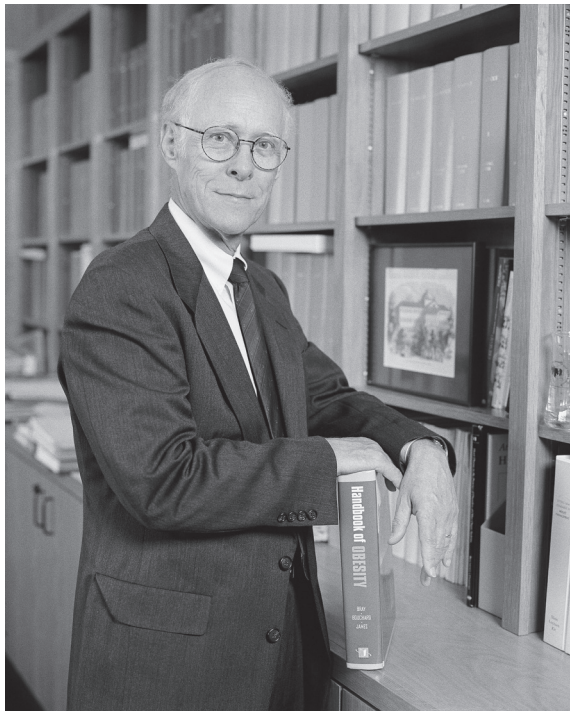

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Why Obesity?

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Abstract

As Erwin Chargaff observed, "Scientific autobiography belongs to a most awkward literary genre," and mine is no exception. In reviewing my scientific life, I contrast the nutritional influences that would have existed had I been born 100 or 200 years earlier than I actually was. With this background, I trace the influences on my formative years in science beginning in high school and ending as a postdoctoral fellow in Professor E.B. Astwood's laboratory, when my directional sails were set and obesity was the compass heading. With this heading, the need for organized national and international meetings on obesity and the need for a scientific journal dealing with obesity as its subject matter became evident and occupied considerable energy over the next 30 years. The next section of this memoir traces the wanderings of an itinerant academic who moved from Boston to Los Angeles and finally to Baton Rouge. The influence of Sir William Osler's idea that there is a time for education, a time for scholarship, a time for teaching, and time to retire has always been a guide to allocating time ever since I was an intern at Johns Hopkins Hospital. It was in Baton Rouge that the final phase began: I agreed to become the first full-time executive director of the Pennington Biomedical Research Center, a decision that changed my life. The article ends with a quotation from Tennessee Williams that reflects the theater, which has given me so much pleasure over the years: "There is a time for departure even when there's no certain place to go."

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INTRODUCTION

> Science is, for those who study it, a source of exultation. It is as if a force outside ourselves, say an angel, pulled us away from our previous level to a higher level in an indescribable, incomprehensible manner.
>
> —*A. Pais* (54)

The challenge of writing a memoir or autobiography about my life in nutrition, science, and medicine was made very clear in the quote by Erwin Chargaff, in which he points out that scientists don't write very well:

> [A] scientific autobiography belongs to a most awkward literary genre. If the difficulties facing a man trying to record his life are great—and few have overcome them successfully—they are compounded in the case of scientists, of whom many lead monotonous and uneventful lives and who, besides, often do not know how to write. [49; *Science* (1968), vol. 159, p. 1448]

Another challenge in writing this memoir was deciding what point of view to take. Walter Bradford Cannon, the renowned Harvard Professor who described homeostasis, lets William James, another famous Harvard philosopher, define the problem:

> William James set forth the illuminating idea that everybody has as many social selves, or social "me's," as there are distinct persons or groups of persons who see him in a particular role and whose good opinion he specially prizes. As a father, a man reveals an aspect of his nature different from that which he reveals as the member of a profession or as a boon companion in a club; and with his children he enjoys a reputation different from that enjoyed among his fellows. So what perspective do we take? (28, p. 2)

Some memoirs and autobiographies take a direct, straightforward chronological perspective on life's events. The journey from a Kansas youth to an internationally acclaimed scientist McCollum described in his autobiography (48) took this chronological tack to separate the various "me's" identified by William James. An alternative approach, and a bit more whimsical one, was used by the Nobel Prize winner Sir Peter Medawar in his *Memoir of a Thinking Radish* (49), and by Charles Swithin in his *Memoirs of a Semi-Distinguished Professor*, where in brief one- to three-page chapters he described "events" using the real names of institutions but pseudonyms for people (65). Medawar tells one whimsical story about his brother Philip that is germane to the discussion of obesity that follows later.

> Philip was a good-looking man and in spite of his physical and, as I thought, mental infirmity, he was very attractive to women and married two (successively, of course). Because, I suppose, of the frustration he suffered, he ate enormously and became rather obese. "Peter," he once said to me, "why do you think I get a sort of fluttery feeling in my stomach?" Being now a bit fed up with his overeating, I replied, "You must try to think of it as a poor caged bird struggling desperately to get out before it is stunned again by the delivery of another huge meal." (49, p. 14)

Two other anecdotes from Medawar's book are also too good not to pass on. Describing his reading as he grew up, he said, "I was omnivorous and read as much as the victims of certain hypothalamic lesions eat, this is, continuously and compulsively" (49, p. 21).

On getting a visa to the United States in the time of McCarthy and the Un-American Activities Committee (1950–1952), Medawar said, "Then, on being asked to make the formal declaration that I did not intend to overthrow the Constitution of the United States, I was fool enough to reply that I had no such purpose, but that if I were to do it by mistake I should be inexpressibly contrite. The official was naturally puzzled and annoyed, but in spite of these misgivings I secured my Visa to the US" (49, p. 117).

Another example of a medical autobiography, titled *As I Remember Him*, is the life of Hans Zinsser as told in the third person by R.S., the pseudonym that Zinsser used for his poetry and other nonmedical writings (74). Zinsser was a world-famous microbiologist who was intimately involved in the discovery and treatment of lice-born diseases. His third-person approach to an autobiography gave a different perspective on his life events. He, too, had a wry sense of humor. When asked why more babies are born at night than during the day, he answered, "Babies are born at night because gestation is 9 months" (74, p. 167).

We are all constrained by the times in which we live, the situations we are in, and the people we meet. Suppose I had been born 100 or 200 years before I actually was. What background would I have had for the study of nutrition, science, and medicine?

If my life had begun in 1731 instead of 1931, the town in Illinois where I was born wouldn't have existed, and Chicago, founded in 1837, would still be on the horizon. By this time in my life

(age 80), I would have lived through the French and Indian War in the New World (1754–1763), the American (1776–1781) and French (1789–1794) Revolutions—one on each side of the Atlantic—and the founding of the United States in 1789 with its first 13 colonies. The Louisiana territory was purchased in 1803 by Thomas Jefferson, then president of the United States, from Napoleon Bonaparte, more than a decade before the Napoleonic era ended at the Battle of Waterloo in 1814. This purchase was essential for the westward expansion of the American colonies. Who could have suspected that it was in the southern part of this territory that the Pennington Biomedical Research Center would be built nearly 200 years later with a gift from a wealthy oilman—who even knew what oil was or that Louisiana had such an abundance of oil and gas?

The major scientific event related to obesity and nutrition between 1731 and 1814 was the discovery of oxygen and the formulation of the oxygen theory of combustion by Antoine-Laurent Lavoisier (1743–1794), who was beheaded in 1794 during the French Revolution—a loss for us all (45). He realized that metabolism in the body was similar to the combustion of a candle. And it was Lavoisier and his associates who also demonstrated the increase in oxygen uptake following a meal—what we now call the thermic effect of food, or why you feel warm after eating a big meal on Thanksgiving.

It would also be a period during which the first monographs on obesity were written, one by Thomas Short (1690?–1772) in 1727 (62) and the other by Malcolm Flemyng (?–1764) in 1760 (30). These were complemented by two books published in the early nineteenth century, the first a charming book by the surgeon William Wadd (1776–1829), first published in 1810 (68), and the other by a Frenchman named Ange Maccary (?–?), published in 1811 (46). Obviously, obesity was a problem in the early nineteenth century, long before our current interest in it. Moreover, it was gaining the attention of physicians, who were writing about it.

Had I been born 100 years earlier, in 1831 instead of 1931, my birthplace in Winnetka, a town with an Indian name north of Chicago, would not yet exist, but Chicago, founded in 1837, would be in its infancy. By this time in my life, I would have lived through the Civil War (1861–1864) (or the War of Northern Aggression if you are a southerner), the Spanish American War (1898), and the gilded age, brought to life by the captains of industry and their wealth. I would have lived through the graduation of my grandfather, William John Hamilton (35) (1866–1957), and 10 others from the graduating class at the University of Arkansas in December of 1892. My grandfather always had an academic bent and was a schoolteacher for a time before passing the bar examination in 1894 and settling in a small town in Arkansas, just south of Fort Smith, where he was mayor, a merchant, and a leading citizen. His interest in education was passed on to his two younger daughters, one of whom was my mother, who in turn passed it on to me. He would have been proud to see me graduate from college 60 years after he did. By 1914, we were on the verge of the First World War, which began in August 1914, the same year that that the Panama Canal was opened.

During this period (1831–1914) nutrition underwent major changes. First, the surgeon William Beaumont (1785–1853), working at the US Army fort on Mackinac Island in Lake Michigan, published his now classic work on the human stomach in 1833 using Alexis St. Martin as his subject (7). This unfortunate man had a fistula or hole into his stomach that developed after an accidental gunshot wound to his abdomen. In 1833 there were no antibiotics and no anesthetics; he was lucky to have survived at all. Beaumont's book was the first major scholarly contribution to medical science from the United States and provided insight into the function of the stomach.

I would also have lived through the discovery and first use of anesthesia during surgery at the Massachusetts General Hospital in 1846 and the discovery in 1861 by Semmelweis (1818–1865)

(61) in Vienna and by Oliver Wendell Holmes (1809–1894) at the Harvard Medical School (39) in Boston that childbed fever could largely be prevented if doctors simply washed their hands before entering the delivery room. About 50 years later, at the turn of the twentieth century, the first vitamins were discovered, and the word "vitamine" was coined by C. Funk (1884–1967) in 1914 (31). The first calorimeter had been built by Pettenkoffer in Vienna, but in 1896 Wilbur O. Atwater (1870–1951) and Rosa built one at Wesleyan College in Connecticut that was used by Atwater and F.G. Benedict to show that human beings, like animals, followed the law of conservation of energy (3). This finding serves as the basis for modern ideas about energy balance and was formulated in the mid-nineteenth century by H.V. Helmholtz (1821–1894) (the man who also invented the ophthalmoscope) (37). My life 100 years ago would also been at the time when damage to the base of the brain was found to cause obesity (hypothalamic obesity) by Alfred Frohlich (1871–1953) (27) [and independently by Joseph Babinski (1857–1932) (4)] in 1900 and when Harvey Cushing (1869–1939), in 1912, published his classic paper on obesity associated with tumors of the pituitary gland (29).

Writings about obesity increased sharply in the nineteenth compared to the eighteenth century. In my view, one of the most important books, and the first popular "diet" book, appeared at this time. It was written in English in 1863 by William Banting (1797–1878) (6), an undertaker in London, who described his personal use of a diet that reduced his body weight by 50 pounds in a year. His book was so popular that "Bantingism" became a synonym for dieting, just as Mr. Boycott's name became a synonym for protests against buying items. The popularity of Banting's diet continued for more than a decade; it was widely translated and went through many American and European editions.

There are a couple of lessons for me buried in this brief historical review. First, scientific developments take time. From the discovery by Lavoisier in the late eighteenth century that oxygen combined with carbon during metabolism in the body—the oxidation theory of metabolism—it was just over a century until the first human metabolic chambers were built in 1896 to confirm the ideas about the conservation of energy in human beings. And it would be another century before the possibility of using the oxygen and hydrogen from metabolism to measure energy expenditure in freely living people was realized by the so-called doubly labeled water method, which integrates human energy needs over several days. This method has shown that food records usually underreport how much food energy we actually consume.

The second lesson is that the number of scientists has increased at an almost logarithmic rate for several hundred years (73). More than 75% of all scientists who have ever lived are now alive and practicing scientific pursuits. I return to this in relation to the founding of the *International Journal of Obesity* in a later section.

Being born in 1931 gave me a totally different perspective and thus another framework for my life and opportunities for scientific research. To put my life into perspective with other historical events and scientific events, and with events related to obesity, I have prepared a table that is available online (**Supplemental Table 1**; follow the **Supplemental Material link** in the online version of this article or at **http://www.annualreviews.org**) (58). It has four columns to reflect each of these areas. My birth was at the peak of the Great Depression, and events related to my mother's side of the family can be found in the autobiography prepared by my maternal grandfather, William John Hamilton (35); events on my wife's side can be found in the book *A Peek into the Life of a Surgeon*, by Carl O. Rice, M.D., PhD (57). My middle school years were during the Second World War. The college years of my contemporaries were interrupted by the Korean conflict, and my early research years were during the Vietnam conflict. Sort of looks like war is part of the human condition—a third lesson.

Supplemental Material

MY FORMATIVE/EDUCATION YEARS—THE ROAD TO OBESITY

The Years Before College

Before my early introduction to science in high school, one teacher had said, "George is doing good average work in all subjects" (Hubbard Woods School, 1942). The atomic bombs of 1945 stimulated a great interest in science among most people. The discovery of penicillin before World War II and its availability to treat human diseases after World War II was another stimulus. In biology class, the instructor let me get some penicillin and test its effect on the growth of bacteria on culture plates. It was wonderful to see the clear area around the penicillin where the bacterial "bugs" didn't grow. It gave me a flavor of the thrill of science that can come with discovery. These ideas were included in a letter I wrote for a national scholarship to Harvard University in January 1949:

> Ever since I took my first science course in high school, I have been interested in the infinite possibilities of science. Biology was the first science that I took. To me, the dissection of frogs and all of the other things that are connected with biology were extremely fascinating. So much so, in fact, that I did some extra credit work with mold cultures that I grew. The work that was presented in chemistry was also very interesting. When we came to organic chemistry I found it very intriguing to try to write the formulas for unknown compounds that I found in miscellaneous chemistry books. This year I am taking physics. Besides being easy for me as all of the other sciences have been, it is explaining many of the natural phenomena that occur all around us every day.

How I Chose Brown University in Providence, Rhode Island

College choice helps determine many future options and closes some doors. My high school education was in a public school system north of Chicago, where over 90% of the graduates went on to college, mostly to schools in the Midwest, but some went to Ivy League schools and others went west or south. During the run-up to my senior year, a number of universities visited the high school for "college nights," and there were always the friends of the family who wanted you to go to this school or that. In those days very few students traveled to see a college campus since transportation was mostly by car or by train—air travel for most people was still in the future. So, selecting a college was, in a sense, like "a pig in a poke"—you had to rely on the indirect inputs. My grades and SAT scores were competitive for most schools, so I ended up applying to half a dozen—the University of Michigan because I liked their gymnastics program, Trinity College because it had an active local alumnus living in our town, Stanford University because of its excellence, Harvard University also because of its excellence, and Brown University because of its excellence and because of a friend of the family, and finally Northwestern, a nearby Big Ten school (it was in Evanston, the next town south). Financial help was offered by three of these schools: Stanford, Harvard, and Brown. From Chicago to San Francisco by train, the way we traveled in those days, was a long haul, and so it got dropped from the list early on. For help with the decision between Harvard and Brown, I went to see Mr. Kahler, the high school dean who had earned a graduate degree in education from Harvard. He asked what I wanted to do after college, and I said I was thinking of medicine and that Harvard was on my list. He replied that I didn't want to spend eight years in Boston and he advised me to go to Brown—so I did.

My Years at Brown University

For me the choice of Brown University was fortunate, indeed, because at the freshman dance I met my current wife. It was not quite love at first sight on her part, however. We dated during most of the freshman year, and I wrote her letters during the summer of 1950. At the beginning

of the sophomore year, however, she told me, politely, to "get lost" because she had other boys interested in her. We both graduated in 1953—she went to Yale where she met her first husband, and the father of her five children. I went to Harvard to learn to be a doctor. We didn't come back together until our 25th class reunion, but we have been almost inseparable since then.

College was where I got my first real exposure to research. I was a chemistry major, and I particularly liked organic chemistry. One of the chemistry professors, Dr. Harold Nace, asked me if I wanted to work on an organic synthetic project he was doing. My job was to measure the optical rotation of the compounds he was synthesizing. It was a great introduction to quantitative chemical methods. The courses in organic chemistry also taught me lessons about the importance of basic science as an underpinning for later applications. In the early part of the twentieth century, a German scientist became interested in the chemical nature of the colors of butterfly wings. He worked out the organic structure, but this observation sat unused for nearly half a century. At the time I was in college, the tetracycline antibiotic drugs were discovered, and the chemical nature of butterfly wing colors turned out to be an important clue to the chemistry of these drugs. Science for science's sake has great value.

As a chemistry/premedical major I also took biochemistry. We had a very dynamic professor and a wonderful textbook. As part of the course we were asked to pick a topic to write about. The Krebs cycle (citric acid cycle) was a prominent part of biochemistry in those days, and I went back to the original papers written by Krebs and felt the excitement of the sequential description of the steps involved in showing how molecules were converted one into another during this important cycle. Again I experienced the excitement of discovery, even if only through reading the scientific literature.

During two summers in college I extended my laboratory experience by working for a local pharmaceutical company near Chicago. This company, G.D. Searle, would one day have as its CEO Donald Rumsfeld, with whom I had played as a child and who went to the same grammar school, junior high school, and high school that I did but was one year behind me.

During the first summer at G.D. Searle my job was as a relief worker in the vivarium, where I learned about the care and cleaning of rats and how to care for dogs and cats—or at least to keep them clean and fed. The next summer I was promoted to a laboratory technician's job and worked under Drs. Francis Saunders and Frank Sturdevant. Steroid hormones from the adrenal gland were receiving great notoriety following their successful use to treat the pain and inflammation of rheumatoid arthritis for which Philip Hench (1896–1965), Tadeus Reichstein (1897–1996), and Edward Kendall (1886–1972) received the Nobel Prize. Steroids from the adrenal gland could also produce hypertension in animals, and this was a hot research topic during my second summer at G.D. Searle. My summer job was to screen compounds that might block the hypertensive effect of steroid-induced hypertension. We came up with several compounds that fit this bill, but as often happens in drug discovery, they failed further up the line in human trials.

My time at G.D. Searle was just after Frederick Sanger (1924–2014) had described the structure of insulin. During occasional breaks I went to the very well equipped science library at Searle and read through this exciting series of papers. Unraveling the puzzle of insulin was like successfully assembling a very complex picture puzzle. He took the insulin molecule apart step by step and found out how it had to be assembled to provide the final structure. No wonder he won the Nobel Prize for this work.

My Years at Harvard Medical School in Boston

My research experience continued in medical school, where I got a research job between my first and second years in medical school working in the laboratory of Dr. Daniel Funkenstein

(1911–1994), a professor of psychiatry. Dr. Funkenstein was a wonderful and friendly mentor. At that time I still thought I might want to be a psychiatrist, but as a classmate of mine remarked later, "You would be like a fish out of water!" The results of my work with Dr. Funkenstein formed my first research publication. For the project, we measured the response to an infusion of either norepinephrine or epinephrine, the two major neurotransmitters of the sympathetic nervous system. They had strikingly different effects: Epinephrine produced alertness and arousal, as W.B. Cannon, a professor at Harvard, had suggested in his "flight or fight" thesis (28); norepinephrine had no such effects but produced detectable metabolic changes including a slowing of the pulse.

By the time my fourth year began I had already eliminated several medical specialties from my list of potential areas for patient care. I decided that I would concentrate on what is called internal medicine. This area of medicine has many potential subspecialties, and during my fourth year in medical school I took electives in three of them: (*a*) endocrinology, the study of glands and their secretions; (*b*) renal medicine, at a time when hemodialysis was in its infancy and a topic on which I published a case report in the *New England Journal of Medicine* with Drs. Warren Guild and John Merrill in the lead positions (34); and (*c*) pulmonary medicine, where we did a study on the pulmonary function of people with Marie-Strumpell arthritis, a bone disease in the back that makes coughing painful. I lived at the Peter Bent Brigham Hospital (now Brigham and Women's Hospital), and to earn my room and board, I was fortunate to work with Dr. George W. Thorn, chief of medicine and an internationally known endocrinologist, who was one of the first to use adrenal steroids to treat people with defective adrenal glands. These were very informative sessions and piqued my interest in endocrinology. The other exposure to endocrinology was in an elective at the Massachusetts General Hospital with Fuller Albright, another famous endocrinologist. Sadly, Dr. Albright underwent surgery for his Parkinson's disease during the summer before my elective and was unable to resume his work as an endocrinologist – I missed out on one of the most exciting teachers but still took the endocrine elective with his colleagues. At the end of my senior year both endocrinology and renal medicine were still contenders for my future career of clinical practice and research.

My Year at Johns Hopkins Hospital: The Spirit of Sir William Osler

During the internship process I was assigned to the Osler Service at Johns Hopkins Hospital in Baltimore. In addition to being the first chair of the department of medicine, Sir William Osler (1849–1919) was a noted medical historian and a great book collector (52, 53). Sir William Osler's humanitarian spirit still roamed the halls of the Johns Hopkins Hospital when I was an intern and added a new dimension to the medical education that I had gotten at Harvard.

During my time at Johns Hopkins Hospital I first read the advice of Sir William Osler in his famous "Fixed Period" essay (52), and it has continued to echo in my brain throughout my career. Osler divided the life of a physician-scientist into three phases: Phase 1 is the Period of Education, which usually lasts to about age 20 or a bit longer; Phase 2 is the Period of Scholarship, from age 20 to 40 or so; and Phase 3 is the Period for Teaching, from age 40 to 60. He noted that after age 60 few people make important scholarly or artistic contributions and should probably retire—with tongue in cheek he actually suggested they might be chloroformed, which got headlines in the *New York Times*. With this advice in my head from my internship on, I had anticipated retiring when I was 60 or 65, the usual time for most people.

My Years at the National Institutes of Health: Mentor Dr. Robert W. Berliner

During the last year of medical school I had applied to work at the National Institutes of Health (NIH) after my internship at Johns Hopkins Hospital and was accepted into the Research Associate

Program in both the National Heart Institute (now the National Heart, Lung, and Blood Institute) and the National Institute of Arthritis and Metabolism. After completing my internship I was off to the NIH to learn the rudiments of research. I had the great good fortune of selecting the laboratory of Dr. Robert W. Berliner (1915–2002) in the renal and electrolyte section of the National Heart Institute at the time when Dr. Berliner was its intramural director of research (32). This opportunity furthered my exposure to renal medicine, which had been a career contender at the end of medical school.

My arrival at the NIH was just after the area of renal physiology had been turned on its head, so to speak, by the publication of the countercurrent theory of urine concentration, which viewed the renal tubule as an anatomically functional unit, with the long-thin loop of Henle serving to concentrate urine in the kidney medulla much as a heat exchanger does in air conditioning. One assumption of this theory was that the contents inside the small loops at the bottom of the kidney medulla would have much lower concentrations than the fluid outside the tubule during water diuresis. My advisor, Dr. Berliner, set me to work measuring the freezing point depression of frozen sections of kidney slices from animals that had been loaded with water to produce a water diuresis. The more solute that is in solution, the lower the temperature needed to freeze the solution. Working in a cold room was no picnic, but the result was clear support for this new theory and provided the opportunity my first oral presentation at the Federation of American Societies for Experimental Biology (FASEB; now Experimental Biology) in Chicago. This meeting occurred just after jet airliners went into wide service, and I got my first trip on one in 1959 on the way to Chicago.

Shortly after that, Dr. Bodil Schmidt-Nielsen, one partner of a famous husband-and-wife science team, showed that sheep were able to maintain differences in urea concentration across tubules of the kidney. Urea is a small molecule produced in the liver during metabolism of amino acids and that is excreted by the kidney. It is generally considered to be quite diffusible—that is, it can cross membranes easily. Sheep have a different renal structure than many mammals, and we were interested in whether the concept of urea transport would apply to another mammal, the rat. One problem we confronted was how to easily measure radioactivity in a solution like urine. Urine is a very complicated mixture of molecules that, because of the high concentration of sodium and other excretory products, can readily quench radioactive emissions from radioactive compounds. One by-product of my renal research was the development of a simple method for measuring small amounts of radioactivity in urine and other watery solutions. This cocktail became known as "Bray's Solution" and resulted in one of my most highly cited publications (10). The other outcome was the demonstration that rats, like sheep, could maintain gradients for urea in their kidney (24).

So ended the exciting years at the NIH that confirmed my choice of a research career and left me leaning toward endocrinology. During my second year at the NIH, Martha Bardenhagen (1933–2005), a nurse whom I had met when I was an intern at Johns Hopkins Hospital, and I got married and began domestic life alongside the research life.

My Year at Strong Memorial Hospital in Rochester, New York

After completing my two years at the National Heart Institute, I became a medical resident at the Strong Memorial Hospital of the University of Rochester in Rochester, New York. By now it was obvious to me that I was on a track for a research career. After completing my medical residency I became an endocrine fellow with Dr. Christine Waterhouse (1916–2004) and Dr. John Plager (1927–2008) in Rochester. It was also during this 18 months that George Hamilton Bray (1961–1990) was born in May 1961, just before the annual Lilac Festival in Rochester.

My Year in London: Mentor Dr. Rosalind V. Pitt-Rivers

During my two years at NIH I had the good fortune to meet Dr. Rosalind V. Pitt-Rivers (1907–1990), who was a visiting scientist from the National Institute for Medical Research at Mill Hill in London, England (66). She had just recently discovered a new form of thyroid hormone called triiodothyronine (T3). T3 turned out to be the active form of thyroid hormone. I asked her if I might spend a year in her laboratory at the National Institute for Medical Research in Mill Hill after my medical residency. She graciously said yes, and in November 1961 my wife, Martha, my 6-month-old-son, George, and I set sail for Southampton.

My research in London revolved around thyroid hormone and the sympathetic nervous system. We had observed that thyroid hormone alters the way in which drugs that mimic the sympathetic nervous system work. The drug reserpine, which is isolated from plants, was in use for the treatment of high blood pressure in humans. We found that its action was blunted in animals whose thyroid gland had been removed, as well as in animals whose adrenal glands had been compromised.

My Years in Boston: Mentor Edwin B. (Ted) Astwood

After returning to the United States in the fall of 1962, I joined Dr. Edwin Bennett Astwood's (1907–1996) laboratory for my third postdoctoral fellowship—similar to the number of postdoctoral years spent by many young scientists today. Dr. Astwood was a member of the National Academy of Sciences based on his discovery of antithyroid drugs for the treatment of hyperthyroidism (33). Dr. Rosalind Pitt-Rivers, a member of the Royal Society and with whom I had worked in London, was noted for her work in discovering T3, so a career in thyroid research seemed right over the horizon.

MY SCHOLARLY YEARS

> When you come to a fork in the road, take it!
>
> —*Yogi Berra*

Obesity Research Wins Out Over the Thyroid and Kidney

Professor Astwood's laboratory was one of the leading training grounds for endocrinologists at the time I was a postdoctoral fellow. The first studies I did after moving to Boston were in collaboration with another postdoctoral fellow, Dr. H. Maurice Goodman, who subsequently became chairman of the Department of Physiology at the University of Massachusetts in Worcester. While working together we charted the time course for induction by T3 of biological activity in adipose tissue exposed for various periods of time.

One day as we were performing one of our collaborative experiments, Professor Astwood came into the laboratory and described a group of fat animals that he had recently received. They were a gift from Dr. Lois Zucker and carried the name of the husband-and-wife team of Zucker and Zucker, who first identified these animals. They were genetically obese rats that inherited their obesity as an autosomal recessive trait. Weak willpower was clearly not the reason why these rats were fat—it was something in their genes. That genetic trait is now known to be a defect in the leptin receptor, but this was not even guessed at in 1962, since the discovery of leptin was still 30 years in the future.

A number of genetic diseases had been unraveled in the 1960s and found to reflect a single enzyme defect, which led to the one gene–one enzyme hypothesis for inherited diseases. Dr. Astwood suggested that the study of these animals would make an interesting project. His

suggestion may have been stimulated by the Endocrine Society Presidential Address, entitled "Heritage of Corpulence" (2), that he was preparing to give. Without knowing any better, I started some early studies on these animals while keeping up my thyroid hormone research.

Research work requires money. To fund my research work, whatever it was going to be, I wrote two grants for the NIH. One of them elaborated on the work with T3 and adipose tissue, and the other one focused on unraveling the mystery of the Zucker rats. When Study Sections at the NIH reviewed these grants, the one examining the Zucker fatty rats received a high score and was funded; the other got a low score and was not funded. My directional sails were thus set—it was the beginning of a career in obesity research from which I have not looked back.

Research in Boston

One of the challenges in obesity research is to separate the cart from the horse—did obesity drive the changes we observed, or were the changes we observed the cause of the obesity? Thus, some sort of "controls" or comparative systems were needed to separate cause from effect. For the genetically obese Zucker fatty rats, the development of an animal model that became fat eating a high-fat diet was one obvious comparator. Another was an animal with an injury to the ventromedial hypothalamus, which had been known to produce obesity in human beings since the reports by Frohlich (27) and Babinski (4) and the work of A.W. Hetherington and S.W. Ranson (1880–1942) (38, 47) in rats. And so my basic animal models were chosen, and off we went.

As a clinician, I always felt an obligation to translate my animal work into studies that might benefit my overweight patients. Identifying genetically obese human beings was one approach, and several such examples were known at the time, although they were relatively rare. Alternative comparators were individuals with obesity that follows hypothalamic surgery for certain types of brain lesions. The neurosurgery department at Tufts University Medical School had several patients who had developed obesity in association with a craniophyringoma—a tumor on the pituitary stalk that leads from the brain to the pituitary gland. In one study we found that serum insulin concentrations did not fall as expected in these patients during fasting as compared to normal or obese individuals who did not have hypothalamic injury (20).

Another type of human obesity results from overfeeding to produce weight gain, a theme that began during collaborative studies between our group in Boston and Dr. Ethan Sims (1916–2010), who pioneered this approach from his laboratory in Burlington, Vermont. A key question in the Vermont studies was, again, what comes first, the chicken or the egg, so to speak: Does the obesity produce insulin resistance, or does insulin resistance precede obesity and play a role in its development? Are other hormonal and endocrine changes that we measure a result of being obese, or do they contribute to the onset of the obesity?

To address this question, Sims and his colleagues (64) asked healthy young normal-weight men to overeat until they increased their body weight by 25%. By comparing the men before and after weight gain, these researchers showed that the extra fat was stored in larger fat cells and that there was no increase in the number of fat cells. An increase in insulin resistance and a reduction in growth hormone release after overeating were also seen. I was fortunate enough to participate in one of these overfeeding studies and to measure the production of fat in fat cells obtained from adipose tissue biopsies. This early experience with overfeeding would resurface throughout my career.

Transition: From Boston to California

As the 1970s came to an end, several unsettling events were on the horizon at the Tufts-New England Medical Center. First, as happens to all of us, Professor Astwood, that wonderful and scholarly man, was preparing to retire, which would leave a big void in the Endocrine Division.

In addition, the chairman of the Department of Medicine, Dr. Samuel Prodger, was also retiring, which left a void at the top of the administration. As I was stewing about potential options, a colleague invited me to Los Angeles to visit the Harbor-UCLA Medical Center and to consider a job as director of the Clinical Studies Unit there. I flew to Los Angeles reluctantly but liked what I saw. On a cold winter's day a few weeks later, I looked out my bathroom window and saw that the thermometer read 10°F. I had already shoveled my driveway several times that winter, and as I mulled over the situation, Los Angeles looked better and better. So with fond adieus to Tufts-New England Medical Center, my family and I decided to move from Boston to Torrance, California.

My first postdoctoral fellow at Tufts was Dr. David A. York (see **Figure 1**), who came from the University of Southampton in England. He was in the midst of his two-year fellowship when I accepted the offer from Harbor-UCLA Medical Center. I discussed the options with David. He could stay in Boston, where his wife had gotten a job, and work with another mentor at Tufts, or he could move to Los Angeles and continue to work with me. Without hesitation he decided to move. The moving van came and packed up our belongings, we packed up the children, one of whom required a couple of stitches from a cut generated when he hit his head on a kitchen cabinet in his enthusiasm, and we headed west.

My Years at Harbor-UCLA Medical Center in Torrance, California

The move to the Los Angeles area proved very productive. The chairman of Medicine, Dr. David Solomon (1923–2013), had moved from the main UCLA Medical Campus in Westwood to the Harbor Hospital in Torrance and began recruiting faculty. The senior faculty made the endocrine program at Harbor-UCLA one of the best and most attractive in the country. When Drs. Bill Odell and David Solomon offered me the position in Los Angeles in 1970, I couldn't say no.

One of the key research findings from my laboratory during this decade was the important relationship between obesity and the autonomic nervous system. Several studies buttressed this relationship. The first was that cutting of the vagus nerve, a key neural connection between the brain and the gastrointestinal track, prevented the obesity and the rise of insulin that follows hypothalamic injury. In a critical experiment, we showed that transplantation of the beta cells from the pancreas to the kidney capsule prevented hypothalamic obesity (42).

The sympathetic nervous system is another part of the autonomic nervous system that connects the brain to the rest of the body. Damage to the ventromedial hypothalamus at the base of the brain reduces sympathetic activity. In contrast, damage to the more lateral hypothalamus increases activity of the sympathetic nervous system (51, 72). Establishing these relationships was an important contribution from my laboratory (43).

In Los Angeles we also added another clinical type of obesity to the group of patients I was studying. These were patients with a syndrome first described in 1956 by Prader, Labhart, and Willi in a Swiss child who had been a floppy baby with hypotonic musculature and required early feeding, then began to eat almost anything in sight and became obese. Patients with what is now referred to as Prader-Willi syndrome (Labhart's name was dropped) have a congenital disease in which the affected children from different families look more like each other than other members of their own family. This disease can be diagnosed before birth because the babies move very little in the womb. They are born as floppy, or hypotonic, babies and often have trouble feeding and may need to stay in the hospital for a few extra days. Within a short time after birth these children begin to overeat and become very fat. They also have slow mental development, have trouble keeping up in school, and they do not develop sexually. We asked whether this reproductive problem could be reversed by clomiphene, a drug that modifies estrogen receptor responses in the brain. This drug was indeed effective in initiating the hormonal responses that precede puberty. When we stopped

Figure 1

A caricature of George Bray and his first fellow David York at a conference commemorating Dr. Bray at the 1999 meeting of the North American Association for the Study of Obesity. Dr. Bray is depicted as Don Bray after the errant knight Don Quixote and Dr. York as his inseparable sidekick Squire York. The caricature was drawn by Dr. Leslie Kozak from the Pennington Center.

the drug, the reproductive system returned to the preadolescent stage it had been at before the study began (19).

The other model of obesity that we continued to pursue in Los Angeles was the response to overfeeding. The first overfeeding study, which began a few years after my arrival, examined whether overfeeding changed muscular efficiency during exercise. Since I was going to ask normal-weight people to gain weight, I thought I should go through the experience first. My plan was to double my food intake. Instead of one sandwich for lunch I had two, and so on. This didn't last very long, however. The volume of food was too much, and I needed more ice cream and fatty foods to be able to ingest enough calories. After three months of stuffing myself, my weight increased from

165 to 196 pounds. It was one of the most unpleasant experiences of my life. I had few clothes I could wear. I was so stuffed that I couldn't sit down comfortably. Sleeping was difficult because I was too warm; whereas I normally needed blankets during the winter, when I was overeating I needed none at all. I was glad when I reached my target weight and the overfeeding could stop. As with almost all overfeeding studies in healthy people, my weight just slid right down to where it had been before I started and where it remains today, more than 40 years later.

International Congresses on Obesity and the *International Journal of Obesity*

The year was 1972. Richard Millhouse Nixon had just been re-elected president of the United States, in spite of the continuing Vietnam conflict. The Watergate scandal would soon be unearthed. The Vietnam War continued, with public unrest still at high levels (although 50,000 men were killed, and it should have officially been a "war," it was never declared one by Congress). The John E. Fogarty International Center for Advanced Study in the Health Sciences at the NIH had been formed in 1970, and as one of its early projects, the Fogarty Center director decided to organize a series of international conferences on significant public health issues. The first conference was about diabetes, and the second focused on obesity. Considering the subsequent explosion in the prevalence of obesity, it may be difficult to believe that obesity could have been considered a major public health problem as far back as 1972. But it was.

At the time that planning began for the Fogarty Center International Conference on Obesity, I was one of the few mid-career physicians doing research in obesity and was asked to chair the organizing committee (11). A cover of the publication from this meeting is shown in **Figure 2**. At the same time as the Fogarty Center was beginning to tackle obesity, the Senate Select Committee on Nutrition, under the leadership of Senators Robert Dole and George McGovern (1922–2012), began a series of hearings on the nutritional issues behind the rise of chronic diseases in the United States following World War II. As the hearings progressed, those of us involved with the Fogarty Center conference testified about the issues related to obesity. On the basis of these hearings, the Select Committee developed a set of nutritional recommendations or guidelines for the public that were published in the Congressional Hearings Report of 1976 (**Supplemental Table 1**; follow the **Supplemental Material link** in the online version of this article or at **http://www.annualreviews.org**) (60) and set off a wide-ranging debate in the field of nutrition.

Supplemental Material

The spring of 1972 was also the time when I met Dr. Alan Howard for the first time. We had both been invited to an international meeting in Germany. I knew of Alan's work since he had coedited with Ian McClain-Baird the *Proceedings of the Association for the Study of Obesity* meeting held in London in 1968 (5). To get better acquainted we drove to the pleasant town of Bingen am Rhein to have glass of Rhine wine. We talked about obesity—where it was, where it could be, and how it might get there. It was a prophetic meeting. Planning for the Fogarty Center Conference to be held in 1973 was well under way. We realized that a larger international congress was also needed, and Alan began to organize the First International Congress on Obesity at the Royal College of Physicians in London in 1974. There were just over 500 attendees. Other international congresses followed.

The idea for the *International Journal of Obesity* was also conceived at our meeting in 1972 (21), and specific plans moved forward after the 1974 International Congress in London. With Bray and Howard as the initial editors, the search was on for scientific articles. The first quarterly issue of the journal was published in January 1977 (**Figure 3**). The birth of a new journal, even in 1977, is not a guarantee of success (15). Indeed, there is a quite high early mortality. Before it could enter the list of journals included the Index Medicus, the citation system of the National Library of Medicine, a journal had to be published for two or more years and then be selected for indexing

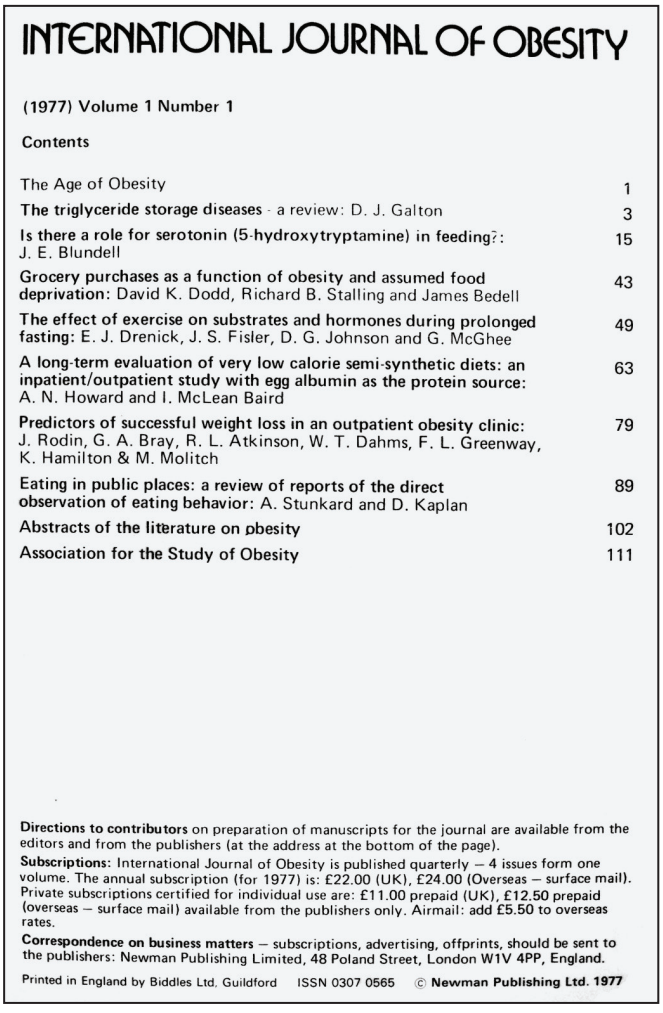
Figure 2

Cover of the publication from the 1973 Fogarty Center International Conference on Obesity.

based on its quality and relevance to medical research. Thus, the earliest papers in the *International Journal of Obesity* were not indexed and are often difficult to cite because they are not included in the indexing services. This was compounded by the fact that the initial volumes of *IJO* lacked an index of the content in the journal itself. To fill out each of the first issues, we included abstracts of papers published elsewhere—a strategy similar to that of many journals in the eighteenth and nineteenth century (15).

In an editorial in the first issue entitled "The Age of Obesity," Howard & Bray (41) felt confident in stating, "Obesity is the most prevalent nutritional disorder in developed countries, yet research on this condition has been much neglected compared with other diseases of civilization." Since the founding of this journal the prevalence of obesity has only become more severe, and research has increased dramatically.

The late 1970s were hectic for me. Research work was going well. There were the Congressional hearings on nutrition and then on obesity. The Second International Congress on Obesity and the Second Fogarty International Conference, both of which I organized, were held in Washington, DC, in October 1977. My 25th reunion from Brown University was in 1978. As a freshman at Brown I had met Marilyn (Mitzi) McClanahan (nee Rice), and we had dated for nearly a year.



INTERNATIONAL JOURNAL OF OBESITY

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Contents

Directions to contributors on preparation of manuscripts for the journal are available from the editors and from the publishers (at the address at the bottom of the page).

Subscriptions: International Journal of Obesity is published quarterly – 4 issues form one volume. The annual subscription (for 1977) is: £22.00 (UK), £24.00 (Overseas – surface mail). Private subscriptions certified for individual use are: £11.00 prepaid (UK), £12.50 prepaid (overseas – surface mail) available from the publishers only. Airmail: add £5.50 to overseas rates.

Correspondence on business matters – subscriptions, advertising, offprints, should be sent to the publishers: Newman Publishing Limited, 48 Poland Street, London W1V 4PP, England.

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Figure 3

Cover of the first issue of the *International Journal of Obesity*.

However, after that we each went our separate ways. We were both present at the 25th reunion and saw each other "across a crowded room," as the song from the movie *South Pacific* goes, and we gradually drifted together. She was working as the director of the High Blood Pressure Council in Los Angeles, so we were almost neighbors. It wasn't long before we began to see each other regularly, and in 1982 we were married and have been happily so ever since.

In 1972, Alan Howard and I also looked into the crystal ball and saw the need for an organization in the United States focusing on scholarly work in obesity, similar to the Association for the Study of Obesity in the United Kingdom. It would take most of the decade for this to come to pass. The NBC *Today* show sent reporters to a 1972 debate in which Dr. Robert Atkins (1930–2003) and I participated; it was held during a meeting of the American Society of Bariatric Physicians in Las Vegas, Nevada. NBC subsequently produced a full-length television show about obesity, which indicated to me that obesity had "come of age." In 1973, the US Food and Drug Administration approved fenfluramine, the first new drug approved to treat obesity since 1960. This event and

the publication of many popular diet books with advice on treating obesity, as well as the Fogarty Center conference (11), propelled interest in obesity to a high level and gave hope for a bright future.

The first International Congress on Obesity was held in 1974, and others were scheduled to be held at three-year intervals. While planning for the second Congress in Washington in 1977, I had begun to scout for places to hold the third Congress. Italy was a good potential European location. The Union Contro L'Obesita, with Dr. Michelangelo Cairella as its leader, was an active Italian academic society interested in obesity, and after some discussions this group agreed to host the third International Congress in Rome in 1980.

Treatment for patients with obesity has always been a challenging and sometimes frustrating experience for me. In Boston I had limited my medical practice to individuals who weighed more than 300 pounds, but there was no shortage of these patients. As I was moving to Los Angeles, surgical approaches to treating obesity were just beginning to appear. The first of these, and the one we worked with for several years, was the jejuno-ileal bypass, which shortened the length of absorptive intestine through which food flowed by making a "blind" loop where there was no flow. This blind loop turned out to be the downfall for this surgical technique; bacteria lived in it and produced bacterial products that caused other diseases, such as arthritis, because the microbes were never flushed out of the intestine by the flow of intestinal juices. Eventually this operation was abandoned in favor of the gastric bypass introduced by Drs. E.E. Mason and C. Ito in 1967 (47), which is now one of the main approaches to the surgical treatment of major obesity.

Popular books about how to treat and "cure" obesity have been published for more than 250 years (6, 30, 50, 62, 68). As the field of behavioral treatment for obesity began to expand during my time in Los Angeles, the time appeared ripe to try to use my experience in a more public way. Dr. Judith Rodin, one of the young scientists at the Fogarty Center conference in 1973 and now head the Rockefeller Foundation, came to Los Angeles after the conference to spend a bit of time doing research in my laboratory. We began planning a book about the treatment for obesity. When Dr. Rodin moved back to Yale to continue her meteoric rise up the academic ladder, this book project came to an end. Although other potential books popped up over the years, none came to fruition. There was one with a food writer from the *Los Angeles Times*, one with a science writer from *Time* magazine, and a couple of others, none of which ever saw the light of day. This reinforced the sentiment I quoted from Chargaff at the beginning of this article that scientists (and physicians) "often do not know how to write." Years later, however, I did write a book on my own that contains the elements of the clinical program that I had developed in Los Angeles some 30 years earlier (18).

Transition: 1978 Sabbatical and Nutrition Coordinator

After the second International Congress on Obesity in 1977, I took what I considered to be a well-deserved nine-month sabbatical leave. It was divided into three main parts: The first part was in California; the second part in Washington, DC; and the third part was split between London and Gothenburg, Sweden.

For three months I commuted from Los Angeles to the University of California campus in Berkeley to work on energy expenditure in older Americans with Dr. Sheldon Margen (1919–2004) and Yves Schutz, a graduate student. We published an interesting paper showing that heart rate could estimate energy expenditure during exercise but that it was not a very good surrogate measure for energy expenditure for people at rest.

The second three months were spent in Washington, DC, working in the Department of Health, Education, and Welfare (now DHHS) on the issues raised during the Congressional

hearings on nutrition and obesity a few years earlier under the egis of Senators Robert Dole and George McGovern (60). I learned a great deal about how things got done (or didn't get done) in Washington, and I developed great admiration for the high quality of the staff members working in Congress. They were smart, hard working, and dedicated to their jobs. During my time in Washington I worked for Dr. Michael McGinnis in the Office of the Surgeon General of the Public Health Service.

The final three months of my sabbatical were during the summer of 1978. I left Washington in late spring for London to work in Sir Peter Medawar's laboratory, investigating whether changes in a particular enzyme we were interested in remained abnormal after transplanting tissues from a genetically obese animal to a nonobese animal. In short, the enzyme changed to the same level as in the recipient tissue and did not remain like that of the donor. I also took a course on the history of medicine at the Wellcome Unit for the History of Medicine, with Dr. Christopher Lawrence as the instructor. As my project I wrote a paper on the history of obesity (13). While working on this project, I came across a fascinating dissertation published in 1875 by Dr. Lewis Sedam Worthington (1839–1919) (71). Dr. Worthington was an American from Cincinnati, Ohio, who had gone to France to learn more about clinical medicine, as so many Americans did during the nineteenth century. Worthington's 179-page dissertation about obesity (71) was written at a time when there was no Internet, no Google, no PubMed, and no Library of Congress, yet he was able to identify 40 other dissertations related to obesity that had been defended in universities across Europe in the eighteenth and first part of the nineteenth century. As I read Dr. Worthington's dissertation I marveled at his ability in the nineteenth century to make his way through the information generated in many universities all over Europe that focused on the theme of obesity. Hats off to you, Dr. Worthington!

The other part of the summer was spent doing a project in Sweden with Dr. Per Björntorp (1931–2003) (63) and Dr. John Kral. Per and I were born within a couple of months of each other in 1931, and he and I had met at both the first and second International Congress on Obesity. He was a delightful man and a highly skilled cellist in addition to being an excellent physician-scientist and a sailor to boot. The young clinical investigators who were working in his laboratory have gone on to do some of the best obesity research in the world.

We got the preliminary work set up for our experiment in a few days, and then because the Swedes take a long summer vacation, I left Sweden and returned in early September to resume our project. Liver biopsies were a routine part of the surgical treatment of obese patients in Sweden, and Dr. Kral (a surgeon) collaborated in providing samples for our investigation into whether a specific enzyme (Na-K ATPase) that I was also studying in London was altered by obesity. It was not, and the results were sufficiently interesting to be published in the *New England Journal of Medicine* (22). Also while in Gothenburg, Björntorp and I began to work together to support Professor Cairella's efforts in organizing the third International Congress on Obesity in Rome, which turned out to be a smashing success in large measure because of Björntorp's input.

As I was completing my sabbatical leave in London, a most unusual opportunity opened up—to be the first nutrition coordinator in the Department of Health and Human Services in Washington, DC. Dr. Odell, chairman of medicine at the Harbor UCLA Medical Center, was supportive of this additional time away, and I spent the next nine months working with Dr. Michael McGinnis, who was responsible for many public health initiatives in the Public Health Service. During this time we began to assemble what are now known as the Dietary Guidelines. This was done in collaboration with the US Department of Agriculture, where one of my teachers from Harvard Medical School, Dr. Mark Hegsted (1914–2009), was working on the same project. This was an active time for nutrition in Washington, DC, but I was concerned about getting "Potomac Fever," a disease that draws people into the miasmic environment of Washington, from which they never

escape (12), so I reluctantly returned to Los Angeles in 1979. I realized that it would be the best long-term decision for someone who was basically a clinical investigator.

Being gone from Los Angeles for nearly two years had strained my research credentials. My absences from the Harbor-UCLA Medical Center for a sabbatical leave and then the position as nutrition coordinator at the Department of Health, Education, and Welfare had slowed my basic research work. I had a lot of scientific literature to read, and I needed to do it rapidly. It was through the help of a grant from the Nutrition Foundation and another from the Weight Watchers Foundation that I managed to bridge the time until I could get my NIH grants refunded. My research work gradually geared up again as the NIH grants got renewed. When the opportunity opened up in 1981 to become the University of Southern California (USC) County Hospital Chief of Diabetes, the time was ripe to move, and I did so.

Founding of the North American Association for the Study of Obesity (The Obesity Society)

The year 1980 was important for the obesity plan developed in 1972. At a meeting of the Nutrition Committee of the American Heart Association that year, Dr. John Brunzell (1937–2015), a clinical investigator at the University of Washington in Seattle, again suggested to me that there was a need for an organization to focus on the scientific aspects of obesity. This was what Dr. Alan Howard and I had concluded nearly a decade earlier, and it was now time to take up the challenge. Over the next two years I planned the first meeting for the North American Association for the Study of Obesity, or NAASO as it came to be called. With a grant from the NIH for a conference on childhood obesity, a planning committee composed of Bray, Dr. Marci Greenwood (chair of the Department of Biology at Vassar College), and Dr. Wayne Calloway (an internist from the Mayo Clinic who was serving as the third nutrition coordinator in the US Department of Health, Education, and Welfare) put together a program for the first meeting of NAASO at Vassar College in October 1982 (**Figure 4**). Thirty-nine abstracts were presented at this meeting, along with scientific papers for a joint forum.

The second meeting of NAASO occurred in 1983, simultaneously with the Fourth International Congress, in New York. This second NAASO organizational meeting, which I chaired, brought together many of the North American leaders in obesity, who ratified the structure for NAASO. Dr. Barbara Hansen was elected president of NAASO, and she, along with her husband, who is both a physician and a lawyer, solved the legal issues needed to put NAASO on the path it has taken over the past 30 years.

My Years at the University of Southern California, Los Angeles

While on sabbatical from UCLA in 1978, I had relinquished the leadership of the Clinical Studies Center at the Harbor-UCLA Medical Center. When I returned nearly 18 months later I felt a bit lost. It was at this time that Dr. Jack Bethune, chairman of the Department of Medicine at USC, offered me the opportunity to lead the Diabetes Section at the Los Angeles County Hospital and to become a professor of medicine at USC. With a large laboratory, I was set to do nearly a decade of basic research before the next call came. During these years, the NAASO got off the ground and became a growing and thriving entity. The *International Journal of Obesity*, which I had edited, was also thriving. I was ripe for another challenge.

Clinical studies were also a part of the research program at USC. We continued to pursue the control of feeding in individuals with hypothalamic injury, whom we had begun to study in Boston nearly 20 years earlier. Cholecystokinin is a gastrointestinal peptide involved in release of bile from the gallbladder and which also reduces food intake. We were interested in whether this

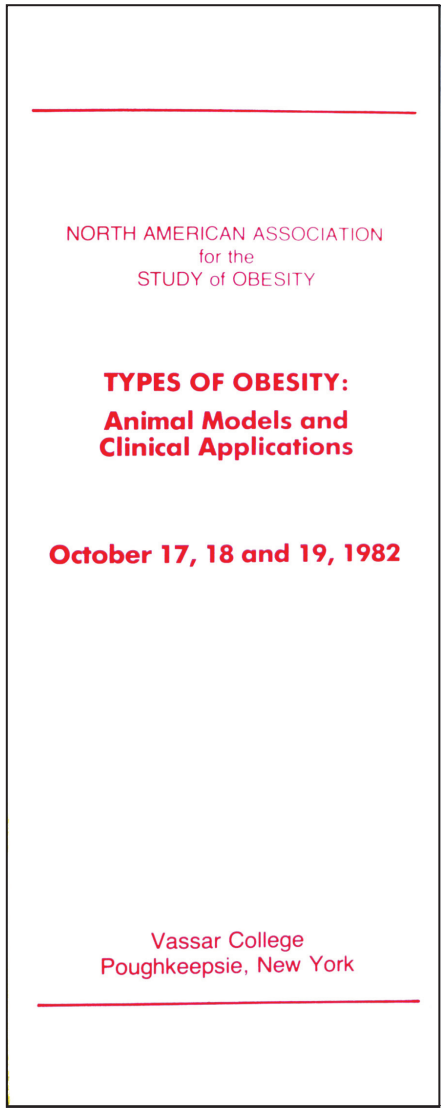

Figure 4

Cover of the publication from the first meeting of the North American Association for the Study of Obesity.

reduction in food intake was abolished by hypothalamic injury. Utilizing the Clinical Research Center at USC, we found that this peptide was just as effective in patients with hypothalamic obesity as it was in individuals with other types of obesity, meaning that some centers for feeding control were still functioning when others had been damaged (9).

My eight years at USC were heavily involved with academic service, much as the "Fixed Period" essay of Sir William Osler (52) had predicted would be the case. During this decade I served for four years on the Advisory Council to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), for four years on the Board of Regents of the American College of Physicians,

and as president of the American Society for Clinical Nutrition. In addition, I did my teaching and medical care at the Los Angeles County Hospital. To use the words of Hassall, the man who was among the first to describe the fat cell under the microscope in the nineteenth century, I had a very busy life (36).

THE ADMINISTRATIVE/SCHOLARLY YEARS AT THE PENNINGTON BIOMEDICAL RESEARCH CENTER

Transition to Executive Director

It was the fall of 1987—some six years since I had moved from UCLA to the USC Medical Center—when a letter arrived from the Louisiana State University (LSU) in Baton Rouge describing a newly established nutritional research center and asking whether I would be interested in being a candidate for the position of executive director and vice-chancellor in the medical center. The letter was intriguing enough that I took it to Dr. Bethune, my department chairman, to get his sage advice. Dr. Bethune noted that my research space at USC was about 10,000 square feet and occupied the lower floor of a four-floor building that provided 40,000 square feet of research space. This building was in turn attached by corridors to a second wing that had an additional 40,000 square feet. Dr. Bethune pointed out that the Pennington Center, with 225,000 square feet of space, was equivalent to nearly three buildings the size of the one I was in at USC! He said the opportunity was too good not to explore.

In January 1988 I took my first trip to New Orleans to interview for the job at the Pennington Center. I was met at the airport by Dr. Donna Ryan, vice-chancellor for clinical affairs at the LSU Health Sciences Center. I met with Dr. Allen Copping (1927–2011), president of the University, who had secured the original donation of $125 million from Claude Bernard "Doc" Pennington in 1981.

I first met Mr. Claude Bernard Pennington (1900–1997) while being recruited and continued to meet him periodically over my 10 years as executive director. He had been an optometrist until his father, a physician, died in 1920. The story I heard was that his given names, "Claude Bernard," were based on information his father had learned during his training; I presume that this refers to the French investigator, Claude Bernard, who worked in Paris during the middle of the nineteenth century. After his father died, Mr. Pennington began his lifelong search for gas and oil. He had made money off and on until his large oil finds in the 1970s. When I went into his office I saw an overweight man with a pronounced rhinophyma—or a bulbous nose. He usually wore the same houndstooth jacket whenever I saw him. It had many small holes left from the sparks, evidence of the pipe and cigars that he had smoked for years. His morning breaks were said to feature crispy fried bacon. Clearly he was a man whose genetic background allowed him to reach his advanced age in relative good health in spite of nutritional and lifestyle habits that would confound most of us.

The opportunity was certainly attractive, but as an individual educated in the East and working in California, the issue of whether I could recruit high-level scientists to work in Louisiana continued to give me hesitation. I ran this question by a number of people, and after a second visit in April 1988, I asked Dr. Barbara Hansen, a longtime friend and research administrator, if she would evaluate the opportunity objectively. She arranged a visit to Baton Rouge, and at the end of her visit she said, "You'd be a fool not to take it."

During the first half of 1989 I was again on sabbatical and spent part of my time in Southampton, England, with Dr. David York, my first research fellow from the early 1970s in Boston. He was getting restless at the University of Southampton. When I discussed the Pennington Center with him, he said he would be interested in the possibility of joining me there. When I took up the

position on August 1, 1989, Dr. York was my first candidate for recruitment. He brought the whole family—his wife, Barbara, and their children, Duncan and Emily—to visit Baton Rouge and the Pennington Center on a hot, humid Louisiana summer day. He was impressed and took the offer.

Dr. York was the first of what I call the three musketeers, the people without whom the Pennington Center would not have risen to its current level of excellence. The second of these key people was Dr. Donna Harrington Ryan. Dr. Ryan is a native of Louisiana and had graduated from LSU Medical School in New Orleans, where she stayed to do her clinical training in hematology and oncology. Her skills with the house staff and administration were evident to Dr. Copping, then the chancellor of the Medical Center, and he appointed her as a vice-chancellor for clinical affairs. In this position she was a teacher par excellence, a clinician loved by her patients, and a hands-on administrator. When the Pennington Center received money from the US Army, Dr. Copping turned to Dr. Ryan to organize its use, which she did so effectively that it was a win-win situation for everyone, and the US Army has continued to work with the Pennington Center ever since it opened in 1989. When I was looking for an associate executive director for clinical science, Dr. Ryan applied and was by far the best candidate. We started to work together in the winter of 1989–1990, and my working relationship with her has been one of the most enjoyable of my career. Although trained in cancer medicine, she took to obesity medicine like a "duck to water" and headed many of the initiatives that put the Pennington Center on the map. I will be forever indebted to Donna Ryan just as I am to David York, who spearheaded the basic science efforts at the Pennington Center.

The third member of the three musketeers was Mr. William Silvia, the chief financial officer. Bill was one of those "bean counters" who viewed his job as "How can we get things done?" rather than "You can't do that." He had worked in several parts of the Louisiana administration before he came to the Pennington Center. Bill was one of the people that Dr. Copping had also spotted, and he said I could move Bill to the Pennington Center from the main administrative offices to help get things going. The 10 years I was director, working with Bill Silvia, Donna Ryan, and David York, were 10 of the most exciting and rewarding years of my life. The success of the Pennington Center is in large measure a tribute to their great and diverse skills. Thanks, guys and gal!

As the spring of 1990 rolled around, the annual legislative session of three months was about to begin. It was time to meet with Governor Charles Elson "Buddy" Roemer to remind him of his $2 million financial commitment, which he had made at the time of my appointment. A group including Mr. John Barton and Mr. Kevin Reilly from the Pennington Foundation, along with Dr. Ryan and Mr. Silvia and I, arranged a meeting with the governor through his chief of staff. On the appointed day we all arrived at the capital and were ushered into the governor's office, where he was sitting behind the desk with his feet up. We exchanged the usual pleasantries, and the Governor then said, "I think I promised to give you $5 million for the Pennington Center, didn't I?" How could we contradict the governor? Of course we knew he had only promised us $2 million, but we politely said, "Yes sir, you could be right—I think that's the figure." From this point onward the $5 million line-item appropriation began to move its way from the governor's office through the legislative system and eventually into law. At one point there were 98 items on the "ancillary budget" and we were 96th, just behind a new carpet for the lieutenant governor's office. However, when all was said and done, our appropriation survived, and we had the money we needed to move ahead.

So, how do you grow a building known only to its neighbors into a nationally recognized research institution? When I arrived there was enough space for each of the 25 individuals to have 10,000 square feet for themselves. The name Pennington Biomedical Research Center had little recognition except to its nearby neighbors. One of my first challenges was to give the institution

a "brand" that would be recognized as a place for excellence in nutrition research. I had learned a lot about this in Los Angeles from Dr. David Solomon. He had branded the Harbor Hospital Medical Center in Torrance as distinct from the main UCLA Medical Center in Westwood by continually introducing himself as from Harbor Hospital Medical Center in Torrance rather than UCLA. Since Dr. Solomon was well known for his work on the thyroid and in endocrine circles, it took only a short amount of time to bring unique recognition to Harbor-UCLA. I followed Dr. Solomon's lead and consistently introduced myself at meetings as from the Pennington Center and left it at that. It didn't take long for people to recognize that the Pennington Center was an academically serious research institution in Baton Rouge.

Having made this initial step, the next one was to identify people who might be willing to join us. This was easier said than done. Senior scientists are hard to move, particularly to Louisiana. However, young scientists were easier to recruit, and over the first few years we recruited a number of very bright young individuals, several of whom have gone on to be presidents of the Obesity Society and to make major scientific contributions to the field. The use of annual symposia focused around the interests of the Pennington Center helped spread our name by bringing experts to Baton Rouge to see our outstanding facilities. Mr. Pennington's gift was a real boon to the entire community.

As the Pennington Center was coming out of the "gate," a second research facility, known as the Center for Advanced Micro Devices, or CAMD for short, was built with congressional money that allowed LSU to construct a linear accelerator that could be used for making micro machines. At their inception in 1990, both required about $3 million to operate. Their growth trajectories, however, were very different. At the 10-year mark, the Pennington Center had an annual budget of nearly $20 million, but CAMD had hardly grown beyond its initial budget. In retrospect, two important differences may account for the growth of one and not the other. First, the Pennington Center was overseen by the president's office, and CAMD by the vice-chancellor for research. Second, academic appointments at the Pennington Center were locally controlled, whereas the physicists at CAMD who wanted academic appointments had to negotiate them with the department of physics. Within this environment, one institution grew rapidly and the other did not.

Obesity Research: A New Journal is Born

Since the *International Journal of Obesity* began in 1977 and NAASO was founded in 1982, the field of obesity research had continued to grow logarithmically (56, 73). This has, of course, been a feature of the scientific enterprise ever since the mid-seventeenth century. The doubling time for scientific journals is around 20 years and reflects the multiplying number of scientists. In fact, over 75% of all scientists who have ever lived and worked are now alive and working (56, 73). As this growth occurred, more journals were needed to communicate scientific findings. As I looked at the field of obesity in 1990, I concluded that NAASO would soon need its own journal. After the 1990 meeting, I went to the board of directors of NAASO and proposed that they establish a new journal. They agreed and asked me proceed with its organization and publication.

My plan was to begin with a bimonthly publication and expand the issues as more articles appeared. To fill a new journal while you are waiting to enter the Index Medicus can be challenging because the articles in the first few volumes may not be readily retrieved later (15). Thus, I approached scientists in the field who were already well known, who wrote a lot of scientific papers, and who would be likely to cite their own articles in subsequent publications. A second strategy was to republish a group of "classic papers" from the field of obesity research along with a commentary. Over the five years of my editorship, 30 such classic papers were selected with the help of an advisory group. These historical commentaries received many positive responses, and

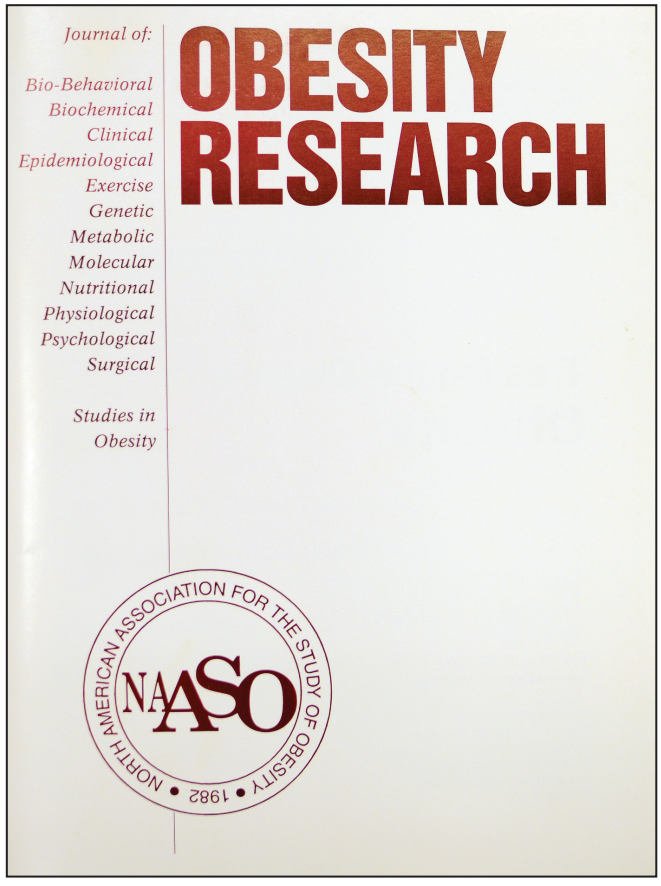

Figure 5

Cover of the first issue of *Obesity Research*.

after leaving the editorship I pulled them together in a book titled *Battle of the Bulge: A History of Obesity Research*, which can serve as a basis for individuals wishing to have a historical overview of this subject (17). The first issue of *Obesity Research* appeared in January 1993, and I continued to serve as its editor for the first five years, during which time the journal went to monthly publication (**Figure 5**) (15).

The completion of the Claude B. Pennington Jr. Conference Center in 1995 gave us a chance to host a meeting of the NAASO and the Society for Ingestive Behavior. It turned out to be a well-subscribed meeting, with attendees including both the director of the National Institute of Alcohol and Drug Abuse and Martin Rodbell (1925–1998), a Nobel Laureate.

Translating Clinical Research

Translating the results of basic science research into clinical outcomes is an essential step in research. A clinical research center, which I used when at the Tufts-New England Medical Center and at USC and which I directed at the Harbor-UCLA Medical Center, provides an essential tool in this process. However, the operation of these centers is expensive. We were fortunate at the formation of the Pennington Center to have an attentive congressional delegation whose

members sat on many influential committees in Congress and were able to provide significant help. The first help came as a "carve" out of money from the US Army nutritional research budget. Our challenge was to turn this money to good use for both the US Army and the Pennington Center. Dr. Allen Copping, the LSU president, asked Dr. Donna H. Ryan, who had worked with him as vice-chancellor for clinical affairs in New Orleans, if she would take on this challenge. With her inimitable skills, Dr. Ryan worked with the US Army Nutrition Program in Natick, Massachusetts, to see what would benefit both organizations. One benefit was to establish a stable isotope laboratory that could measure energy expenditure in troops working in various potential military situations. To head this laboratory she recruited Dr. James DeLany, who was just finishing his fellowship work at the University of Chicago with Dale Schoeller, one of the leaders in this field. Another program provided clinical laboratory support for US Army field studies and was headed by Dr. Jennifer Rood, another of our early recruits and who is still heading this successful program. A third project was to work with the US Army Special Forces to develop the most effective nutritional package that could be devised. The final undertaking, designed in collaboration with Dr. Gerald Berenson at the LSU Medical Center in New Orleans, was to offer a program to the Army to manage or prevent overweight in its soldiers. Both the Pennington Center and the US Army nutrition research program were beneficiaries of these programs, which have continued to this day.

Funding for equipment is a second essential element in research. The money to equip the Pennington Center came from the US Department of Agriculture through congressional set-asides or earmarks, as they are called. With these funds we were able to provide one of the most up-to-date nutritional research facilities in the country. Our equipment included two metabolic chambers for the study of human metabolism around the clock. These two chambers are among the most widely used pieces of equipment at the Pennington Center. The US Department of Agriculture also included funding to conduct studies on the relation of dietary fat and energy expenditure. We showed that the rate of adaptation to a high-fat diet was speeded up by exercise compared to adaptation to a similar diet without exercise. That is, exercise helps burn fat.

The lower Delta region of the Mississippi River is one of the poorest in the nation and has one of the highest rates of obesity. We reasoned that a collaborative project between schools in Arkansas, Mississippi, and Louisiana might be attractive for federal funding, particularly if the project had a mix of predominantly African American schools and state schools. With help from the three congressional delegations in these lower Mississippi Delta states, we set up the Delta Nutrition Intervention Research Initiative (Delta NIRI) in 1994. Delta NIRI involved the Pennington Center and Southern University in Louisiana; the University of Arkansas Medical Center in Little Rock and the University of Arkansas at Pine Bluff; and the University of Southern Mississippi in Hattiesburg and Alcorn State in Alcorn, Mississippi. These six institutions began a collaborative arrangement that lasted for 10 years and parts of which still continue, although the leadership has gradually shifted. Dr. Catherine Champagne, our lead research nutritionist, and Dr. David Harsha gradually took the leadership roles as Dr. Ryan and I moved on to do other things.

NIH-Funded Multicenter Clinical Trials Begin

The early 1990s were a good time for nutritional research. The NIH was in the process of doubling its budget over 10 years. Part of this money went to fund several important multicenter clinical trials, and the Pennington Center was able to participate in several of them. The first was a project built around the effects of different dietary fats on risks associated with heart disease, called the Dietary Effects on Lipoproteins and Thrombogenic Activity (DELTA). With the help of Dr. Paul Roheim from the LSU Medical Center in New Orleans, who was a well-funded investigator in the

area of lipoprotein metabolism, the Pennington Center was selected to participate in this project along with Columbia University, Pennsylvania State University, and the University of Minnesota.

The second big coup for us was a multicenter grant to examine the effect of different dietary patterns on blood pressure. This project was funded at four centers including the Harvard School of Public Health, Johns Hopkins University, Duke University, and the Pennington Center. With these two awards we knew we had begun to make our mark and had "branded" the Pennington Center as a site for research excellence. This latter trial developed the DASH (Dietary Approaches to Stop Hypertension) diet to lower blood pressure and which has been the subject of several popular books (1, 50). The DASH diet has been included in the Dietary Guidelines for Americans and selected by *U.S. News & World Report* as the best diet. This project spawned three additional sequential grants, including DASH-Sodium, PREMIER, and Weight Loss Maintenance, which were led by Drs. David Harsha and Philip Brantley while I moved on to other grants.

Two other multicenter grants fill out the portfolio of clinical trials with which I was involved while director of the Pennington Center. The first was the Diabetes Prevention Program, a trial that asked whether a lifestyle program or the antidiabetic drug metformin could delay or prevent the development of diabetes in individuals at high risk for diabetes (prediabetes). The trial has now completed 20 years and has clearly shown that an average 5.5% weight loss lasting for an average of 2.8 years could reduce the risk of developing diabetes by 58%. In the same trial, metformin-treated participants reduced their risk of new diabetes by 31%. This early effect lasted for 10 years, with the weight loss group having significantly fewer cases of diabetes than the control group (44).

The final trial asked whether a lifestyle program similar to that used in the Diabetes Prevention Program could reduce cardiovascular mortality in patients who already have diabetes. This trial, known as Look AHEAD (Action for Health in Diabetes), has shown many positive benefits of lifestyle intervention, including reduced blood pressure, improved mobility, lessened depression, and reduced sleep apnea, but it did not reduce cardiovascular mortality (70). Both Dr. Donna Ryan and the head of the behavioral medicine group, Dr. Donald Williamson, played key roles in designing the highly effective lifestyle intervention and in conducting the trial.

RETURN TO SCHOLARSHIP: THE BOYD PROFESSOR YEARS

Even with all this fun there comes a time to move on. When I left the directorship of the Pennington Center in 1999 after 10 years, I returned to my life's work as a clinical investigator. As these years began, I recalled again the words of William Osler in his "Fixed Period" essay, which had directed my career moves until now (52). Men and women over the age of 60–65 contribute few masterpieces, in contrast to younger men and women, and he suggested that it might be best for people of this age to retire (he proposed chloroform). I decided to give his ideas a test, since many people now live longer, healthier lives than they did at the turn of the twentieth century.

The first major research project that was funded after I stepped down as director was a two-center clinical trial asking whether the macronutrient composition of diets played a role in enhancing weight loss. Dr. Frank Sacks at the Harvard School of Public Health, a friend and colleague since the DASH Diet trial days in the 1990s, and I were the principal investigators for this trial, called the POUNDS LOST (Preventing Overweight Using Novel Dietary Strategies) study. Between 2003 and 2007, we completed this important trial, which included 811 overweight people. We showed that weight loss at six months, one year, and two years was essentially identical with diets containing 20% or 40% fat and diets with 15% or 25% protein, from which we concluded that the macronutrient composition of the diet was not important for weight loss—all diets will work if you stick to them. We have learned since that several important genes modify the response

to the diets used in these studies. This may be an opening into personalized medicine, in which a diet is prescribed for an overweight patient based on the patient's genetic profile (59).

The other major project during this time rounded out the overfeeding studies that began in the late 1960s. Dr. Steven Smith, a young man who did his obesity fellowship at the Pennington Center and then rose to faculty status before leaving to head his own research institute in Orlando, Florida, and I asked whether the efficiency of metabolism during overeating could be modified by the protein content of the diet. We found that low levels of dietary protein had profound effects on body composition during overfeeding. The volunteers who ate a low-protein diet had no increase in body protein; in contrast, body protein stores increased in the groups that ate normal- and high-protein diets. However, the individuals eating the low-protein diet stored more fat as a percentage of the energy eaten than the other groups. The major effects were thus on changes in various subcompartments of the body such as muscle, liver, and fat (25).

SUMMING UP

It is through the lens of 45 years that I look back over my research career related to nutrition and obesity. The organizations [NAASO/TOS (The Obesity Society), International Association for the Study of Obesity (IASO)], journals [*International Journal of Obesity* (1977), *Obesity Research* (1993), *Endocrine Practice* (1995)], and monographs [*Obese Patient* (1976), *Contemporary Diagnosis and Treatment of Obesity* (1998), *Guide to Obesity and the Metabolic Syndrome* (2011)] that I have developed speak for themselves.

During these 45 years, four research themes have emerged in my work. The first was the idea that changes in the endocrine and autonomic nervous system might play an important role in the onset and maintenance of obesity. Removing feedback connections to either the sympathetic or parasympathetic nervous system can prevent or reverse some types of obesity. Similarly, removal of the adrenal gland and replacement with a fixed daily amount of steroids prevents or reverses most types of experimental obesity. This hypothesis is called a metabolic and endocrine hypothesis of obesity (26) and later became known as MONA LISA, which stands for Most Obesities kNown Are Low In Sympathetic Activity (14).

A second theme revolved around the responses to overfeeding. When I moved to Los Angeles, I picked up this theme, which began in collaboration with Ethan Sims in the 1960s. In Los Angeles we used a bicycle ergometer to determine whether overfeeding changed the efficiency of muscular work. Over the normal range of muscular work we could find no effect on muscular efficiency of increasing body fat by overfeeding. At the Pennington Center we tested the idea that overfeeding a low-protein diet could impair metabolic efficiency. In this setting extra calories were primarily stored as fat, and there was no evidence for metabolic inefficiency.

A third integrating theme was based on the idea that the prevention of obesity, similar to the prevention of dental caries, might come from environmental factors. Although brushing and flossing teeth regularly will significantly reduce dental disease, adding fluoride to the water supply does a much better job. Thus I introduced the "FLUORIDE hypothesis for the prevention of obesity" (16). The cost of petroleum and its by-products (gasoline, fertilizer, and pesticides) could be one such agent. In the past half-century, farming has become ever more dependent on oil. According to the author Michael Pollan, we used about 0.5 kcal of oil to produce 1 kcal of food energy in 1940 (55). This rose to 10 kcal of oil (fertilizer, pesticides, transport, etc.) for each 1 kcal of food energy by the early twenty-first century—a twenty-fold increase. As we shift to renewable sources of energy and the cost of oil rises, the availability of oil-based products for food production and distribution will clearly produce major changes that will affect the prevalence of obesity.

A fourth theme arose from a study of the food supply, in which we noticed that after the introduction of high-fructose corn syrup in the 1970s, there was a sharp rise in obesity. Although association is no proof of causation, it prompted my interest in this source of food energy and in its components in relation to obesity. The largest amounts of high-fructose corn syrup and sugar are used to prepare soft drinks and many frozen foods. The consumption of soft drinks rose from 10 gallons per person in 1950 to 50 gallons per person in 2000—a five-fold increase. There is now clear evidence associating the rise in soft drink consumption with the increasing prevalence of obesity, and two clinical trials suggest that reducing the intake of soft drinks can reduce the rate of weight gain in adolescents (23). Fructose and glucose are covalently combined in equal amounts in sugar and in nearly similar amounts in the mixture that makes up high-fructose corn syrup. As the intake of sugar or high-fructose corn syrup increases, the load of fructose that the body must dispose of also increases. If you want to test the "detrimental" effects of anything, provide increasing doses (23). Nonalcoholic fatty liver disease did not exist when I was a medical student. It appeared in the 1980s, and it is now a significant precursor, if not the leading one, of end-stage liver disease and liver transplants (23). The consumption of soft drinks had doubled by the 1980s. This suggests to me that the rising intake of fructose in soft drinks could play a role in the development of nonalcoholic fatty liver disease.

Having sketched my life's journey and some of its joys and sadness, it is now time to draw my presentation to an end. For that purpose I would like to quote a few words from two graduates of the Harvard Medical School and from one of my favorite playwrights, Tennessee Williams.

The first of these authors, Dr. Walter Bradford Cannon (8, 28), came to Harvard from the Midwest and spent his entire professional life there as chairman of the department of physiology. He said:

> I was beginning in physiology [in his thirties] and for the first time attended a meeting of the American Physiological Society. It was held in Philadelphia, and to the delight of the younger members of the organization Dr. S. Weir Mitchell, one of the founders—a medical investigator, an eminent neurologist, a novelist and a poet—was present to talk to us. He appears to me to be *so old as to be almost ancient* [italics added].

And now I find that at the time, he was not quite my present age! Although I still seem to myself no older than I felt a decade ago, I recognize that the changes of senescence have begun to appear and will probably increase until the end. In Dr. Mitchell's words (28, p. 223):

> I know the night is near at hand.
> The mists lie low on hill and bay,
> The autumn sheaves are dewless, dry;
> But I have had the day.

Dr. Oliver Wendell Holmes is the second graduate from the Harvard Medical School that I quote here (40, 67). He was a poet, dean of the Harvard Medical School in the mid-nineteenth century, and author of a dissertation about prevention of childbed fever. Here are a few lines from one of his poems about aging (40, p. 161):

> Though young no more, we still would dream
> Of beauty's dear deluding wiles;
> The leagues of life to graybeards seem
> Shorter than boyhood's lingering miles.

And finally, from Tennessee Williams's *Camino Real* (69):

> There is a time for departure even when there's no certain place to go.

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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