UNIVERSITY

I met Professor Doisy the day after I arrived in St. Louis, a hot day early in September, 1938. Doisy, who had studied chemistry at the University of Illinois and biochemistry at the Harvard Medical School, under the tutelage of Professor Otto Folin, was a no-nonsense, taciturn man, direct in speech, well organized, and very successful in applying chemical methods to biological

problems. After obtaining his PhD degree in 1920, he became an instructor in biochemistry at Washington University in St. Louis and began studies of the ovarian hormones, collaborating with anatomist Edgar Allen. Together, they developed a bioassay for estrogenic hormones based on changes in the vaginal smear of rats. In 1923, Doisy moved across town to become the first Chairman of the Department of Biochemistry at St. Louis University. In the 1930s, he had successfully isolated estrone from urine and estradiol from sows' ovaries. By the time I arrived in the Department, he was actively engaged in the attempt to isolate vitamin K from various sources, a project that in 1939 came to fruition.

Choline Deficiency in Rats

At the end of the first semester, Professor Doisy suggested that I consider working with Associate Professor Wendell H. Griffith, who in the last year had returned from a sabbatical at Oxford with Sir Rudolph Peters, where he had studied the effect of benzoate on the respiration of tissue suspensions. More relevant to my ultimate work with Griff, as his friends and students called him, was a new interest he developed, from conversations with Professor Channon in Liverpool during his sabbatical, on the role of choline and various amino acids in the prevention of fatty liver in rats. On his return to St. Louis, Griffith began studies of choline deficiency in young rats, which he thought would have higher requirements for choline and the related amino acids. Furthermore, he had access to an abundance of male weanling rats from the Doisy Wistar rat colony set up originally to breed female weanling rats for estrogen assays. The year I arrived was an exciting time in Griffith's laboratory because he had just discovered that weanling rats put on choline-deficient diets developed hemorrhagic kidneys in addition to fatty livers (26).

In the summer of 1939, Dr. Griffith asked me to join him to study the effect of choline deficiency on serum lipids in the rat. I worked on the project for two years and showed that the rat developed hypolipemia in inverse ratio to the accumulation of fat in the liver (58). It was a problem I was to take up again at the University of Pittsburgh after World War II, which interrupted my career development in a serious way. The first interruption was in October of 1941. Dr. Griffith was recruited into the armed services to serve as Chief of Nutrition Branch, Office of the Surgeon General in the European Theater. He went to England to help the Allies prepare for the invasion of Europe.

The Bioassay of Adrenal Cortical Hormones

After Dr. Griffith left, Professor Doisy decided that no one in the department was qualified to oversee my work on choline and recommended that my thesis topic be changed to the effect of adrenal steroids on glycogen deposition in

the rat. Doisy had received a war-time contract with the Office of Science and Research Development (OSRD) in Washington, headed by Dr. Vannevar Bush, to study the biological activity of the various adrenal cortical extracts, with an aim toward improving the performance of military flyers at high altitudes. He thought I could contribute to that effort.

I was very disappointed at having to give up my studies of fat transport in choline deficiency, but I agreed to join a new research group assembled by Doisy to study the biological activity of adrenal cortical extracts. This group included two faculty members, Professor Sidney Thayer in biochemistry and Professor Nelson Wade in biology, plus four graduate students, Francis Jacobs, Dan Richert, L.J. Kopp, and myself, to carry out assays of commercial adrenal cortical extracts by four different methods. These included (*a*) growth and survival of adrenalectomized rats, (*b*) glycogen deposition in adrenalectomized rats, (*c*) urea clearance in adrenalectomized dogs, and (*d*) sodium retention in normal dogs. The unsettled question at that time was whether or not one could use a single assay to appraise the total biological activity of any given adrenal cortical extract. My assignment was to devise a reproducible assay for the glycogenic adrenal cortical steroids.

Because high-protein feeding increases gluconeogenesis, I discovered that a high-protein diet (58% casein) fed to 10-week-old adrenalectomized rats given 1% saline drinking water for 4 days prior to subcutaneous injection of the cortical steroid gave the best and most reproducible glycogen deposition in the liver. Corticosterone, the principal glucocorticoid synthesized by the rat, was used as the standard for the glycogenic assays, and desoxycorticosterone, which had no glycogenic activity, was used as the standard for the other bioassays. We decided early in our investigation that no single bioassay was adequate for all adrenal cortical extract activities because adrenal cortical extracts showed no parallelism between glycogenic potency and the three other assays relating to the action of the mineralocorticoid, desoxycorticosterone (78). The development of our modified glycogenic assay led to the discovery that, in the 17-OH series of glucocorticords, the 11-β oxygen had to be reduced for maximum activity (87). We also were able to estimate the rate of corticosterone secretion in the rat from the glycogenic effect by giving various doses of the hormone to the adrenalectomized rat. This finding agrees with more recent estimations of the daily secretory rate of corticosterone in the rat (23).

By the summer of 1943, I had completed all of the experimental work for my dissertation and was writing up my findings for publication (78, 87). The question facing me was whether I should stay at St. Louis University as an instructor or move to another institution. I had received the offer of an instructorship at Yale University from Professor C.N.H. Long, Chairman of the Department of Physiological Chemistry in the medical school, who had site-visited our project during the previous year on behalf of the OSRD. Doisy

urged me to stay as an instructor in biochemistry at St. Louis University and matched the salary offered me at Yale. For the next year I worked on various fungal organisms, looking for an antibiotic with the activity of penicillin. I did isolate helvolic acid from one strain of organism, but its antibiotic activity was low and not promising as a substitute for penicillin. The high point of 1943 for the Department of Biochemistry was the announcement from Stockholm that, jointly with Henrik Dam from the University of Copenhagen, Doisy had won the Nobel Prize in medicine or physiology for his work on vitamin K.

By the spring of 1944, I had finished my work on antibiotics, received my PhD from St. Louis University, and was engaged to marry Catherine Silvoso, a nurse working at the St. Louis Children's Hospital. Thoughts of war, however, were increasingly on our mind. On June 6, 1944, the Allies landed on the Normandy coast and began their victorious trek to Berlin. In the Pacific, the amphibious island hopping had brought American forces to victory in New Guinea and the Marianas, but Japanese resistance was stiffening as the Americans came closer to the Philippines, Okinawa, and Japan. Professor Doisy promised me a continued deferment if I stayed on at St. Louis University, but after extensive soul-searching I applied for a commission as Ensign in the U.S. Navy and entered the service in the summer of 1944. After basic training at Princeton, I returned to St. Louis, where Catherine and I were married. After additional training in communications at Harvard, I was sent to Camp Pendleton in Southern California for amphibious training and thence to Port Huenemi. While we were there our eldest daughter, Barbara, was born.

Also while we were there, in August, 1945, atomic bombs were dropped on Hiroshima and Nagasaki, which led to the end of the war. I learned later that Operation Olympia, for which I trained in California, was aimed at the invasion of Kyushu, one of the islands that was part of the Japanese mainland. In lieu of going to Kyushu, I was sent to Wake Island to help rebuild the airbase, which had been bypassed by the American forces in 1942. After serving a year as the communications officer for Airbase Wake, in June of 1946, I was mustered out of the service and rejoined my wife and daughter in St. Louis.

HARVARD MEDICAL SCHOOL AND THE PETER BENT BRIGHAM HOSPITAL

When we arrived in Minneapolis, the home of my parents, I found waiting for me the offer of an instructorship in biochemistry at Harvard Medical School. When I reported to Professor A. Baird Hastings, Chairman of the Biochemistry Department, in the fall of 1946, he told me he had some good news and some bad news. The bad news was that the funds he was expecting to pay for my fellowship had not materialized, and the good news was that Fredrick Stare, who had recently been appointed to head a Nutrition Department at Harvard,

did have funds to support me. Dr. Stare obtained a PhD in biochemistry from the University of Wisconsin and an MD from the University of Chicago. After that he did postdoctoral work with Philip Shaffer at Washington University, St. Louis; David Keilin at Cambridge, England; Albert Szent-Gyorgyi in Szeged, Hungary; and Paul Karrer in Zurich. He interned at Barnes Hospital in St. Louis and was appointed Assistant Professor of Nutrition and Chairman of a new Department of Nutrition in the Harvard School of Public Health in 1942 (94).

The Effect of Vitamin Deficiencies on the Respiration of Cardiac Muscle

Dr. Stare was interested in continuing work in the role of vitamins in biological oxidation and asked me if I would consider studying the effect of selected vitamin deficiencies on cardiac metabolism. In 1937, Hans Krebs at Sheffield had proposed the citric acid cycle as a mechanism for aerobic oxidation of carbohydrate, which involved several vitamin-containing coenzymes (35). In fact, Stare had studied fumaric acid as a catalyst for tissue respiration with Keilin at Cambridge (95).

The initial work we did with thiamin-deficient rats and ducks showed the expected biochemical result in heart muscle, namely an inability to oxidize pyruvate, with a resulting fall in oxygen consumption, which was corrected by giving thiamin to the deficient animals (83). Then we became more adventurous and took on the study of two other vitamins, which we thought *should* be required for normal metabolism of the heart, namely pantothenic acid and biotin. In 1947, Lipmann and coworkers discovered that pantothenate was a component of the acetylation coenzyme, coenzyme A (CoA) (40). Since pyruvate was oxidized to acetate and was able to produce citric acid in tissues, it seemed reasonable to suspect that CoA was catalytic in the synthesis of citric acid. I called Professor Lipmann, who at that time was at Massachusetts General Hospital, to discuss this hypothesis, with the idea of testing it in nutritional experiments. He supported the proposal and asked Nathan Kaplan, one of his postdoctoral fellows, to collaborate with me on this study.

Kaplan and I showed that CoA levels were decreased in the tissues of pantothenate-deficient ducks and rats and were restored to normal by supplementation of the deficient animals with pantothenate (79). We also observed that pyruvate oxidation was reduced in the tissues of pantothenate-deficient animals and that pantothenate supplementation would restore pyruvate oxidation to control values. Subsequently, I showed that CoA added in vitro to homogenates of heart muscle from pantothenic acid-deficient ducklings would stimulate citrate synthesis, which supported the hypothesis that acetyl-CoA was required to acetylate oxalacetic acid in the synthesis of citrate (74). The

simultaneous and independent work of Stern & Ochoa, using an acetone powder of pigeon liver, also demonstrated the catalytic activity of CoA in citrate synthesis from acetate and oxalacetate (96).

The Study of Medicine

Although before my induction into the navy I had considered studying medicine, principally because of discussions I had had with Peter Danis, the Chairman of Pediatrics at St. Louis University, my contact in the navy with medical officers led me to consider it again, before arriving at Harvard for postdoctoral work. In 1946, I decided to broach the subject with Baird Hastings, the Chairman of Biochemistry, and Fred Stare, my direct supervisor. Stare was enthusiastic, but Hastings, who listened politely, was not very positive about the idea. Nonetheless, I decided to apply for admission to Harvard Medical School. To my delight, I was admitted to the class of 1951. Dr. Stare was very pleased with this development and said he would support me with fellowship funds and provide laboratory space and a technician for at least two years of my medical studies, providing I would continue to work on cardiac metabolism. He also assigned two graduate students, Neal Miller and Myron Brin, to assist me in this work.

The work I did during medical school was to supervise the dissertation studies of Miller and Brin, which led to a number of publications on the effects of deficiencies of thiamin, biotin, and pyridoxine on the metabolism of heart muscle (7, 8, 43, 81, 86). With the availability of $^{14}CO_2$ after the war, I also carried out a number of isotopic organic and biological syntheses of radioactive substrates (acetate, pyruvate, lactate, succinate, and glucose) for studies to permit better quantitation of substrate utilization in heart and other tissues. One of our discoveries was that tumor slices oxidized [^{14}C]glucose better than liver did, in contradiction to Warburg, because of the contrasting regulation of the phosphofructokinase in liver and hepatoma (50). I also did a pathophysiologic study of the hemorrhagic renal syndrome in choline deficiency with Helen Deane of the Department of Anatomy at Harvard. We found that the uremia and electrolytic disturbances coincident with the renal ischemia caused an outpouring of both glucocorticoids and mineralocorticoids from the adrenal cortex (69). The precise cause of the self-limiting, choline-related renal hemorrhage in young rats is still not fully understood.

My medical training was also very stimulating because of the tutelage of George Thorn, Sam Levine, and Lewis Dexter at the Brigham; Fuller Albright at Massachusetts General; Charles Davidson and William Castle at City Hospital; and Herrmann Blumgart at the Beth Israel. William Schwartz, who was then a fellow in medicine at Brigham, and I wrote a review on the metabolism of the heart in congestive heart failure, summarizing findings in both animals

and human beings (85). In my last year of medical school, I was offered an internship at the Brigham in Boston. I was also offered a job by Dr. Thomas Parran, the new Dean of the Graduate School of Public Health of the University of Pittsburgh, as Professor of Biochemistry and Nutrition and head of the department, to take effect in 1952 following my internship.

DEVELOPMENT OF A CAREER IN CLINICAL NUTRITION

My appointment at the University of Pittsburgh in 1952 marks my earliest commitment to a career in clinical nutrition. I was, of course, determined to pursue biochemical studies, but in the light of their probable elucidation of a problem in clinical nutrition. I recruited a faculty of scientists in biochemistry and nutrition, which included Eric Ellenbogen from Harvard, Maria Fuld from Tufts, James Dinning from Arkansas, Ronald Bentley from Columbia, Ivy McManus from Western Reserve, Charles Sweely from the National Institutes of Health (NIH), and John Vester from the Brigham, and was able to attract an array of graduate students and postdoctoral fellows. My first laboratories were in the old Municipal Hospital of Pittsburgh, adjoining the University of Pittsburgh campus, which also housed the laboratories of Jonas Salk, who at that time was perfecting his heat-killed polio vaccine.

I was able to establish a nutrition clinic at Falk Clinic, the outpatient department of the School of Medicine, and make arrangements for metabolic ward facilities at St. Margaret's Hospital and later at Presbyterian University Hospital. Dr. Max Lauffer, Professor of Biophysics at the University of Pittsburgh, had been recruited by the NIH to participate in a multicenter study of the Gofman hypothesis, which postulated that certain ultracentrifugal-identifiable lipoproteins (Sf_{12-20}), now known as intermediate density lipoproteins (IDL), correlated better with the risk of coronary artery disease in humans than did total serum cholesterol (25,47). I saw an opportunity to resume my research on the hypolipemia of choline deficiency, which had been interrupted by the war, and to characterize the defect in terms of lipoproteins. We obtained an ultracentrifuge and were greatly helped by Max Lauffer's group in using it to measure serum lipoproteins in both animals and humans.

Research at the University of Pittsburgh

CARDIAC METABOLISM IN CONGESTIVE HEART FAILURE We undertook a study of cardiac failure in dogs operated on to produce valvular lesions to determine whether or not the increased work and hypertrophy of heart muscle would produce any detectable biochemical lesions. We found that cardiac failure in the dog caused by surgically induced valvular disease (66) or hyperthyroidism

(89) did not produce any defect in substrate utilization, oxygen consumption, or adenosine triphosphate (ATP) synthesis. We examined the energy stores in the heart of normal dogs and those in congestive heart failure and concluded that the biochemical defect in low-output cardiac failure was a defect in the utilization of ATP, which had orginally been attributed to a change in the physical-chemical state of cardiac myosin (72) but was later attributed to a change in the uptake and utilization of Ca^{2+} by cardiac organelles (46).

CHOLINE DEFICIENCY IN RATS AND HUMAN BEINGS We confirmed earlier studies at St. Louis University that plasma lipids were lower in choline-deficient rats than in control rats. By use of the ultracentrifuge we showed that the rat's array of plasma lipoprotein differed from the human's in that the rat's had very small amounts of very low density lipoproteins (VLDL) and low density lipoproteins (LDL) and an absence of IDL; however both species have similar concentrations of high density lipoproteins (HDL). In choline deficiency, VLDL and LDL levels were zero but HDL remained the same (77), which was confirmed in later studies (105). We were impressed, furthermore, with the hypolipemia of alcoholic patients admitted to our metabolic ward at St. Margaret's Hospital. After these patients were fed and rehabilitated, their plasma lipids returned to normal levels. We then carried out a systematic study of the effect of low-protein, low-methionine diets on the plasma lipids of recovered alcoholics and observed findings similar to choline-deficient rats treated with choline or methionine. When dietary protein was reduced from 100 to 25 g/day of vegetable protein at a constant fat intake in a group of recovered alcoholics, serum cholesterol values fell 44 ± 4 mg/dl (14.2%). This decrease was due to changes in LDL and VLDL concentrations in plasma, an effect independent of the type and degree of unsaturation of the dietary fat (88). Later, by using amino acid diets, we found that high levels of glutamic acid had a hypolipemic effect on serum lipids (82).

These findings led us to review the role of the liver and of diet on the secretion of β-lipoproteins and to speculate on the importance of the liver in the causation of atherosclerosis (51). I proposed, furthermore, in the framework of an epidemiologic triangle, that the β-lipoproteins could be considered the agent of atherosclerosis (justified by Koch's postulates), with contributions from both the host and the environment (53).

OBESITY AS A CLINICAL PROBLEM Our obesity study revealed that, on the average, obese people do not eat more than their counterparts, but they exercise less. The composition of the diet they consume is also similar to that of the nonobese person; they get about 10% of their calories from proteins, 42% from fat, and 42% from carbohydrate. They had an increased prevalence of coronary disease, gallstones, arthritis, and diabetes, as had been reported in other studies.

When fed a 1000-kcal diet, obese middle-aged women lost an average of 25 lbs over 18 months, which was associated with a decline in total energy expenditure from 42 to 25 kcal m^{-2} h^{-1}, a fall in energy expenditure that brought them into caloric equilibrium with their therapeutic diet and in many cases arrested further weight loss. Only 5% attained their desired weights over 5 years (52).

THE BIOSYNTHESIS OF UBIQUINONE In 1958, after the announcement of the structure of ubiquinone [coenzyme Q (CoQ)] by Morton et al (45) and Wolf et al (103), we wondered, on the basis of its similarity to vitamin K and α-tocopherol and its role as an electron transport agent, whether or not it was an essential nutrient. To determine its essentiality, we studied its biological activity in tests for vitamin K and E. These studies were all negative (71), so we decided to explore the biosynthesis of CoQ in the rat. The structure of ubiquinone suggested that the benzoquinone moiety was derived from phenylalanine (4, 68), the isoprenyl side chain was derived from acetate, (70) and its methyl groups were derived from methionine (5). These studies, begun in Pittsburgh, were continued to a successful conclusion at St. Louis University after my return there in 1965. In these studies, the biosynthesis of ubiquinone in animal cells was worked out in detail and the enzymes required for each step were identified (24, 31, 93, 97, 98). The pathway of biosynthesis of ubiquinones in eukaryotic and prokaryotic organisms are shown in Figure 1 (84). Ubiquinone and vitamin K are now used to provide electronic shunts in the mitochondria of patients with mitochondrial myopathy to correct deletions in the electron transport chain (1, 6).

Sabbatical at Oxford with Sir Hans Krebs

A CIBA Foundation Symposium was held in London in May of 1960 on "Quinones in Electron Transport," at which I was invited to present our initial studies on the biosynthesis of ubiquinone (71). It was a spirited meeting, attended by Karl Folkers, Britton Chance, Fritz Lynen, Harry Rudney, Sir Hans Krebs, and many others. At that meeting, I approached Sir Hans to inquire if, during the academic year of 1961–62, I could do a sabbatical in his department at Oxford University. I proposed to him that I could carry out some studies of substrate utilization in the isolated perfused rat heart, which I knew was being used in his laboratory, as an extension of my previous studies of cardiac metabolism. He told me he would consider my suggestion, and in due time he responded by offering me a position as a visiting professor beginning in the fall of 1961. He told me that I would have to secure my own financial support, which I was fortunately able to do through a fellowship from the Guggenheim

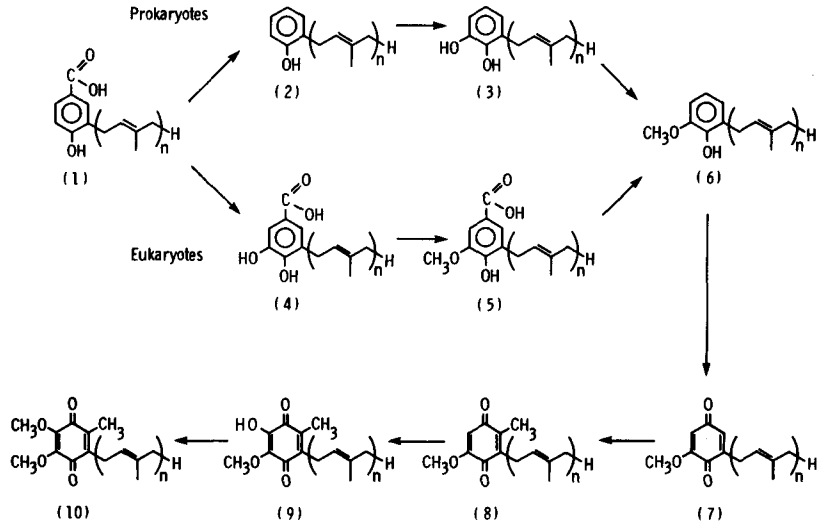

Figure 1 The biosynthesis of ubiquinone. All organisms initiate this biosynthesis by the alkylation of 4-hydroxybenzoate to 4-hydroxy-3-polyprenylphenol, *(1)*. The pathway then diverges for prokaryotes and eukaryotes. In prokaryotes, the next step is decarboxylation followed by hydroxylation to form 6-hydroxy-2-polyprenylphenol, *(3)*. In eukaryotes, *(1)* is hydroxylated to form 3,4-dihydroxy-5-polyprenolphenol, *(4)*, followed by O-methylation to form 3-methoxy-4-hydroxy-5-polyprenylbenzoate, *(5)*. This step appears to be the regulated step in catabolite repression in yeast (93). At this point, the pathways merge by the O-methylation of *(3)* and the decarboxylation of *(5)* to form 6-methoxy-2-polyprenylphenol, *(6)*. This common intermediate then leads to 6-methoxy-1,4-dihydroxy-2-polyprenylbenzene, which is oxidized to the 6-methoxy-2-polyprenyl-1,4-benzoquinone, *(7)*. This intermediate is then methylated, *(8)*, hydroxylated, *(9)*, and O-methylated to form uniquinone-n (36).

Foundation and a Fulbright travel grant. The University of Pittsburgh agreed to provide a half salary for the sabbatical period.

In August of 1961, the Olson family, now composed of my wife, Catherine, and five children, Barbara, Robert Jr, Mark, Mary, and Carol, set sail for England. We rented a house in North Oxford a short distance from South Parks Road, where the Department of Biochemistry is located. It was an enjoyable year for all the Olsons, which included an appointment for me at Merton College. Sir Hans Krebs was an excellent mentor for me in my continuing study of cardiac metabolism, with specific attention to the mechanism by which pyruvate and acetoacetate alter the metabolism of free fatty acids to inhibit their oxidation and promote storage of triglyceride (54, 75). He was always accessible, attentive, and supportive of my work.

I shall never forget one episode, which after leaving Oxford in 1962 changed the direction of my research. Sir Hans gave the lectures in the first-year honors course in biochemistry and the topic for that day was gluconeogenesis. In

passing, he mention the paper of Jacob & Monod (32), who had shown in bacteria that small molecules like β-galactosides could alter the synthesis of β-galactosidase through regulatory genes. He wondered whether the effect of glucocorticords on the rate-controlling enzymes of gluconeogenesis could operate through regulatory genes. After the lecture, I asked him if he thought vitamin D, a secosteroid, and other fat-soluble vitamins might also exert their influence through regulatory genes. I reminded him that, at that time, no one had shown any of the fat-soluble vitamins to form coenzymes. He thought for a moment and said, "Why don't you study the problem? Sounds like a good idea." Although I did not work on vitamin K during my graduate work at St. Louis University, I thought of Doisy's work and concluded that the vitamin K-prothrombin system might be an ideal model to test this hypothesis. I resolved to start work on the problem as soon as I returned to Pittsburgh.

MODE OF ACTION OF VITAMIN K In 1964, we demonstrated that agents that inhibit hepatic RNA synthesis in chicks blocked the action of vitamin K in stimulating prothrombin synthesis. In addition, we predicted that the fat-soluble vitamins as a group would be shown to affect gene expression (56, 57). Later, we showed that vitamin K was a cotranslational effector for prothrombin synthesis by regulating the synthesis of γ-carboxyglutamate in the ribosomal nascent peptide (73, 76). We also showed that the form of reactive CO_2 for the vitamin K-dependent carboxylase is CO_2 and not bicarbonate, which does not require ATP and biotin (33, 76). In addition, we identified an alkylating enzyme for menadione from the smooth endoplasmic reticulum in liver (17, 39). This enzyme forms menaquinone-4 and confers biological activity on the provitamin.

Ironically, it turned out that vitamin K does not modify gene expression but serves as a co- or posttranslational modifier of selected glutamate residues in vitamin K-dependent proteins, as shown in Figure 2 (63). On the other hand, both vitamin A and D generate metabolites, which react with transcription factors to modify the expression of a number of genes (20).

Return to St. Louis University and the Chiang Mai Connection

Shortly after returning to Pittsburgh from Oxford in 1962, I received an offer to return to St. Louis University School of Medicine to succeed Edward Doisy as the Doisy Professor of Biochemistry and Chairman of the Department. I considered it an honor to succeed Dr. Doisy, as well as an opportunity to devote more time to basic studies on cardiac metabolism, the mode of action of vitamin K, and the biosynthesis of ubiquinone. It also provided an opportunity for me to teach a course in biochemistry to medical students, which would emphasize its application to medicine, including clinical nutrition. I accepted this offer,

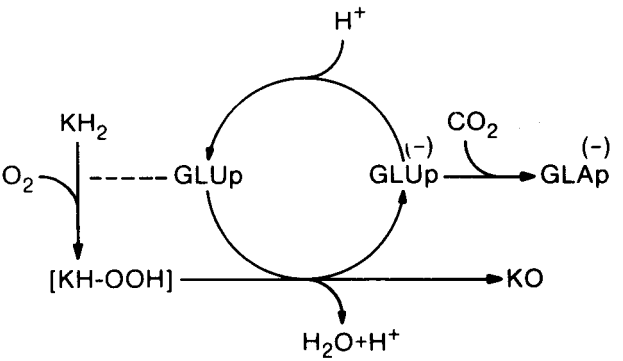

Figure 2 The mechanism for the carboxylation of glutamate residues in vitamin K-dependent proteins. Vitamin K hydroquinone (KH_2), oxygen, and a Glu-peptide (Glu_p) form a ternary complex with the γ-glutamyl carboxylase. The first product is a vitamin K hydroperoxide (KHOOH), which rearranges to a digeminal alkoxide, a very strong basic ($pK_a = 25$), and removes a proton from the γ-carbon of Glu_p (18). The resulting carbanion then makes a nucleophilic attack on CO_2. The products of the reaction are peptide-bound γ-carboxyglutamate (Gla_p) and the 2,3-epoxide of vitamin K (KO). In the absence of CO_2, the enzyme recycles Glu_p and acts like a vitamin KH_2 epoxidase. The epoxide can be recycled by way of two sulfhydril-dependent reductases to form more KH_2, which continues the Glu_p carboxylation (73).

which included an appointment as Associate Professor of Medicine, in time to arrive in St. Louis to begin teaching in the fall of 1965.

Fortunately, I received grants to support my various research projects and a construction grant to expand and renovate the physical space assigned to biochemistry. I recruited Anna Marie Weber from Columbia, Anthony Martonosi from Harvard, Ronald Cockerell from Cornell, Barry Marrs from Wisconsin, George Phillips from Freiburg, Bill Longmore from La Jolla, and Carmine Coscia from Pittsburgh and went to work.

In the fall of 1965, shortly after arriving in St. Louis, I had a surprising call from Nevin Scrimshaw of the Massachusetts Institute of Technology (MIT), who headed the U.S.-Japan Medical Sciences Panel on Malnutrition. He asked if I would consider developing a research station in Thailand. I was flabbergasted! This was during the Vietnam War, after the bombing of Hanoi. Scrimshaw told me that President Lyndon Johnson had decided to organize a medical program in Southeast Asia to improve his image among Asian countries bordering Vietnam. Scrimshaw also offered me an appointment on the U.S.-Japan Medical Science Panel on Malnutrition. My mission, as explained at the panel's meeting in Honolulu in October, 1965, would be to build a research station in Chiang Mai, Thailand, to investigate the pathophysiology of protein calorie malnutrition (PCM), including its anemia. It had been claimed by

investigators in Jerusalem that α-tocopherol was curative for the anemia of PCM (41), but that required further investigation.

I did a great deal of soul-searching about a possible tour of duty in Thailand. I contacted James Dinning, who had been on my faculty at the University of Pittsburgh and was now a scientist with the Rockefeller Foundation. In 1963, he was assigned to Bangkok to function as acting Dean of a new medical school at Mahidol University. He invited me to visit Bangkok and Chiang Mai to appraise the practicality of the proposed mission. The Dean of the Chiang Mai Medical School was an impressive Anglo-Thai physician named Bunsom Martin.

When I returned to the United States it was clear to me that several conditions were necessary before I could consider accepting this assignment, particularly because I was also in the throes of reorganizing a department at St. Louis University. These conditions were (*a*) the creation of a building to house the Center as part of the Chiang Mai Medical School by the Thai government; (*b*) support of the Rockefeller Foundation for heavy equipment; (*c*) NIH support for personnel and supplies; (*d*) the availability of temporary quarters to house the project until the new building was completed; and (*e*) approval of the Dean of the St. Louis University School of Medicine, Dr. Robert Felix, giving me time (about 2 months/year) to create and direct the Center. I was sufficiently serious about this project to make application to NIH in the summer of 1966.

To my amazement, all conditions were met by the spring of 1967, including approval of my NIH grant. I immediately began recruiting personnel to staff the Center, including Jo Anne Whitaker, MD, Mac K. Horwitt, PhD, and Eleanor Fort, MS, from the University of Illinois; Charles Tan, MD, PhD, from Tulane University; Anne Hall, MS, from Baylor University; Helen Sillup, RN, from Belleview Hospital; and Don Gibson from the British Foreign Service. Dr. Martin provided about 2400 square feet of space, which included a research ward, hematology and clinical chemistry laboratories, a diet kitchen, and an office, all distributed within the Chiang Mai Hospital. A memorandum of agreement was negotiated between myself and the government of Thailand to support the Center, which would become the Anemia and Malnutrition Research Center, for a period of ten years. The architectural firm of Norman and Urai Anderson of Bangkok was engaged to prepare plans to construct a building according to my specifications. A medical research building was planned to provide 30,000 square feet on four floors, including an animal house to carry out the research program of the Center. The plans were completed in 1967; construction began in 1969 and the building was completed in 1972.

Ousa Thanangkul, a senior pediatrician at the Chiang Mai University School of Medicine, was initially invited to join our Center, followed by other faculty members, including Panja Kulapongs, Kosin Amatayakul, and Maitree Suttajit.

Avudh Siskriski, who was the Chairman of Pediatrics at Chiang Mai Medical School, served as my opposite number in the governance of the Center. Our Center was officially dedicated by His Royal Highness, the Crown Prince of Thailand, on January 8, 1973, at which time we hosted an International Symposium (59).

In 1970, Robert Suskind, MD, a pediatrician from Johns Hopkins Medical School, was recruited to serve as my deputy director. In addition, two biochemists, both from Mahidol University, Gordon Bailey, PhD, from the University of Florida, Claus Leitzmann, PhD, from Justus Liebig University in Giessen, West Germany, and Joan Caddell, MD, a pediatrician from St. Louis University, were recruited (11).

INACTIVITY OF VITAMIN E IN HEMATOPOIESIS In 1966, Majaj et al (41) had claimed that vitamin E was an important hematinic for children with PCM. Since children admitted to our Center had very low plasma vitamin E levels (0.30±0.05 mg/dl), we designed a study to test the role of vitamin E as a hematinic agent. Seventy children, ranging in age from 1 to 3 years, with second- and third-degree protein-calorie malnutrition and having hemoglobin concentrations of less than 10 g/100 ml were admitted to the study. The total period of observation was 12 weeks. Erythropoietin levels were high at the beginning of the study. The negative control (group I) received an adequate diet for the 12-week period without added iron or vitamin E. The positive control (group II) received both iron and vitamin E. Group III received vitamin E for 6 weeks, followed by iron, and group IV received iron for 6 weeks, followed by vitamin E. The object of this study was to determine if there was a synergism between vitamin E and iron in stimulating an initial reticulocyte response and hemoglobin synthesis, and whether or not—when each compound was given separately for 6 weeks, followed by the other for 6 weeks—a second reticulocyte response would be observed.

The reticulocyte responses appeared to be caused by a combination of protein and iron but not by vitamin E. In group I, there was a minimum response. In group II, which was given both vitamin E and iron, there was a maximum response. In group III, which received vitamin E but not iron, the initial reticulocytosis was the same as group I, but more important, at 6 weeks after administration of iron, there was a second reticulocyte response with enhancement of hemoglobin formation. In group IV, however, which first received iron without vitamin E, there was a good initial reticulocyte response, with no second reticulocyte response to administration of vitamin E at 6 weeks. It was concluded that the main hematinic factors for children with PCM in northern Thailand are protein and iron (36).

PROTEIN AND ENERGY REQUIREMENTS FOR RECOVERY FROM PCM A second clinical study was conducted in malnourished Thai children to determine the

amount of protein and energy required to induce recovery. All subjects were treated the same for a one-week stabilization period, during which they were fed intravenous fluids containing glucose and electrolytes, particularly potassium and magnesium, and were given antibiotics according to need. After day 3, feedings contained an average of 2 g of protein and 100 kcal/kg.

After the one-week stabilization period, the children with marasmus, marasmic kwashiorkor, and kwashiorkor were randomly assigned to four dietary groups. The total period of observation was 12 weeks. The control group was fed an adequate diet, containing 4 g of protein and 175 kcal/kg of body weight for the entire 11-week experimental period. The other three groups received either 1 g of protein and 100 kcal/kg, 1 g of protein and 175 kcal/kg, or 4 g of protein and 100 kcal/kg for 3 weeks, followed by the control diet for the remaining eight weeks.

The administration of 1 g of protein and 100 kcal/kg caused weight loss in all groups during the 3-week experimental period, with good restoration of weight gain in the marasmic kwashiorkor and kwashiorkor groups during the subsequent 6-week period. The marasmic children required a period longer than 12 weeks to attain normal weight for height. The children who received 4 g of protein and 100 kcal/kg failed to gain until put on the control diet. When 1 g of protein with 175 kcal/kg of body weight was fed to them, marasmic children gained slightly for 3 weeks; they gained normally after being fed 4 g/kg. These results emphasize the importance of initial high-calorie feeding to marasmic children. Both kwashiorkor and marasmic kwashiorkor children lost weight on diets containing 1 g of protein and 175 kcal/kg, but they gained normally during the subsequent adequate feeding period. These data indicate that approximately 4 g of protein and 175 kcal/kg are required to initiate cure and support optimal weight gain in children with PCM during the first 12 weeks of treatment (60).

As a by-product of the above study of protein and calorie requirements of children with PCM, we were able to classify plasma proteins in terms of their individual needs for dietary protein. We found that diet-dependent proteins requiring more than 1 g/kg of dietary protein included hemoglobin, serum albumin, transferrin, β-lipoprotein peptide, and complement (C_3). Plasma proteins that responded to 1 g/kg include prothrombin, factor VII, retinol-binding protein, and prealbumin. Those plasma proteins independent of dietary protein intake were the immunoglobulins (60).

REVERSIBLE ACQUIRED IMMUNODEFICIENCEY SYNDROME IN PROTEIN-CALORIE MALNUTRITION We observed that the cell-mediated immunity of children with PCM was dramatically depressed as measured with skin sensitization with dinitrofluorobenzene. These skin tests returned to normal with nutritional repair (19).

Further in vitro studies of cell-mediated immunity in malnourished Thai children showed that, on admission, 24±3% of lymphocytes were T-cells compared with a control value of 57±4%. The B-cell population was not decreased. With nutritional repair, the T-cells increased to about 38% at 15 days and 60±4% at 50 days. These findings were paralleled by studies of phytohemagglutinin-stimulated blast-cell transformation. On admission, 46±6% of lymphocytes could be transformed to blasts (or take up [^{3}H]thymidine), whereas after 29 days of nutritional repair, blast-cell formation reached control values of 93±2% (37). These observations were made at the same time and independent of the study by Chandra (12).

These same defects in lymphocyte function, including a depressed ratio of T4/T8 cells, is observed in HIV infection in patients in whom the acquired immunodeficiency syndrome (AIDS) is not reversible. Also, many of the opportunistic infections seen in HIV-related AIDS are also seen in PCM (44).

DIETARY FACTORS AFFECTING SERUM LIPID LEVELS *Amino acids* In a follow-up of our discovery that low-protein diets in human beings would lower serum cholesterol and LDL levels, we explored the effect of given amino acids on serum cholesterol levels in normal subjects. In diets containing the eight essential amino acids at three times the estimated daily requirement, plus ammonium salts and glycine to supply nonessential nitrogen, there was no change in serum cholesterol from control diets containing 100 g of protein. If glutamic acid were substituted for the nonessential nitrogen, in the formula diet hypocholesterolemia occurred as a result of a fall in LDL (82). Studies of cholesterol turnover using 1-[^{14}C]acetate and 4-[^{14}C]cholesterol coupled with sterol balance studies showed that a high glutamate intake reduced cholesterol biosynthesis (67).

Linoleic acid In 1967, with the aid of [^{14}C]linoleate, we showed that diets high in linoleate reduced plasma LDL levels and enhanced the oxidation of fatty acids (48, 49), a hypothesis revived recently by Beynen & Katan (3), who observed that ketone formation was enhanced during perfusion of liver with high levels of linoleate. More recently, we conducted a study with young men that demonstrated that a high ratio of polyunsaturated-to-saturated fatty acids in the diet negated the effect of dietary cholesterol on plasma LDL and HDL levels (91).

DETERMINATION OF THE REQUIREMENTS FOR PHYLLOQUINONE AND ITS TURNOVER IN HUMAN BEINGS Our basic studies of the mode of activity of vitamin K led to a clinical study designed to determine the requirement of vitamin K in six healthy human volunteers 22–45 years of age. They were fed a semisynthetic diet containing 10 μg of phylloquinone per day for periods varying

from 3–8 weeks. Factors II, VII, IX, and X, prothrombin time, Echis carinatus clotting time, factor II antigen, and vitamin K were measured in plasma at weekly intervals. At the beginning and end of the study, 0.3 mg of all-*trans* phylloquinone (10 μCi) was injected intravenously into each subject, and the specific activity was measured at 10, 20, 40, and 60 min and at 2, 4, and 8 h. During the period of low-vitamin K feeding, factors II, VII, IX, and X ranged from 60–130% of normal, with no trend toward reduction. Plasma vitamin K levels diminished about 50% during the 8-week study. From the isotopic studies, it was calculated that the body pool of phylloquinone is about 1 μg/kg of body weight, and the turnover time is about 30 h (80). These data suggested that the requirement for phylloquinone by healthy young subjects is of the order of 10–15 μg/day (0.2–0.3 μg/kg), which is lower than the 1 μg/kg estimated from previous studies and which is the current recommended daily allowance (RDA) for adults (22).

THE PRACTICE OF CLINICAL NUTRITION IN AN ACADEMIC ENVIRONMENT

Clinical nutrition may be defined as the application of the principles of nutrition science and medical practice to the diagnosis, treatment, and prevention of human disease caused by the deficiency, excess, or metabolic imbalance of nutrients (10).

Over forty years ago, C. Glen King defined nutrition (in general) as the science of food and its relationship to health (33a). This quite accurate definition implies that nutrition is not a single science, but a cluster of sciences related to the production and utilization of food. Furthermore, nutrition, like medicine, is a field for both scientists and practitioners. Nutrition scientists are as diverse as molecular biologists who study nutrient-related gene expression and epidemiologists who track the movement of nutrient-related diseases in populations. The thread that unites them is the study of various aspects of food. The nutritional sciences, in fact, include essentially all biological sciences that can be applied to the study of nutritional problems. Nutrition practitioners (nutritionists), on the other hand, may arise from different backgrounds (medicine, dietetics, nursing, and public health) and apply nutrition science to clinical and public health problems. A clinical nutritionist in an academic setting is both a nutrition scientist and a nutrition practitioner.

The Role of the Clinical Nutritionist in a Medical Center

Clinical nutrition has an ancient and distinguished past. Medical interest in nutrition began in Greece with Hippocrates, five centuries before Christ. Hippocrates recognized that food was the source of energy and body heat. Among

his aphorisms, which constituted the first textbook of medicine, he gave 25 injunctions about diet that reflect in many ways the dietary guidelines in place today. The classic human vitamin-deficiency diseases, namely, scurvy, rickets, pellagra, beriberi, and xerophthalmia, were all described first by physicians (61). In recent years, most physicians have not identified with the great medical traditions that have been established by our forebears in nutrition, but have tended to avoid the subject, plead ignorance of its principles, and delegate the nutritional care of their patients to paramedical personnel. It has become a second-class subject in our medical schools and hospitals.

In 1993–94, only 22% of U.S. Medical Schools offered a required course in nutrition (92). Many (70%) indicated that some nutrition was taught in other required courses, but my experience suggests that medical students do not regard disparate knowledge about vitamins, minerals, and energy exchange taught in biochemistry or physiology as "nutritional" but simply a part of their basic science education (14). What is needed is a bridging course in clinical nutrition given in the preclinical years that will demonstrate the application of nutrition science to the care of patients, and then follow that up in the clerkships of the clinical years.

What has happened as a result of this neglect is the sometimes fatal mismanagement of patients in our hospitals, described by Butterworth in 1974 as "The Skeleton in the Hospital Closet" (9). A sequel to this paper, published in 1994 (38), describes progress that has been made in *some* hospitals to rectify this deplorable situation. Roubenoff et al (90) recently observed that much of the malnutrition in patients admitted to the acute medical service at Johns Hopkins Hospital remains untreated because of lack of physician awareness, something that can be corrected by physician education.

Clinical nutrition is practiced by all physicians in the course of the diagnosis and treatment of many diseases. Inquiry into dietary habits, appraisal of nutritional status in the course of the physical examination, performance of common laboratory examinations that may reflect inadequacy of the diet as well as pathologic physiology, and the institution of diet therapy are all facets of clinical nutrition—and are carried out daily in the practice of medicine. The insight, however, with which the average physician approaches this aspect of his or her practice is limited, largely because of lack of training in this field. The question is how are we in the medical profession remedying this situation, in the interest of improving the overall care of our patients?

The logical place to start is with physicians and patients in an academic environment. The university edifice depends for support on the three pillars of teaching, research, and service. Medical students come to a university for their primary training and many to university hospitals for their clinical training. It is in the university where future generations of practitioners will learn the principles of medical care that should include the principles of clinical

nutrition. The Committee on Clinical Practice Issues in Health and Disease of the American Society for Clinical Nutrition has recently urged that every medical school in the United States appoint to its faculty a physician nutrition specialist (15). They state: "The committee has concluded that there is a vital clinical and educational leadership role for physicians specializing in nutrition in medical school-affiliated hospitals. Recognition of the role of the physician nutrition specialist (PNS) in an academic environment does not add yet another specialty where none has existed; rather, it clarifies and gives credence to a specialty that already has a foundation in selected major medical centers, eg, in physician directorship of nutrition support teams, and offers the potential for further improvement."

There are six main activities that are required of any clinical nutritionist in the academic environment: (*a*) to develop a coherent and thoughtful teaching program; (*b*) to initiate clinical investigations of nutritional problems (usually coupled to some basic research); (*c*) to engage in the practice of medicine in the area of clinical nutrition; (*d*) to train young physicians to be clinical nutritionists; (*e*) to support community-based health promotion programs in nutrition; and (*f*) to carry on professional activities in committees and societies.

TEACHING I agree with the recommendation of the Committee on Nutrition in Medical Education of the Food and Nutrition Board (NRC/NAS). "The committee recommends to medical schools that the basic principles of nutrition be introduced simultaneously with other preclinical sciences as an independent course, and that the precepts of nutrition be reinforced later during clinical training to demonstrate their application to patient care. To cover these core concepts adequately, a minimum of 25 to 30 classroom hours should be allocated to nutrition during the preclinical years" (21, 100–102).

Of vital importance is the continuation of clinical nutrition education during the clinical years, where it can be reinforced by the study of cases.

CLINICAL INVESTIGATION A clinical nutritionist should have a strong, independent research program. It should be problem-oriented. The basic science underlying it could range from epidemiology to any of the basic medical sciences, including genetics. Goldberger used epidemiology to identify the cause of pellagra, followed by nutritional studies of pellagrins fed adequate diets and healthy normal people fed pellagragenic diets. My own work, as previously mentioned, included studies of obesity; protein-calorie malnutrition in children in Thailand and in alcoholic adults in the United States; the effect of various diets, including those containing purified amino acids, on serum lipid levels in young men; the disposition of [^{14}C]linoleate in normal and hyperlipemic subjects; and studies of [^{3}H]phylloquinone in young men on normal and vitamin K-deficient diets.

PRACTICE AND TRAINING I have combined practice and training goals because the clinical nutritionist is expected to practice his or her speciality with the fellows/residents in both inpatient and outpatient settings, and to organize a coordinated nutrition support service for his institution. Standardized training of physicians in clinical nutrition has been described by Halsted (28). In brief, it consists of a course covering the core concepts of nutrition science, i.e. in lectures, seminars, case presentations, and journal clubs, followed by one year of faculty-supervised clinical work in outpatient clinics, inpatient consultations, and nutrition support service, including the use of enteral and parenteral nutrition. A research problem requiring clinical investigation of a nutritional problem, or metabolism of a nutrient in human subjects, should also be required.

Another responsibility of clinical nutritionists is to provide advice to their patients (and to others) about the validity of nutritional claims. I deplore not only the false admonitions of the health food industry about supplements, but also the overzealous application of legitimate diet therapy to persons or groups where no indication exists (65). Food faddism exists because food has emotional rather than rational value to many consumers. The health food promoter capitalizes on this by creating fear of deficiency and touting the wonders of needless meganutritional supplements.

My clinical trainees have included the following medical doctors: Donald Barnhorst, Gaetano Bazzano, Kenneth Brown, Joan Caddell, Paul Carpenter, Brian Chandler, Norman Davis, John D'Elia, Philip Farrell, Andrew Fiori, Stephan Galla, Douglas Griggs, Karl Gugenheim, Deha Gursey, Robert Hoeschen, Seijo Ito, Roger Kipfer, Garry Kneebone, Donald Knowlan, Reinhard Leunissen, Amicar Longarini, Maria Liang, John Muir, Milton Nichaman, Setsuji Noga, Josephina Orteza, George Roush, James Scheuer, Robert Suskind, Charles Tan, Kshetrabasi Tripathy, and Angie Weirsinga.

Relationship to Societies and Boards

Academic physicians are not only teachers, investigators, and practitioners, they should also be advocates for their profession and for the promulgation of their ideals through single and collective activity. It's been my view that clinical nutrition is an orphan specialty, underpopulated, underfunded, and underrecognized, even by fellow physicians, and that it should be promoted. The following is an account of how I have tried to promote clinical nutrition.

AMERICAN BOARD OF NUTRITION In 1948, John Youmans, MD, Col. U.S. Army Surgeon General's Office, recommended that a certification Board for Human Nutrition be created. The idea was supported by the American Institute of Nutrition (AIN), the American Society for Biological Chemistry, the American Medical Association (AMA), the American Public Health Association,

and the Association of American Medical Colleges, and thus, the American Board of Nutrition (ABN) came into being. The aims of the Board were "to establish standards for the qualification of persons as specialists in the field of human nutrition and to certify as specialists persons who comply with such standards." I was a charter member of this Board and was President of the Board from 1962–66. In 1966, the Board decided to certify qualified physicians in clinical nutrition, in addition to offering general certification in human nutrition to nonmedical scientists.

As of 1992, the ABN has certified 368 individuals, of whom two thirds are MDs and one third are PhDs. In 1991, the American Board moved to standardize the content of clinical nutrition training programs and to devise a suitable method for evaluating competence in this core of knowledge (27). Although applications have been made by the ABN to the American Board of Medical Specialties (ABMS), thus far without success, the ABMS has urged the ABN to continue certification and to increase the number of standardized training programs in the United States.

AMERICAN SOCIETY FOR CLINICAL NUTRITION The idea of a clinical nutrition society was first proposed by a group of us at the Hotel Carlyle in New York on September 2, 1959. The meeting was held in conjunction with the meeting of the scientific advisory panel of the National Vitamin Foundation, of which Robert Goodhart, MD, was the director. Also present at this meeting were Omie Waife, Ted Van Itallie, Norman Jolliffe, Maurice Shils, and Michael Wohl.

We thought it was essential to form an academic society patterned after the American Society of Clinical Investigation, which would attract the best clinical nutritionists in the country as members and would provide a forum to improve nutrition education in medical schools, to provide investigators the opportunity to present and discuss their research at annual meetings, to provide a journal for the publication of papers of original work on experimental and clinical nutrition, and to advance the recognition of clinical nutrition as a medical discipline.

To give our embryonic society legal status, the American Society for Clinical Nutrition (ASCN) was incorporated in the State of New York, with Drs. Robert Goodhart, Ted Van Itallie, Norman Jolliffe, Maurice Shils, and Michael Wohl as directors. As a resident of Pennsylvania, I was not a cosigner of the incorporation papers, but I began to do some missionary work to make the ASCN a division of AIN. At the beginning, some clinical nutritionists opposed joining AIN, but after working out an arrangement with the AIN Council that provided semiautonomous status for ASCN, with a right to hold its own meetings (generally with the other clinical investigative societies), operate its own journal, and determine its own membership requirements, all were in agreement.

On May 1, 1960, in Atlantic City, the ASCN held its first meeting as a

division of AIN and presented a program of short scientific papers. The officers elected at that meeting were Richard Vilter, President; R.E. Olson, Vice President; Robert Hodges, Secretary-Treasurer; S.O. Waife, Editor, *American Journal Clinical Nutrition*; and Council Members William Bean, MD, Robert Goodhart, MD, and Willard Krehl, MD. Sixty-nine physicians were inducted into the ASCN as charter members at that meeting. Essentially all were also members of AIN, and subsequent new members were admitted simultaneously into AIN and ASCN. In my presidential address the following year (55), I urged the Society to consider "the education of physicians in the art and science of investigation as important as the education of physicians in applied aspects of our field." In 1960, the active membership was 89; in 1988, it was 750; in 1995, it is 1100. The percentage of MDs, however, has declined from 100% in 1960, to 60% in 1988, to 39% in 1995, which means that, unfortunately, the ASCN, as a whole, is no longer a clinical society.

Finally, I had the privilege of serving the AIN as president from 1981–82. In that presidential address, I urged the AIN to (*a*) insist on scientific excellence in both research and training, (*b*) assert scientific integrity in judging scientific work or conflicts of interest, (*c*) work to increase federal and private support for nutrition research, (*d*) expand recruitment of members to include all biological scientists working on nutritional problems, and (*e*) affirm the unity between the AIN and the ASCN.

COUNCIL ON FOODS AND NUTRITION OF THE AMA The Council on Foods and Nutrition, composed of physicians, physiologists, nutritionists, biochemists, dietitians, and home economists, was created in the 1930s to provide advice to the AMA on nutritional policy, including advice on which foods should carry the Seal of Approval, fortification of foods, guidelines for advertising foods, medical compliance, medical education in nutrition, and the production of monographs on a variety of topics. I served on the Council from 1959–67.

FOOD AND NUTRITION BOARD The Food and Nutrition Board of the National Research Council/National Academy of Sciences was founded in 1941 by President Franklin D. Roosevelt to define nutritional practices by the population of the United States that would maximize health and productivity. The first problem undertaken by the Board was the assembly of a data base that would enable them to recommend allowances of essential nutrients that would assure adequate nutrition in the U.S. population. Such allowances were calculated to exceed requirements by a "safety margin" and were described as recommended dietary allowances (RDA). The Food and Nutrition Board has reviewed the subject of RDAs ten times since 1941, the 10th edition appearing in 1989 (22). The RDAs are defined as "levels of intake of essential nutrients considered, in the judgment of the Food and Nutrition Board (FNB) on the

basis of available scientific knowledge, to be adequate to meet the known nutritional needs of practically all healthy persons." The requirements of persons with illness must be recommended by the patient's physician. More recently, the FNB has published position papers on dietary recommendations aimed at the prevention of a variety of chronic diseases. The first such report, "Toward Healthful Diets," appeared in 1980 and a larger work, entitled "Diet and Health: Implications for Reducing Chronic Disease Risk," appeared in 1989. I was a member of the FNB from 1977 to 1983 and contributed to both the 9th Edition of the RDAs published in 1980 and "Toward Healthful Diets" published the same year.

Membership on Review Panels and Editorial Boards

Productive scientists are important in shaping the future of their science by evaluating proposals for new scientific work, reviewing manuscripts submitted to journals, and evaluating published experiments via editorial work on review journals. I have served on a variety of NIH study sections and training committees, including a term as a member of the Advisory Council for the National Institute of Arthritis, Diabetes, Digestive, and Kidney Diseases from 1981–85. I also had the responsibility for editing *Nutrition Reviews* (1978–88) and the *Annual Review of Nutrition* (1984–94), each for 10 years.

In 1994, I described the function of the *Annual Review of Nutrition* as follows: "The purpose of a critical review is not only to summarize a topic, but also to root out errors of fact or concept and to provoke discussion that will lead to new research activity. The critical review is as essential a part of the overall scientific method as the original experiments and is part of a continuing peer-review process. It is important to point out to new investigators areas of research that give promise for the future. It is equally important to attack questionable hypotheses not supported by successive reports in order to guide research away from these less promising directions. The originality of researchers obviously must take precedence over any peer-review but the results of periodic review of a field should be helpful in the selection of new areas of research and the design of new experiments" (64).

CLINICAL NUTRITION AS A SUBSPECIALTY OF MEDICINE

Rationale

What is the rationale for clinical nutrition as a specialty or subspecialty of medicine? Clinical nutrition qualifies for recognition as a specialty on five counts: (*a*) It deals with a special group of patients suffering from either under- or overnutrition; (*b*) it is undergirded by principles of biochemistry, physiol-

ogy, molecular biology, and pathology, which require specialized knowledge and continuing research; (*c*) its practitioners are able to offer services that improve the care of patients, in individual consultations as well as within the nutrition support service; (*d*) it sponsors three professional societies, each with its own journal; and (*e*) it has federally funded training and research center programs.

Clinical nutrition, like clinical microbiology (infectious disease), clinical pharmacology, and medical genetics, are specialties that are agent-based rather than organ-based. They cut across all of the other specialties, including those that are organ-based, those based on the age of the patient (pediatrics, geriatrics), those based on the method of treatment (surgery and radiology), or those based on holistic and ideologic specialties (internal medicine and psychiatry). Van Itallie first pointed out that clinical nutrition is a specialty largely confined to medical centers, which makes its practitioners an "endangered species" (99). He concluded his presidential address, however, by urging protection for this species because of its essentiality and its relationship to a variety of other subspecialties. It is my view that the medical profession, like the federal government, should protect its "endangered species."

In 1974, David Coursin devoted his presidential address to the ASCN to the accreditation of nutrition as a medical subspecialty (16). He argued that "it is imperative that nutrition become part of the American Board of Medical Specialties as an accredited subspecialty." He supported the idea that the ABN be the instrument for accreditation as a subspecialty Board in conjunction with the Boards of Pediatrics, Internal Medicine, and Surgery. He thought the creation of a primary Board of Nutrition on a par with the major Specialty Boards was not justified. Even then, an application from the ABN to the American Board of Medical Specialties for subspecialty status was rejected for the same reasons that the Board of Internal Medicine rejected an application from the ABN in 1991 (29). These were (*a*) lack of information on how many physicians already qualified in pediatrics, internal medicine, and surgery would apply; (*b*) the need to establish a working group to set standards for training; (*c*) the need to develop standardized training programs of acceptable content and duration; and (*d*) the need to identify a sufficient number of training programs to guarantee a steady flow of applicants for certification. Coursin said that, at that time, both the Board of Pediatrics and the Board of Internal Medicine expressed sympathy for the idea of developing a subspecialty Board in Clinical Nutrition. I strongly support Coursin's proposal, which is as timely now as it was twenty years ago.

Prospects for Recognition

As of now, most of the conditions mentioned above have been met in that working committees of the ASCN have proposed a standardized training

program, thirty-eight training programs in clinical nutrition were identified in the United States by the latest biennial survey (30), and a survey of specialists in pediatrics, internal medicine, and surgery from the ABN interested in clinical nutrition could easily be conducted. As Halsted reported (29), an application to the ABMS was submitted in 1992 and is still pending. Continual pressure on the ABMS in the form of solid evidence of achievement will ultimately, I believe, lead to success if the naysayers can be repulsed (2). The goal of accreditation of clinical nutrition as a subspecialty of medicine is now within reach.

Advice to Young Physicians

In 1978, I appealed to medical students to develop a theme for the study of medicine that would simplify their work and enable them to take charge of their education (62). I recommended nutrition as a theme because of its interdigitation with essentially all areas of medicine. To young physicians contemplating a career in medicine, I invite you to think about clinical nutrition as an area of concentration. It has a distinguished past and will have a great future, both in research and in practice. It will become more important in this era of health reform, which puts more emphasizes on prevention of disease.

According to Childs (13), the dominance of Osler as the preeminent diagnostician of the twentieth century will give way to the genetic concepts of Garrod in the twenty-first century. Garrod, who fathered the concept of inborn errors of metabolism, emphasized chemical individuality as the key to health and disease. He considered disease as the result of an encounter of a unique person with an environment for which he was uniquely unfit. In this context, clinical nutrition is the science most qualified to offer an adjustment of the environment for an individual who is "uniquely unfit." I have always thought that genetics and nutrition were reciprocal and interdependent sciences, both in evolution and medicine. Remember, my young colleagues, that we are in the era of molecular genetics, which is revolutionizing concepts in all branches of biology, including nutrition. Not only vitamins A and D, but many other nutrients, are being shown to directly or indirectly influence gene expression. Finally, be optimistic! Even in these days of stationery support for science, Arthur Kornberg, who is a physician as well as a preeminent biochemist, has urged young people to enter science because of the joy of discovery and its unique association with progress (34).

EPILOGUE

In 1990, I retired from the medical faculty of the State University of New York at Stony Brook as Professor of Medicine Emeritus and continued my unsuccessful attempt to clone the gene for the vitamin K-dependent γ-glutamyl

carboxylase (104). A year ago, due to the kindness of Lewis A. Barness and Jaime Frías at the University of South Florida College of Medicine, I became a Professor of Pediatrics. They welcomed me, they said, because of my work in Thailand with malnourished children. I am happy to be here in the congenial atmosphere of the Department of Pediatrics.

As I think back to my youth, I would never have believed at age 16 when I was devoted to electronics and ham radio that I would enter medicine and concentrate on clinical nutrition as a major career goal. In this autobiography, I have documented the twists and turns that finally led me to clinical nutrition. The tilt toward nutritional science was induced by my unexpected associations with Wendell Griffith, who introduced me to choline deficiency, Fred Stare, who introduced me to cardiac metabolism and clinical medicine, and Nevin Scrimshaw, who introduced me to Thailand. At times, I felt like an "accidental tourist" on my way to an invisible country. Schiller's short answer to that feeling is also speculative: "There are no accidents, only destiny."

Nonetheless, I have had a fulfilling and enjoyable academic career. I have had the benefit of a large cadre of graduate students, postdoctoral fellows, and research assistants who have made my work possible and to whom I am eternally grateful. I am proud of the fact that many have gone on to full professorships in academic medicine or biochemistry.

I have listed some of my clinical fellows above and would also like to acknowledge my indebtedness to my PhD graduate students and postdoctoral fellows. These include: A.S. Aiyar, Charles Allain, Gordon Bailey, Catherine Bauer, William Bettger, David Bowen, Myron Brin, Virginia Campbell, Ivy Celender, Naranjarn Dhalla, Hossein Dialameh, James Drummond, Edward Gardner, Robert Goewert, Steven Goodman, Sunna Hauschildt, Charles Holland, Robert Houser, Raja Iyengar, John Jablonski, Marilyn Johnston, David Kobylka, William Kappel, K.W. Lam, Florence Lee, Claus Leitzmann, L-F Li, Clyde Opliger, Robert Meyer, Neal Miller, Edward Napier, Nicholas Nardacci, Janice Neville, Henry Nowicki, Dorothy Piatnek, Virginia Ramsey, K.S. Rao, Marcia Riegl, Julian Scheinbuks, Ilani Shoshani, Jeffrey Sipple, Charles Tan, Bernard Trumpower, James Wallwork, Daniel Walz, C.M. Yekundi, and R.K.Y. Zee-Cheng, and Pauline Zwitkowits.

I have also enjoyed generous financial support from the NIH, the NSF, and a number of companies and private foundations during the period that has been described as the golden age of support for biomedical research. Finally, I want to thank Rebecca Scott for expert secretarial assistance in the preparation of this manuscript.

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