

A Century of Healthcare and Medical Education from the Viewpoint of a Clinical Chemist

By

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Dedication

This book is dedicated to Wilfred Wiedy “Weste” Westerfeld, PhD, Rhodes Scholar at Oxford University (1938–1940), Harvard Medical School Faculty (1940–1945), Chairman and Professor of Biochemistry at Syracuse University College of Medicine (1945–1950), Chairman and Professor of Biochemistry at SUNY Upstate Medical Center (1950–1979) (successor to SU College of Medicine); Acting Dean SUNY Upstate Medical Center (1955–1960).

Weste received his PhD at age 23 under Edward A. Doisey Sr., PhD, who was Chairman and Professor of Biochemistry at St. Louis University Medical School. Later, Dr. Doisey received the Nobel Prize for the identification of the structure of vitamin K, the vitamin necessary for blood to clot.

Weste set very high standards and the only one I knowingly failed to achieve was learning to smoke a pipe while doing chemical procedures. As Dr. Westerfeld’s first graduate student at Syracuse University Medical College, I was the only graduate student to receive his degree in four years and five summers and from Syracuse University. My training prepared me exceedingly well for both a career in academic Biochemistry and in hospital Clinical Chemistry. Since I was the first of at least four of his graduate students who became clinical chemists, he was proud of my achievements and leadership in the field. My accomplishments were due to his excellent training and instilling motivation in his students and his challenge of “becoming the best you can be.”

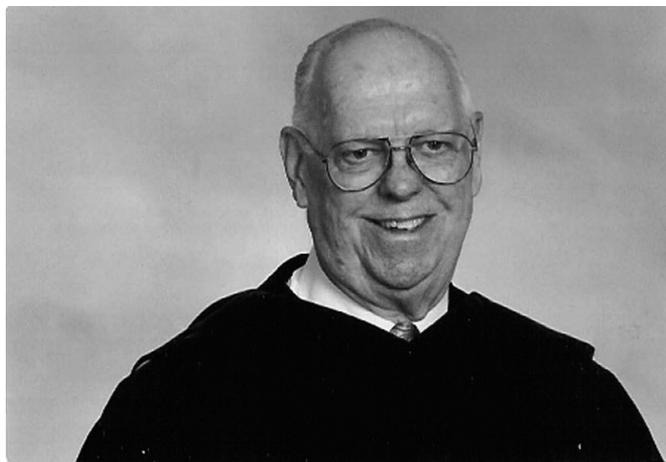
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Preface

Every hospital or institution participating in clinical research involving new experimental drugs, medical devices, or retrospective reviews of patient data is required by the Food and Drug Administration (FDA) to have an ethics review group, called an Institutional Review Board (IRB), approve all such proposals. An IRB consists of a group of physicians and nurses and appropriate people from the community who must approve every proposed clinical research study. Annual review of studies in progress is required. Because of my experience in Laboratory Medicine (formerly Clinical Pathology) and no professional ties to St. Agnes Health Care, I have served as an outside volunteer on the St. Agnes Hospital IRB since June 2002.

On June 5, 2003, Eric M. Meslin, PhD, Professor and Director of the Indiana University Center for Bioethics, delivered a talk to the St. Agnes Hospital medical staff and invited guests of the 2nd annual Raymond J. Donovan, MD, Memorial Lecture on Ethics in Clinical Research. During the question and answer period after Dr. Meslin's lecture, I replied to a question involving transplants in Maryland. My comments sponsored so much interest on the part of Dr. Meslin that he rushed back to me, requested a brief summary of my over 40-year professional background and insisted that I had to write a book on the highlights of the past century of healthcare and medical education.



Raymond E. Vanderlinde, PhD, at age 80 in 2004.

Acknowledgements

I wish to thank Anthony F. Hammond, MD, FACS, for taking the time to review the first draft of this autobiographical manuscript in May 2004. His many constructive suggestions resulted in a complete reorganization and the addition of new content between June 2004 and December 2006, making it much more logical and complete as a history of healthcare and medical education in America. Dr. Hammond, whom I taught as a medical student (University of Maryland, 1957), took the time from his busy life as an ENT specialist to review the revised draft for content and medical errors, for which I am much indebted. In his words: “The section on clinical chemistry greatly impressed me and it crystallized for me the marriage between clinical chemistry and medicine in advancements in healthcare. Clinical chemistry seemed to have been a half-step ahead of medicine in this progression.”

My wife, Ruth Hansen Vanderlinde, MLS, worked with me throughout the writing of the book, making many comments and recommendations that were extremely useful. Her proof-reading was a dedicated and consistent endeavor. I greatly appreciate her very extensive efforts, but as the author, I must take ultimate responsibility for any errors.

I owe a debt of gratitude to the information staff of the local Catonsville Public Library who have very patiently and frequently sought out information for me. In addition, the staff of the St. Agnes Hospital Health Science Library, the librarians of the Chemical Heritage Foundation in Philadelphia, and Thomas Flynn, MLS, Director of the New York State Department of Health Library, have assisted me on numerous occasions.

Introduction

Roman statesman Marcus Tullius Cicero said, “History indeed is the witness of the times, the light of truth.”

My mother kept detailed records of her health and that of my father and their four children from 1912 through 1981, which I describe in the first chapter. I started my graduate studies at the Syracuse University College of Medicine in 1946. In August 1950, I received the first PhD in Biochemistry and Physiology with the goal of teaching either Biochemistry or Physiology (body function) at a medical school. In addition to seven years (1950–1957) on the faculty of the University of Maryland School of Medicine in Baltimore, my 40-year professional career includes serving on the staff of five other medical schools, direction of two university hospital clinical chemistry laboratories, and 12 years in public health where we licensed the hospital and independent clinical laboratories in the State of New York. I received the titles of Emeritus Professor of Pathology and Laboratory Medicine (Division of Clinical Chemistry) and

Emeritus Professor of Clinical Biochemistry as an honorary degree from MCP-Hahnemann University in Philadelphia in 1991, which has since become Drexel University School of Medicine.

After review of my book, Dr. Anthony Hammond stated to me that he never realized how much modern day medicine is founded on clinical chemistry. The goals of this book are to describe the role of clinical chemistry as the foundation of modern medicine, the advances in vaccines, therapeutics, and antibiotics, the role of clinical chemistry in medicine during the last half century, and the major changes in the curriculum of undergraduate and graduate medical education instituted over the past five years. Since all medical terminology is defined, it should be of interest not only to clinical chemists and physicians but as an orientation manual for first-year medical students and as an informative booklet for premedical students and their parents and for the lay public at large.

Chapter 1

A Century of One Family's Healthcare

In the early 1700's, disease and sickness such as smallpox and typhus were so rife in the filthy holds of some ships coming to America that statistics from 1711 indicate only one out of three immigrants survived the crossing, and typhus became known as "ship fever" (1). Nevertheless, New York State, settled by the Dutch beginning in 1624 at New Amsterdam (New York City) and Fort Orange (Albany, New York), grew from a population of just over 4,000 in 1650 to almost 163,000 in 1770 (2). A similar situation prevailed in the middle-Atlantic states, with the populations of Pennsylvania and northern Maryland enhanced greatly by the leader of the Quakers, William Penn, who offered religious freedom to all immigrants. Between 1737 and 1746, over 15,000 Germans landed on some 67 ships at the port of Philadelphia. Similar large numbers of German immigrants came to Maryland, along with many Catholics, who had come as early as 1634 under Leonard Calvert, seeking religious freedom and life in the New World. Maryland expanded from a population of 4,500 in 1650 to almost 30,000 in 1700, and over 200,000 by 1770 (2). Virginia grew from a population of 18,731 in 1650 to the most populated of the 13 colonies in 1770, with almost 450,000 people (2). Thus, in spite of an estimated average age of death as low as 35 years and an infant mortality rate as high as 1 in 3, the total population of the new young British colonies grew exponentially to over 2,100,000 people in 1770, just prior to the American Revolution (2). Population growth was aided by immigration, as well as large farm families, most of which included 10–15 children.

Unlike the first-generation European immigrants who brought their acquired immunity to European endemic diseases with them, the second-generation colonists did not have any such immunity (3). Childhood diseases such as measles, diphtheria, scarlet fever, chicken pox, and mumps often had deadly effects on the adult population. Outbreaks of measles occurred in Boston, Massachusetts, in 1713 and 1714, and five of Reverend Cotton Mather's children died within two weeks (3, p. 16). The most lethal outbreak of diphtheria began in 1735 in Kingston, New Hampshire, where half of the children in the community died. Smallpox periodically ravaged colonial populations in many communities, particularly seacoast ports, where victims were quarantined in isolated smallpox hospitals. In the 1800s, about 20% of all children died before 12 months of age, whereas it was 0.69% in 2000 (3, p. 16). After a cholera epidemic broke out in Boston in 1832, the ensuing average life expectancy of a Bostonian in 1840 was 21 years of age.

Until Louis Pasteur developed his germ theory in 1878, most people believed that illness was due to deadly miasma arising from stagnant water and swamps. However, even when filth, polluted water, and poor sanitation accompanied disease, people failed to recognize the role of mosquitoes, flies, and insects in carrying disease. As a matter of fact, in the 1700s and 1800s, people thought most diseases were the responsibility of the individual and solely the result of lifestyle (3).

In 1900, 11.8% of deaths were due to pneumonia and influenza; 11.3% to tuberculosis; 8.3% to diarrhea, enteritis, and ulceration of the intestines; 8.3% to heart disease; 6.2% to stroke; 5.2% to kidney diseases; 4.2% to accidents; 3.7% to cancer; 2.9% to senility; and 2.3% to diphtheria (4). Thus, the 10 leading causes of death in 1900 accounted for only 64.2% of all deaths in 1900, which indicates the difficulties in data collection before the development of public health systems. By 2002, 86.4% of all deaths were due to six causes: 28.9% from heart disease; 22.9% from cancer; 18.3% from chronic lung diseases, pneumonia, and influenza; 6.6% from stroke; 4.3% from accidents; 2.8% from diabetes; and 2.6% from Alzheimer's (4). Kidney diseases such as nephritis, nephrosis, and nephrotic syndrome accounted for 1.6% of deaths, and suicides, septicemia, chronic liver disease, assault, and the human immunodeficiency virus (HIV) account for the balance. In 1900, more than 95% of all births took place at home, with many infants dying before two years of age. Only 14% of the homes in the United States had bathtubs and indoor plumbing. Although 80% of Americans could read and write, only 6% had graduated from high school. The average worker made between \$200 and \$400 per year. Ninety percent of all physicians had no college education and had attended medical schools with no formal standards—schools that were condemned in the press and by the government as "substandard." However, it was not until the drastic state of many medical colleges was exposed in the 1910 Flexner Report on Medical Education in the United States and Canada that dramatic changes and reform in medical education took place (5, p. 262). The report was prepared by Abraham Flexner, PhD, an academician at Johns Hopkins University who had visited every existing medical school in the U.S. and Canada.

A multitude of changes and tremendous scientific advances have taken place in healthcare in the past century, starting with the discovery of vaccines and, later, antibiotics for

the treatment of communicable diseases. Recent improved chemotherapy and radiological techniques for cancer, as well as newer surgical techniques and the widespread availability of well-trained physicians and surgeons, have increased longevity dramatically (6). In 1900, the life expectancy at birth for males was 46.3 years, but was 74.7 years in 2002; in 1900, the life expectancy at birth for females was 48.3 years, but 79.9 years in 2002 (4). However, both the incidence (rate) and the prevalence (occurrence) of the various types of diseases, both in the United States and globally, are in a constant state of change. In the United States, the percentages of deaths differ between whites and blacks, American Indians, Asians, and Pacific Islanders, with all minorities, including immigrant Mexicans, having shorter life expectancies (6). Although life expectancy in the United States is at an all-time high, infant mortality has actually increased due to inadequate prenatal care of the poor.

MY FAMILY

My Paternal Grandparents

My paternal grandparents, John Vanderlinde and his wife Janna DeLyser, both born in 1866, were married in Schoondyke, Zeeland, The Netherlands, on November 23, 1887, and left for America on August 25, 1888, with their month-old infant daughter, Susan. They settled with other Dutch families in the rural truck farming community of Brighton, which today is barely distinguishable from the city of Rochester, New York. Isaac Edward Vanderlinde, my father, was born in early March 1890 and my uncle, Edward Isaac Vanderlinde, was born in April 1892. Tragedy struck the young immigrant family, however, with the death of two-year-old Susan from “summer complaint” (diarrhea) on July 29, 1890, and the death of John Vanderlinde, my grandfather, from influenza on March 4, 1893. My grandmother survived a high fever, but apparently lost her hair and wore a wig all of her long life (died at age 94 on February 20, 1961). My dad was 3 years old and Uncle Ed was 11 months old at the time of their father’s death. On March 7, 1901, when my dad and Uncle Ed were 11 and 9 years old, respectively, my Dutch grandmother married Jacob DeGraff, a young widower with a son about 7 years old, whose wife had passed away after delivering twins that were then put up for adoption. The three boys grew up together and became lifelong close friends. However, after my grandmother DeGraff became the mother of three more children, Herbert, Janna, and Marie DeGraff, it was a family of “your kids, my kids, and our kids.” Grandpa DeGraff was a supervising nurseryman at the H. S. Taylor Brothers Nursery in Brighton, and after my dad completed grammar school, he learned the trade of nurseryman. This was one of the largest businesses in the Rochester area at the time, Much of Brighton was later incorporated into the city of Rochester.

My Maternal Grandparents and “Seventeen”

In the 1930’s, I remember as a child visiting my maternal grandparents’ farm, Seventeen. The farm had no indoor plumbing

except for a hand pump at the kitchen sink, which was connected to a well. The outhouse, or privy, was a short walk behind the farmhouse. It was a one-holer, with the previous year’s Montgomery Ward or Sears catalog hanging on the wall for use as toilet tissue. Of course, chamber pots were kept under the beds for night usage. Water had to be heated in a tea kettle on the wood-burning stove for tea and coffee and in a large copper tub for the hand-cranked wooden washing machine and the large circular wooden wash tub for everyone’s weekly Saturday night bath. Infants got bathed last, which is where the saying, “Don’t throw the baby out with the bath water,” arose.

On January 23, 1936, during a terrible snowstorm, my grandmother had a mild stroke and developed frost-bitten hands and feet, probably because the farmhouse had no inside bathroom or central heating. However, it was my maternal grandfather, Josie Robinson, who had a stroke and died at age 70 on April 2, 1936, in a Rochester hospital. Although mom’s brother was an unmarried World War I veteran who lived at home, it was my mother who looked after Grandma and tried to be of assistance. Grandma Robinson, however, was very frail and she soon suffered a major stroke and died at age 74 on January 30, 1937.

My Great Uncle Doc

Mom’s maternal uncle, Clifford Beach Rowell, MD, became a veterinarian but switched to medicine, graduated from the Detroit College of Physicians and Surgeons in 1894, and after an additional year in surgical training at the University of Buffalo, became a surgeon in Buffalo. He always loved horses and kept a pair in the large barn behind his huge home office at 224 Massachusetts Avenue, only a couple of blocks from the Peace Bridge to Canada. In 1932, he served as president of the Buffalo Road Trotters Association. Naturally, as a successful surgeon, Great Uncle Doc drove big, exceedingly expensive Pierce Arrow automobiles that were manufactured in Buffalo and had the unique feature of headlights in the fenders. Uncle Doc was a very large tall man who weighed at least 250 pounds, had a full head of curly hair, and chomped on a big cigar. He designed telephone stands, and had them built, with curved neck electric lights for conveniently taking night calls from patients. He owned a dump truck business, handled by his handyman, Archie, who also took care of his horses.

Great Uncle Doc became the sage and patriarch of all of my mother’s Robinson relatives. I can remember as early as age 4 or 5 taking the interconnecting trolley lines from our hometown of Newark to Buffalo, some 100 miles away. The dried human body parts and bladders hanging upstairs in the barn, near the pool table, left me in awe. The waiting room was accessed by the front door entrance into the huge house, which had separate facilities for his practice. The large office examining room with an examining chair and table, where he did some surgery, was surrounded by shelves filled with huge jars of medicines. In his day, one didn’t need to fill a prescription at a drugstore because the physician supplied pills in a small envelope as part of the office visit. Uncle Doc never married, but one of his housekeepers, Clarabell Drake White or “Aunt

Clara,” became his companion. The arrival of Uncle Doc and Aunt Clara with oxtail soup and special meats and goodies for the annual Robinson family reunion at his sister’s farm at Seventeen, some 75 miles away, was the signal for the games and activities to begin. On occasion, Uncle Doc, an avid hunter, and some of the men would shoot clay pigeons near the fence by the side of the barn. Meanwhile, anyone with a medical or other problem would discuss it with Uncle Doc, who never failed to listen and give advice about any relative’s need.

My Parents

Life expectancies of Americans in 1900 and the first colonists in 1620 were fairly similar, except for occasional epidemics of smallpox or influenza that wiped out entire communities. My parents, born in 1890 and 1891, kept meticulous health and financial records (7–9). Their lives and those of their children are representative of the era when the average life expectancy was 46.3 years for men and 48.3 years for women (4). No wonder education usually stopped after grammar school and most boys then learned a trade or began farming and girls were married at 15–18 years of age or worked in canning factories or as domestics. Such was the environment my parents grew up in and why they both had only grammar school educations. Dad learned the trade of nurseryman and my mom’s first job was in a canning factory.

My mother, Hazel Robinson, born in June 1891, grew up on a farm in the town of Perinton, about 10 miles east of Rochester, New York. After completing grammar school, she helped on the family farm and worked at the local canning factory. However, she soon learned that after the canning season was over in the late fall, she was without a job. Using her savings, she commuted by trolley to business school in Rochester for the first six months of 1909 (7). After training in the business practices of the day, including typing and shorthand, my mother became a typist and later a secretary at the H. S. Taylor Brothers Nursery in Brighton. There she soon met my dad, a 19-year-old nurseryman, and they were married on June 12, 1912.

After being married, my mom and dad lived with her parents, who had just bought their first farm and probably needed my parents’ board money for cash flow. Because trolley stop number 17 was conveniently located about a quarter of a mile away, my grandparents’ farm became known as “Seventeen.” Thus, my parents commuted to work at Taylor’s Nursery for a few months before my oldest sister, Dorothy, was born on January 21, 1913. In May 1914, my father became a conductor on the Rochester, Syracuse & Eastern Trolley System, and my parents and Dorothy moved to a rented house some 20 miles eastward in the village of Newark, the headquarters of the trolley system. Although my parents lived in Newark, they traveled to Seventeen for the birth of my brother Donald, who was born in late May 1915, with my grandmother assisting Dr. James Fox.

From 1914–1924, my family lived in the northerly half of a double house at 37 Grace Avenue, about seven houses from the Rochester, Syracuse and Eastern trolley system administrative headquarters and car barns. My arrival at the end of February 1924 delayed their move to a rented house on East

Maple Avenue, where we lived for 9 months. Before I was one year old, we moved into a new custom-built house on Heath Street. My brother Don, who was nine years older than I, used to tell me about Dr. Johnson arriving by sleigh on a cold, snowy morning in late February. When Don came home from school at noon that day, he learned he had a new baby brother. I was a large healthy baby, weighing over 8 pounds, but had a crooked right ankle and needed to wear high shoes and knickers until age 14, when I got my first pair of long pants. My oldest sister, Dorothy, was 12 when I was born and I became her “living doll” to take care of, and she became like a second mother to me. Hence, I always referred to her as my “Big Sister.”

My Dad’s Health

My dad had a spot on his lung since he was 16, and after he had made multiple trips to Buffalo beginning in January 1916, Uncle Doc operated on him on October 10, 1917, and removed his left parotid gland (salivary). A big, long scar, ran angle wise from the rear of my dad’s left jawbone down to his neck. I never knew the reason for the surgery until about four years ago when writing up my family history. In my mom’s diary for the years 1906 to 1919, I found the word “TB” written in red ink over the phrase “salivary gland tumor” and a note that the surgery had “saved his life” (7, p. 24).

Except for the removal of my dad’s tubercular salivary gland tumor in 1917 and a broken ankle from a fall on the ice in about 1960, his health was excellent. Dad enjoyed bacon and eggs for breakfast and wiped out the grease in the frying pan with a piece of bread. No one worried about cholesterol levels back then, and up to 300 mg/dL was considered normal for older adults. In 1963, my dad developed heart disease and went on medication, but on November 24, 1964, at age 74, he died instantly of a massive dissecting heart attack while out walking the family dog.

My Mom’s Health

After six children, including two stillborns, my mom had a hysterectomy on November 11, 1947, spent two weeks in the hospital, was cared for by a practical nurse for a month, and went back to work part time on January 12, 1948. This contrasts with my wife’s hysterectomy on November 30, 1999; she was released for travel on December 22 and we left for Florida by car on December 28, just four weeks to the day after her surgery. What a remarkable change in healthcare after surgery over the past 50 years!

In 1939, nylon yarn was developed by DuPont, and soon nylon scarves, hats, stockings, and clothes were popular. In the early fall of 1952, my parents bought a new 1953 Chevrolet and had clear nylon plastic seat covers installed to protect the upholstery from their dog, Rex. My mother liked and wore nylon stockings. By the time they arrived at their camp in Eagle Bay on their first trip to their camp in the new car—3 hours and 47 minutes later (my mother’s preciseness)—the hose covering the backs of her legs was in shreds and the backs of her legs were split open and bleeding (8). My mom subsequently discovered that she was allergic to nylon and seldom attended

church services because any exposure to persons wearing nylon clothing caused her to break out in sensitive body areas.

Mom had severe astigmatism from age 30 and her eye glasses had to be precisely in the right position or she would suffer dizziness. For this reason, she had to quit her job as a bookkeeper at Woolworths shortly before she turned 60 in 1951.

In the 1950's, my mother also developed balance problems due to Meniere's disease, a defect in the fluid in the semicircular canals of the ears, which at the time was treated by a high protein diet but is treated today by a diet restriction of 2 grams of salt per day. Additionally, at some stage, mom ate pork that was not thoroughly cooked and developed trichinosis (infection with a slender nematode worm), ending her days of eating pork products.

In her early 80's, my mom slipped on overflow water in a commercial laundry, broke an ankle, spent a few weeks in a nursing home, and was then able to continue living alone in the old family homestead. Otherwise, except for occasional colds and routine aches and pains, she remained healthy and lived alone.

At age 90, my mom still lived alone with her dog, but when my oldest sister's husband was diagnosed with brain cancer and subsequently placed in a hospice, mom collapsed, and then went to live with my sister, Marge, and her husband on their farm. The old family home—where we grew up and where mom had lived for 57 years—was kept heated and the lawn mowed for a year. In May 1982, however, my brother, my sisters, and I agreed that our mom was incapable of ever living alone again and we agreed to sell the family home. Meanwhile, my mom enjoyed living on a farm since she had been brought up on one, but she failed rapidly and it soon was necessary for her to enter the Baptist Home in Fairport, just a half block away from the farmhouse where her paternal grandparents from England had settled in 1885. My mother hated living in the Home, became wheelchair bound, deteriorated rapidly, and died of an acute stroke in January 1984 at age 92.

Dorothy's Health

Dorothy was born prematurely on January 21, 1913. She only weighed 3.25 pounds, had no fingernails, and was so small and fragile that my parents carried her around on a pillow. Although she gained weight rapidly, matters were made worse when my mother developed scarlet fever when she was nursing 6-week-old Dorothy and their farm was quarantined (7). Although she survived her very difficult start in life as a premature infant, Dorothy was a very sickly child. Mom's notes show bronchitis as well as numerous bilious attacks (gall bladder disease) with vomiting, and she never could tolerate chocolate or fried foods, even as an adult (7). After the family moved from "Seventeen" to Newark on November 20, 1916, Dorothy continued vomiting. In April 1917, she had a stoppage of her bowels, with four convulsions on April 8, and five more the next night. Perhaps this is when she was placed on barbiturates (no prescription needed) and kept on them for many years. On June 8, 1919, at age 6, she had her tonsils removed, which was done as a routine procedure on many children up until about 1970. Her health records state, "Dr. Sanford used chloroform as an anesthetic and performed the

surgery on the living room library table." Dorothy had both regular and German measles, the whooping cough, and chicken pox. In November 1921, at age 8, she became seriously ill from "nerve exhaustion" and was taken out of third grade. She lost an additional two years of schooling and then went half days, which resulted in her being in the same high school graduating class of 1933 as our younger brother Don, who was two years younger.

Within a month of our father's death, Dorothy was stricken with an acute heart rhythm problem. She was hospitalized at Genesee Hospital in Rochester for almost a month, and diagnosed on January 10, 1965, as having classical mitral valve disease due to rheumatic fever. Hence, her "nerve exhaustion" in 1921–1922, when she lost two years of schooling, was diagnosed some 43 years later as rheumatic fever. She was treated with various cardiac drugs for the next ten years when, in mid-December 1975, she was taken to Genesee Hospital by ambulance, where she was in a critical state for several weeks. All of the relatives rallied around, not knowing if she would recover. Dorothy, however, was determined to survive and after her condition improved the last two weeks of January 1976, plans were made to transport her on February 4, 1976, to the Rochester General Northside Hospital for open heart surgery. However, her condition delayed the transfer until February 19. On February 20, she had a commissurotomy, the clipping open of the flaps of the damaged mitral heart valve. Her open heart surgeon, Dr. Zarro, told me that they had pulled her back from three pulmonary arrests and that she was in the worst condition of any patient he had ever performed surgery on. The total bill for her healthcare exceeded \$23,000, but except for just over \$1,000, it was covered by her husband's BC/BS healthcare plan. Much credit for surviving the surgery must be given to my "Big Sister," Dorothy, who had a fantastic and courageous will to live and, as a result, had an additional 14 years of quality life before the condition returned and led to her demise in early September 1990 at the age of 77.

Donald's Health

My brother Don, two years younger than Dorothy and born in late May 1915, was soon nicknamed "Buster," perhaps ironically as an omen of things to come. Mom always referred to him as such, even though he became Don to everyone else. Early on, Don developed rickets, accompanied by bowed legs that required custom-made metal braces, which he started wearing on November 29, 1916, at age 18 months. The braces were adjusted in Rochester on December 7, 1916, and he wore them for about two years (7). The discovery of vitamin D in 1925 soon led to elimination of rickets by giving infants and young children cod liver oil or halibut oil supplements, which I detested. Exposure to sunshine converts 7-dehydrocholesterol, a metabolite of cholesterol in the skin, to its active form vitamin D3. According to a recent newspaper article that summarized a study carried out by Dr. Michael Holick, a vitamin D specialist at Boston University, "couch potato children" run a risk of weak bones due to the lack of outdoor activity in the sun and a deficiency of active vitamin D3. Also, many children currently overeat, especially snacks and junk food, and obesity

is a major public health problem for both our youth and adult Americans.

Like Dorothy, Don had occasional bouts of dysentery and the usual childhood diseases and had his tonsils removed by Dr. Sanford, using chloroform as an anesthetic, on June 8, 1919, on the living room library table. Although Don had most of the childhood diseases before he was 8, he didn't have mumps until December 27, 1927, at age 12. I was almost four at the time, and I crawled up on his bed and also developed mumps.

After Don graduated from high school in 1933, he worked for a Sunoco gasoline station in Rochester and boarded weekdays. When he was 20, he suffered a bout of pneumonia, but by then he had already been smoking for five years. In 1936, he came home to Newark with scarlet fever and before our home was quarantined for six weeks, I was invited to live a few doors away with the family of my best friend, Robert Heath. As a result of Don's bout with scarlet fever, Don developed chronic high blood pressure.

Although Don was 29 years old, married, and working as a machinist in the machine tool industry, which brought automatic deferral from service in World War II, he joined the Navy in March 1944 and was accepted on April 8. The scarlet fever had left him with a blood pressure of 165/80, but he talked the Navy examining physician into fudging his medical report. After training as a Diesel Motor Machinist's Mate, Don served on a Landing Ship Transport (LST) in the South Pacific from April 30, 1945, through December 19, 1945. Although Don would never discuss his wartime experiences, he did tell me about the terrible typhoon they encountered off the coast of Japan. Four of the five open boat LSTs in his group were swamped by the 50- to 60-foot waves and went to the ocean bottom, and Don admitted to being extremely scared about whether he would survive the ordeal.

At age 60, Don, the head of the two machine tool divisions at the Gleason Works in Rochester, New York, married his fourth wife, Dorothy Clark, a secretary in the main office of the plant. As required by company policy, on May 1980, at the age of 65, Don retired. After his wife, Dorothy, died of emphysema from heavy smoking and our mother passed away in back-to-back weeks in early January 1984, he proceeded to live a quiet retirement life with a very fixed routine. He enjoyed eating out with his daughter's family, including two grandchildren, for the next 11 years and passed away at age 81. Don smoked almost two packs of cigarettes a day since he was 15 years old, but like our older sister, Dorothy, he was not predisposed to lung disease. Unlike our two older siblings, however, both my younger sister and I inherited lung traits that made us subject to multiple pneumonias.

Marjorie's Health

My sister, Marjorie, born in November 1919, developed pneumonia at 7 months of age and a second time at 14 months of age. During the 1920's, she had the usual whooping cough, chicken pox, and measles, but at age 7, in November 1926, she was stricken with acute appendicitis and had her side packed in ice to forestall surgery. Her bout with lobar and bronchial pneumonia,

which began on September 20, 1935, when she was 15, was very significant in her life. I recall, as an 11-year-old, waiting out the "pneumonia crisis" to see whether she would live or die. Antibiotics were unknown in 1935, so all we could do was pray and hope that she recovered. The crisis passed after five days, and she dressed for the first time on October 9. Mom wondered what else could be done for Marge. After a new bright young physician named Joseph Kaufmann, MD, had practiced in our hometown for a few months, she took Marge to him. They were pleased with his suggestions, and on December 20, 1937, he removed her tonsils at the Newark Hospital. However, my mother, dad, and I continued to go to elderly Dr. Dwight Johnson, the village's country doctor, who had delivered me in 1924.

Because Marge lost a year of school and I had skipped kindergarten, even though Marge was slightly over 4 years older than I, she was in the Newark High Class of 1939, and I followed in 1941.

In September 1941, during my first month at Syracuse University, Marge developed pneumonia for the fourth time, with permanent lung damage known as bronchiectasis. Marge had taken a business course in high school, became an office worker in Newark who lived at home, and had occasional bouts with colds or bronchitis. Marge was small and short in stature like our mother, only about 5 ft 2 or 3. At age 30 she married 43-year-old Roy Ellsworth, and my first trip back to Upstate New York from Baltimore, where I had joined the University of Maryland Medical School faculty on September 1, 1950, was to attend their wedding on October 14, 1950. Their only child, Rocky Roy Ellsworth was born in Fairport, New York, at the end of March 1952, some 3 months after the birth of my older daughter. Today he operates the Roc Ells Dairy Farms near Hilton, New York, where his parents moved in 1969. One of Rocky's three children has mild cystic fibrosis. Marge, as a young teenager, had been given mercury sunlamp treatments on her summer vacations at the office/home of great "Uncle Doc," my maternal grandmother's brother who was a surgeon in Buffalo, New York. In 1958, as a result of the exposure, Marge began having multiple basal cell carcinomas and although benign, they were very painful and required surgical removals about twice a year. Marge retired as a bookkeeper at Hilton High School on December 31, 1984. Unfortunately, multiple pneumonias predisposed Marge to lung cancer, and she succumbed at age 67 in November 1986. Marge had never smoked a cigarette in her life, and after her funeral, our brother Don, who had smoked almost two packs a day most of his life, turned to me and said, "Ray, it should have been me."

ABOUT ME

I, Raymond Edward Vanderlinde, am the sole survivor and the compiler of this book. I am the youngest and first member of my family to go to college.

In early September 1941, I entered Syracuse University Colleges of Liberal Arts and Education on a scholarship. I was not permitted to work part time in college, however, because of

my family's extensive history of tuberculosis. In addition to my dad's history with TB, my dad's brilliant nephew, Edwin Vanderlinde, who was two months from graduating with a PhD in Economics from Columbia University at age 23, developed pneumonia and died of TB on May 28, 1936. Dad's younger stepbrother also died of TB (of the bone) while a theological student, and there were several other relatives who had recovered from the condition. To supplement my scholarship and some funds from my dad's pay, my mother, therefore, went to work as a Woolworth's clerk and paid for most of my undergraduate college education.

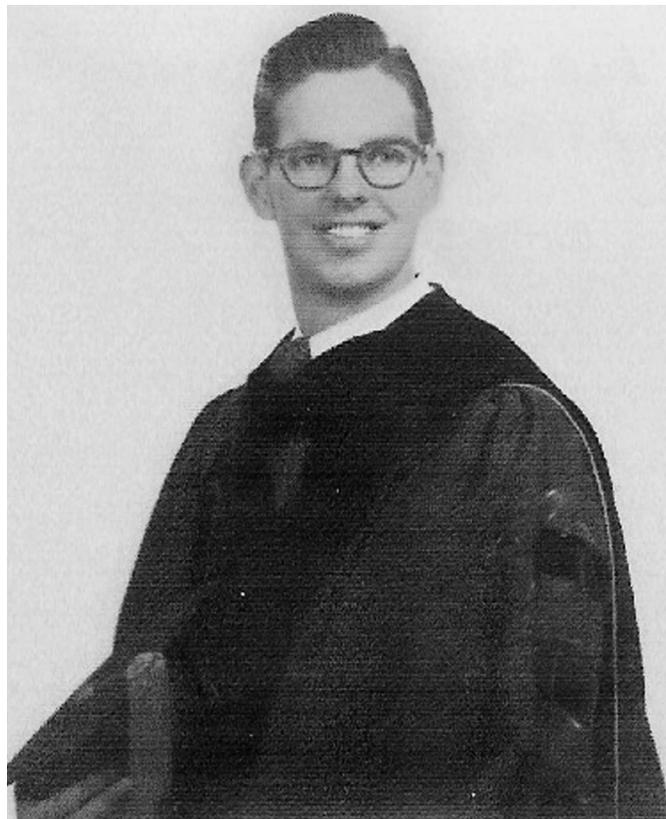
I graduated in May 1944 with an AB (*magna cum laude*) in Science Education, with Honor Society memberships in Phi Beta Kappa, Sigma Pi Sigma (Physics), Pi Mu Epsilon (Mathematics), and Kappa Phi Kappa (Education). In fall 1945, I returned to Syracuse University for a Master of Arts degree in Science Education, which was awarded May 2, 1945. The following Monday, I became a high school science and math instructor at Gorham Central School in Gorham, New York, for May and June, prepping the students for the New York State Regents in Chemistry and Biology. I taught five different science and math courses at the same school and became very discouraged by my heavy teaching load. When given the opportunity in July 1946 to be the first graduate student in the new Division of Medical Sciences of Syracuse University College of Medicine, I was able to pay my own way for one year from the money I had saved from teaching. I also received a full tuition scholarship. In August 1947, I was awarded an MS in Organic Chemistry from the Syracuse University Department of Chemistry. My thesis was the "Synthesis of Isomers of Diethylstilbestrol," carried out under W. W. Westerfeld, PhD, Chairman and Professor of Biochemistry at the Medical School. I joined the American Chemical Society in 1947 and was invited to join Sigma Xi as an Associate Member, the graduate scientific research honorary.

I was funded as a Research Fellow in Biochemistry and Physiology, from 1947–1949, by a grant from Bristol Laboratories to Dr. Westerfeld. In 1949–1950, I served as a Graduate Student and Teaching Fellow at the State University of New York (SUNY) Upstate Medical Center, contract successor to the Syracuse University College of Medicine.

In June 1948, I married Ruth Louise Hansen, the daughter of George and Louise Johnson Hansen, in the First Methodist Church in our hometown of Newark, New York. We have lived the American dream, which is desired by parents worldwide for their children.

In August 1950, I was awarded the first and only PhD in Biochemistry and Physiology with minors in Endocrinology, Steroids, and Nutrition from the Syracuse University College of Medicine Graduate Division of Medical Sciences and the Graduate School. All subsequent graduate students received their degrees from the SUNY Upstate Medical Center.

My professional career included seven years on the Biochemistry faculty of the University of Maryland School of Medicine; stints at hospital clinical laboratories in Syracuse, New York, and Cumberland, Maryland; 12 years at the Division of Laboratories and Research of the New York State



Raymond E. Vanderlinde, PhD, age 26; taken August 31, 1950.

Department of Health; and 14 years at Hahnemann University in Philadelphia, from which I retired as Emeritus Professor of Pathology and Laboratory Medicine (Clinical Chemistry) and Emeritus Professor of Clinical Biochemistry in 1991. In 2002, MCP-Hahnemann School of Medicine became Drexel University School of Medicine.

In the early 1970's, my junior colleague, Bob Rej, who later received a PhD under my direction, developed the first pure enzyme, the material that makes chemical reactions take place in the body. Subsequently, it became the first and only national and international standard for an enzyme, namely serum SGOT (serum glutamic oxalo transaminase) or aspartate aminotransferase, the main clinical laboratory test for liver disease.

In the late winter of 1974, I served for five weeks as a visiting scientist at the Korean Institute for Science and Technology in Seoul, Korea, and toured most of the country while I was there, my first trip overseas. Following completion of my tour of duty, I met my wife at Haneda Airport in Tokyo and we toured Singapore, Bangkok, and Hong Kong, and spent a week touring Japan, including visiting the two shrines at Nikko and the Great Buddha at Kankamura, viewing Mt. Fuji, and taking the bullet train to Kyoto. In October 1974, Dr. Calderon, Dr. Loria, and Senora Maria Castillo de Sanchez, MD, and her husband from Mexico visited our State Public Health Laboratory in Albany for three days of training in Quality Control in Clinical Chemistry. While there, we entertained them for dinner at our home.

In 1975, Professor Angelo Burlina of the University of Rome invited me to be a member of the Enzyme Committee of the World Association of Societies of Pathology (WASP). Later, in 1984, I served as an honorary member of the Scientific Committee for the ISCE Symposium in Rome, where I was Professor Burlina's guest for a week, with all expenses paid at the Hilton Hotel Cavalieri.

From February 27 to March 4, 1978, I attended the meeting of the International Federation of Clinical Chemistry (IFCC) in Mexico City, where I was an invited speaker and guest of Senora Sanchez de la Castillo, President of the IFCC. I also attended the satellite meeting of the International Society of Clinical Enzymology (ISCE) in Cancun through March 8, 1978.

In 1981, I was on the Nominating Committee of the IFCC and we spent a week visiting Congress Hall Palace, where our meeting was held, and seeing the sights of Vienna. We also attended the satellite enzyme meeting of the ISCE in Salzburg, Austria, and took a tour of Bavaria since we had flown in and out of Frankfurt, Germany, and on into and out of Munich.

In 1993, Ruth and I moved to the 2,300-person Charlestown Retirement Community in suburban Baltimore, Maryland, where we have excellent healthcare available on a 24-hour/seven-days-a-week basis from six full-time physicians, all certified in internal medicine. Our medical records were just recently computerized (GE Centricity), so they are available to our staff physicians at any location, including office, home, or at nearby St. Agnes Hospital in Baltimore. This advanced technology was implemented in 2004 by our Medical Director, Matthew Narrett, MD, who has been our personal physician since he arrived September 1, 1993, only three months after we moved in. In retirement, Ruth has been fortunate by surviving breast cancer and kidney cancer, both treated at the University of Maryland Medical System. She also had a hysterectomy at Johns Hopkins Bayview Medical Center after a precancerous uterus was discovered in 1999. I had knee replacement surgery

in 1997 and have had pneumonia five times, the fifth occurring in the summer of 2001. I also have bronchiectasis, with some permanent lung damage. However, I am able to participate regularly (two to three times per week) in our on campus health club. Our lives in retirement illustrate vividly the progress that has been made in healthcare in the latter part of the 20th century. We are especially grateful for the medical care Dr. Narrett has provided us; he is the Gold Medal winner of all the clinicians I have known. Very recently, Dr. Narrett was promoted to Corporate Vice President for Health Affairs and is in charge of the recruiting and staffing for the 15 current Erickson Retirement Communities, which are growing at a rate of three to five per year. Our new physician is Dr. James Evans, who has over 30 years of experience treating elderly patients.

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Chapter 2

Highlights in the History of Medicine

Modern medicine evolved over many centuries and is built upon the intellectual and physical pursuits of many known and unknown figures throughout history. In one chapter, it is only possible to select a few highlights, which the compiler considers particularly relevant or of interest.

EARLY MEDICINE

Although medicine was practiced in Egypt as long as 4,500 years ago, the Therapeutic Papyrus of Thebes, written in 1552 BC, is the most interesting and important of all the Egyptian scrolls. However, Herodotus of ancient Greece, the “Father of History,” is the source of our knowledge of early medicine (1). The most significant of the early Greek physicians was Hippocrates (460–375 BC), the son and grandson of physicians, who was born on the Greek island of Cos. He separated medicine from philosophy in a rational environment, characterized as one of the most memorable epochs in the intellectual development of the human race. His extensive writings on medicine include “The Oath” and “The Law.” He practiced medicine in Athens and became known as “The Father of Physic” (2). Historically, physicians have always taken “The Hippocratic Oath” at the beginning of their medical education or before starting the practice of medicine, and it has survived for well over 2,300 years and is still in use.

A Modern Version of THE OATH OF HIPPOCRATES:

I solemnly swear or affirm, by whatever I hold most sacred;

That I will be loyal to the profession of medicine and just and generous to its members;

That I will lead my life and practice my art in uprightness and in honor;

That into whatsoever house I shall enter, it shall be for the good of the sick to the utmost of my power, holding myself far aloof from wrong, from corruption, from the tempting of others to vice;

That I will exercise my art solely for the benefit of my patient, and will give no drug, or perform no operation, for a criminal purpose, even if solicited, far less suggest it;

That whatsoever I shall see or hear in the lives of patients which is not fitting to be spoken, I will keep inviolably secret.

These things I do swear or affirm.

The administrator of the oath then says:

And now, if you be true to this, your oath, may you prosper and good repute be yours. The opposite, if you shall prove yourselves foresworn (3).

Galen (130–200 AD) brought to a close the medicine of ancient Greece and in its place introduced experimental physiology, the study of the basic functions that occur in the cells and tissues using physical and chemical methods (1).

In the 1300’s in Europe, human bodies were first dissected by physicians in order to learn anatomy and then teach human anatomy.

Giovanni Bocaccio, an Italian poet, wrote in 1348 that the bubonic plague struck Europe, for which “neither the advice of physicians or the power of medicine appeared to have any value.” “It began with swellings in the groin and armpit, in both men and women, some of which were as large as apples and some of which were shaped like eggs . . . certain indications of coming death.” “Worst of all whenever the disease mixed with healthy people, like a fire through dry grass or oil, it would rush upon the healthy.” One-third of the population of Europe was struck down by the Black Death (4). We now know the unassuming culprit was a safety-pin shaped bacterium named *Yersinia*, of probable strain *Mediævalis*, which was carried by flea-infested rats that had overrun many of the cities in Europe. Today, about a dozen Americans are infected with the plague each year, mostly in the rural West and Southwest; worldwide it affects about 3,000 people annually.

Leonardo da Vinci (1452–1519) is best known for his portrait of Mona Lisa and his religious scene, *The Last Supper*, but he was one of the most versatile geniuses in history. He studied anatomy by dissecting human corpses and made scientific drawings that not only clarified the appearance of bones, tendons, and other body parts, but also their motion and function. Da Vinci further extended his investigations to human reproduction and embryology and blood, none of which were understood at the time. He was interested in the proportions of the human body and, based on the statement by the first century BC Roman architect, Vitruvius, that the “well-shaped man” fits into perfect shapes of the square and circle, his drawing of the Vitruvian man, in about 1487, is one of the most famous images of European art. Shortly after da Vinci’s death in 1519,

anatomy was codified in the hands of Doctors of Physik; Versalius wrote a treatise on human anatomy in 1543.

Thomas Linacre, MD (1460–1524), was an early English physician and classical scholar who promoted humanist “New Learning” and whose students included St Thomas More. Among Dr. Linacre’s early London patients was King Henry VIII, whose approval he obtained, in 1518, to found the Royal College of Physicians. The College decided who should license physicians throughout England, ending the indiscriminate practice of medicine by barbers, clergymen, and others.

William Harvey, MD (1578–1657), was physician to both King James I, in about 1618, and to his successor, Charles I. Dr. Harvey’s elucidation of the blood circulatory system expanded the role of physiology into how our cells, tissues, organs, muscles, and bones function. This hypothesis depended on his own observations and reasoning, numerous animal dissections, autopsies, and clinical observations. His book, in 1628, clarified the function of heart valves, proved that blood did not pass through a septum (dividing wall) into the heart, and explained the purpose of valves in the veins (to prevent backward flow of blood) and that pulmonary circulation is necessary for the oxygenation of blood. Also, Dr. Harvey showed that blood is pumped from the upper left atrium (compartment) into the lower left ventricle (compartment) to the lungs, from which the oxygenated blood is pumped back through the right atrium into the right ventricle and hence throughout the body. Thus, pulse rate reflects the number of heart contractions per minute.

Robert Hooke (1635–1703) was an English physicist whose achievements and theories were very diverse. Hooke became the greatest of several English microscopists and his *Micrographia* in 1665 contained the first description and drawings of a biologic cell. As an astronomer, he was an expert on Jupiter and Mars, discovered the diffraction of light, and was one of the first to propose evolution. Hooke was the only person in his century who knew the art of auscultation, listening to the sounds of the heart and lungs (2).

William Shippen, Jr., MD (1736–1808), was born in Philadelphia and earned his MD at the University of Edinburgh in Scotland. In 1762, he established the first American maternity hospital in Philadelphia and in 1765, with John Morgan, organized the Medical Department of the College of Philadelphia, later the University of Pennsylvania, the first medical school in the American Colonies, where he became the teacher of anatomy, surgery, and obstetrics. He was the first to use dissection of human bodies to teach anatomy to students (2).

Benjamin Rush, MD (1745–1813), was an American physician who served as surgeon general of the Continental Army and became an important figure in public life. He was born near Philadelphia, graduated from the College of New Jersey (now Princeton University) at the age of 15, and received his medical degree from the University of Edinburgh in 1768. Dr. Rush practiced in Philadelphia, and in 1783 he joined the staff of Pennsylvania Hospital, the first and oldest hospital in the United States, founded in 1751 during the colonial period, and an independent entity for over 250 years (2). It was financed by public subscription and a grant of \$2,000 from the

Pennsylvania Assembly. In 1791, Dr. Rush became professor of chemistry, physiology, and medicine at the newly founded University of Pennsylvania, the oldest medical school in the United States (2). He was the most influential physician in the United States, but his use of oral calomel (mercurial bichloride) for purging the body of poisons and his use of blood letting were extreme even for his day. Abigail Smith Adams (1744–1818) and her husband John, Vice President for eight years under Washington and the second President of the United States (1797–1801), lived in our nation’s first capital, Philadelphia for many years. There, in the hot steamy summer of 1793 when the mosquitoes from the Schuylkill River made downtown Philadelphia rampant with one of the worst yellow fever epidemics in history, Mrs. Adams was treated with extensive blood letting by Dr. Rush, from which she barely survived (5). Some 4,500 residents, or 10% of the population of Philadelphia, died from yellow fever. Physicians at the time misguidedly believed blood-letting freed the body of miasmas and poisons. In 1796, Dr. Rush established the first free clinic in the United States. In addition, he investigated the causes and remedies for madness and other diseases of the mind. Dr. Rush wrote to past President John Adams in 1812, “The subjects of them have hitherto been enveloped in mystery” and “I have endeavored to bring them down to the level of all other diseases of the human body, and to show that the mind is moved by the same causes and subject to the same laws” (5, p. 609). Dr. Rush’s publication became a standard guide for mental illnesses and he has been called “The Father of American Psychiatry.” As a citizen, Dr. Rush helped found the first American antislavery society, served as a member of the Continental Congress, signed the Declaration of Independence, and was Treasurer of the United States Mint from 1797–1813. He died in 1813 of typhus, a severe infection transmitted especially by body lice.

Edward Jenner, MD (1749–1823), was an English surgeon who as a youth had noticed that people who had been sick with the relatively harmless disease, cowpox, did not contract smallpox. In 1796, he demonstrated this was a fact by vaccinating a young boy against smallpox and then showing he was immune to the often fatal disease. Over the years, vaccination became common place in both England and America and prevented the wiping out of entire villages (2).

Although Pennsylvania Hospital in Philadelphia, the oldest hospital in the United States, was founded in 1751, and the New York Hospital chartered in 1771, the latter didn’t function as a hospital until 1791 due to its destruction by a fire shortly after it was built, followed by the Revolutionary War (6, pp. 56–57). The Charity Hospital of New Orleans antedates New York Hospital but did not become part of the United States until the Louisiana Purchase from France took place in 1803. The first major hospital to be organized after 1810 was the Massachusetts General Hospital in Boston, which included several unique features such as the training of undergraduate and graduate medical students, 24-hour emergency services, outpatient clinics, admission of paying as well as pauper patients, and the maintenance of detailed case records (6).

Baltimore established an almshouse in 1774 and in 1793 established the first continuously operating public health department in the United States. Dr. James Smith (1771–1841) started the practice of vaccinating against smallpox in 1801, his first patient being a 7-year-old girl who was a resident of the almshouse. From the earliest colonial days of Baltimore, the almshouse was the only place where the poor and sick were taken care of with some funding provided from the state. Because of socioeconomic changes and the acceptance of mental patients as well as sick patients, it became Bayview Asylum in 1866 and in 1890 was moved several miles eastward to near the fringes of Baltimore City. Both University of Maryland and Johns Hopkins medical students served clerkships and received medical training in the large wards at the newly built Bayview Hospital, which became the Baltimore City Hospitals in 1925. In 1929, overall plans were made to construct a new general hospital, a tuberculosis sanitarium, a service building, and a nurses' home. Subsequently, the most prominent physicians in Baltimore, including those from University of Maryland and Johns Hopkins medical schools, practiced medicine there. The Department of Welfare operated the hospital from 1935 to 1955 and physicians took their specialty training there from all over the United States. In 1940–1941, the Gerontological Research Unit of the National Institutes of Health (NIH), under the leadership of Nathan Shock, PhD, was established there and in 1966 an \$8,000,000 facility was built to accommodate its expansion. Subsequently, the National Institute for Drugs of Abuse was established there.

In 1956, a Department of Physical Medicine and Rehabilitation was started "to make certain that all patients at the Bayview Hospital attained the highest degree of independence and returned, if possible, to home, family, and job" (7, p. 35). In 1960, the first Family Practice training program in the United States was established at Bayview (7, p. 54). In 1963, a new Department of Chronic and Community Medicine was started and all new patient applications were evaluated as to whether they would receive the best care at Bayview or at one of the State Chronic Disease Hospitals. Also in 1963, the older facilities were renovated, a new hospital was built, and garden apartments for house staff added with Bayview renamed as the Francis Scott Key Medical Center. University of Maryland and Johns Hopkins operated Bayview jointly for many years but with expansion in the 1990's of the University of Maryland at Baltimore (UMAB) Medical System to a 50 acre downtown campus, the Francis Scott Key Medical Center became the Johns Hopkins Bayview Medical Center. The changes that have taken place at Bayview over many years reflect the socio-economic changes that society has undergone since the days of almshouses.

EARLY FUNERAL CUSTOMS

Daniel Hartzler, a local mortician in our area who is a writer and entertaining speaker, spoke at our local genealogy club, on November 1, 1995, on early funeral customs. The following excerpts, with some paraphrasing, were recorded by the Club

secretary, Linda York: Pennies were placed on the eyelids of the dead to pay the boatman to cross the River Stix. More than one-half of children died in birth or infancy from smallpox or anthrax. Widowers with children often married a younger sister of the mother and it was not unusual for either men or women to marry three times during their lifetimes. It was customary to bury the deceased the day after they died. By the end of the 17th century, funeral eulogies were spoken. On the second day, the simple wooden coffin was moved outside the home because of decomposition of the body. Starting about the 1740's, the bodies were wrapped in a sheet which contained alum, pitch, or wax. People walked to the grave and the coffin was carried on the shoulders of pallbearers. It was a public event and received a lot of publicity through the use of printed broadside pamphlets decorated with a sickle. Others were decorated with an hour-glass as the narrow eye represented God. After the interment, often there was a feast, which could go on for days. By the 1760's, wagons were used to carry the coffins, which developed during the 1800's into handsome horse drawn hearses still observed in the early 20th century and by royalty today. Males wore black crepe armbands and women wore black bonnets. There were even "mourning swords" for the men. Often, there was a wake where a relative stayed up all night. Viewing came into vogue but depended on the weather. Undertakers came into being and graves were dug six feet deep, just as they are today.

The 1850's saw the development of caskets made of several different materials, including rosewood and lead. Burial garments became shrouds or robes. Some caskets had an ice tray underneath and caskets cost from \$11 to \$50. Cadavers meant money to grave robbers, as the bodies were sold to medical schools. This led to improved burial cases to prevent them from easily being opened and in 1871, a life-detecting casket was built, which had a chain and a bell on the top. Dr. Thomas Holmes, who experimented with chemicals and the preserving of bodies during the Civil War, has been called the "father of modern embalming." He realized its commercial potential, embalmed over 4,000 bodies at \$100 each, and became very wealthy. After the Civil War, embalming soon became associated with the selling of furniture, and many of us, who grew up in small villages, remember this tradition.

OTHER EARLY CONTRIBUTIONS

During the 19th century, numerous physicians and scientists contributed to the early development of medicine as a science and to sanitation and public health, with the number growing to hundreds of thousands by the last half of the 20th century. Those cited below were selected from many sources, including references 1, 2, 4, 6, and 8, with numerous others added from the medical literature by the compiler.

John Dalton (1766–1844) was one of the fathers of modern physical science and described color blindness in 1794.

Rene Laennec (1781–1826), a French physician, made the first stethoscope out of a rolled tube of paper, later replaced by a hollow wooden tube. He investigated diseases of the chest and liver and described audible pulmonary and cardiac lesions,

which he later confirmed by autopsy. Portal cirrhosis, which is replacement of normal liver structure by abnormal lobules of liver cells, often hyperplastic, giving the appearance of a finely nodular surface is called Laennec's Disease.

In 1839, C. W. Pennock, MD, of Philadelphia was the first to devise a flexible tube stethoscope to replace a cumbersome wooden-box affair then in use in the United States.

William Beaumont, MD (1785–1853). No doctor–patient relationship is recorded in more detail in the literature than Dr. Beaumont's medical and surgical care of Alexis St. Martin, a French Canadian voyager with an open stomach wound received in 1822, who permitted Dr. Beaumont to make direct observations on his gastric juice and the physiological phenomena of gastric digestion for almost a decade.

Thomas Addison, MD (1793–1860), first described Addison's disease, a primary failure or insufficiency of the adrenal cortex (outer ring of cells of the adrenal gland located just above each of our two kidneys). They secrete the adrenal cortical hormones, cortisone, and hydrocortisone, which were identified about a hundred years later.

Robert James Graves, MD (1796–1853), first described a disease, characterized by an excess of thyroid hormone with thyroid enlargement, emaciation (a wasting condition of the body), sweating, tachycardia (increased heart beat), exophthalmos (bulging eyes), and tremor named Graves' disease.

Thomas Hodgkin, MD (1798–1866), reported on Hodgkin disease in 1836, a diffuse glandular adenopathy (enlargement) of the lymph glands, which is a form of cancer. Until the 1980s, a difficult differential diagnosis was distinguishing Hodgkin lymphoma (HL) from non-Hodgkin lymphoma (NHL), the former being characterized by Reed-Sternberg giant cells (9, pp. 708–712).

In 1850, Henry I. Bowditch, MD (1808–1892), of Boston introduced thoracentesis for drawing off accumulations of fluid in the chest.

In 1842, Crawford Long, MD (1815–1878), was the first to use ether as an anesthetic in Athens GA where its effect had been discovered at “ether parties” held as social events.

Horace Wells, DDS (1815–1848), a dentist in Connecticut, discovered the anesthetic effect of nitrous oxide in December of 1844 and in 1845 had a colleague extract his teeth in front of a group of physicians at the Massachusetts General Hospital but was booed for his efforts (2). However, in 1846, at the same hospital, another dentist, William T. G. Morton of Boston, who had experimented with ether for dental extractions, administered ether for a surgical operation by John C. Warren, MD (7, p. 79). Ether soon became widely used for surgical and obstetrical procedures.

Rudolph Virchow, MD, (1821–1902), was a German pathologist, anthropologist, and statesman who is known as the “Father of Modern Pathology.” He coined the terms thrombosis (blood clot) and embolism (stoppage of blood flow by a gas bubble or fat) while disproving that phlebitis (inflammation of a vein) causes most diseases (2).

In 1847, Ignaz Semmelweis (1819–1865), an obstetrician at a Vienna Austria hospital, at age 28, recognized the need to wash one's hands to prevent the mysterious illness, childbed

fever, which killed up to 25% of obstetric patients and resulted in epidemics (2). His recognition of the importance of clean hands went largely unheeded at that time and infection is still a danger in hospitals today.

Sir Francis Galton (1822–1911) coined the word “Eugenics” and described the statistical law of ancestral heredity in his monograph on Natural Inheritance in 1839.

FLORENCE NIGHTINGALE

Florence Nightingale (1820–1910) became a national British heroine and determined reformer who founded the profession of nursing. In the middle of the 19th century, she launched a movement in England, which the physicians did not fully comprehend, that transformed nursing from a religious service by nuns to a scientific discipline and from menial servitude to eminent respectability. In 1854, she organized a unit of 38 nurses for service in the Crimean War and had a hospital base built at Scutari where her devoted service won the admiration of 10,000 troops. After returning to England, she received the highest decorations of the British Empire and founded the Nurses Training School at St. Thomas Hospital in London, which became a model for others that followed. She demanded intense training, high academic standards, feminine supervision, firm discipline, and a rigid separation of nursing duties from those of a physician. One of her trainees at the St. Thomas Hospital in London, Louisa Parsons, who had served with her in Crimea, came to America in 1889 and became the first director of the University of Maryland School of Nursing in Baltimore (10, p. 225).

Miss Nightingale collapsed at her London home at the age of 37 and for three decades rarely strayed from her couch or bed and complained of a puzzling variety of symptoms ranging from pain in her spine to “recurrent spasms of the heart.” Then in 1888, at the age of 68, her affliction suddenly and mysteriously disappeared. An article entitled “Bipolar Disorder Found in the Lady with a Lamp” was published in the University of Maryland Alumni Bulletin (11). Katherine L. Wisner, MD, MS, Professor of Psychiatry, Ob/Gyn, and Pediatrics at the University of Pittsburgh, spent six months researching Florence Nightingale's chronic medical problem. On May 2, 2003, Dr. Wisner made a case presentation to more than 200 physicians, medical students, and “armchair historians” in 193-year-old Davidge Hall at the University of Maryland in Baltimore. Dr. Wisner concluded that Miss Nightingale's lingering malady was bipolar disorder with bursts of manic depression. In previous case presentations, guest experts have diagnosed the ills of Edgar Allen Poe, a Baltimore poet who died at age 40, as rabies; Beethoven's as syphilis; and Alexander the Great's as typhoid fever.

OTHER GREAT SCIENTISTS

Louis Pasteur (1822–1895) was a French chemist and microbiologist who showed the “Pasteur effect,” the fermentation of

alcohol and the souring of milk without oxygen. As a result of his observations, he deduced that fermentation and food spoilage were due to microorganisms, which could be excluded by destroying them. Subsequently, he developed the process of heat sterilization, known as pasteurization, which permitted vinegar, wine, and beer to be produced and transported without spoiling. In 1881, he developed a way to isolate and weaken germs and went on, following Edward Jenner's example, to develop vaccines against anthrax in sheep and cholera in chickens. Next, Pasteur turned his attention to rabies and in 1885 saved the life of a boy bitten by a rabid dog by inoculating the boy with a weakened virus. In Paris in 1888, he founded the Pasteur Institute for rabies research, prevention, and treatment.

Emil Fischer (1852–1919) was a German chemist who pioneered research on the structure of several natural products, including sugars, dipeptides and polypeptides (small proteins), purines (in the nucleus of cells), and the synthesis of tannins that are used to convert animal skins to leather.

Walter Reed, MD (1851–1902), entered the Army Medical Corps in 1875 and investigated the spread of typhoid fever in military camps and, through controlled experiments, proved that yellow fever was carried by mosquitoes. Later, he became Professor of Bacteriology at the new Army Medical College, and subsequently the army hospital in Washington, DC, was named in his honor (2). Dr. Reed's colleague in the identification of mosquitoes as the carrier of yellow fever was James Carroll, MD (University of Maryland, class of 1891) (1856–1907), who served on the U.S. Army Yellow Fever Commission that was sent to Cuba, a land blighted with the disease. Thus, Dr. Carroll became second in command under Dr. Reed and shares the credit equally.

William Gorgas, MD (1854–1920), served as a surgeon in the United States Army and was in charge of sanitation measures in Havana where, in 1898, he conducted experiments on the transmission of yellow fever by mosquitoes and eliminated it. In 1904, he eradicated yellow fever from the Canal Zone and brought malaria under control, removing the chief obstacles to the building the Panama Canal. He was surgeon general of the United States from 1914–1918.

SANITATION

Even though the ancient Romans had sewer systems and aqueducts for pure water, which they even built on the eastern coastline of the Mediterranean in Caesarea, the residents of London as late as 1875 were throwing their chamber pot wastes into the streets with the call "Look out below." It was 1880 before sewers were built in London. Thus, the poor in London lived in squalor and deplorable living conditions for centuries, leading to much sickness and early death. With the industrialization of America after 1850 many American cities used a combination of sewers and privies but changed over to sewer systems in the early 1900's. However, many farms continued the use of privies until after rural electrification took place in the 1930's but was slowed down due to the unavailability of iron for sewer pipes during World War II.

The World Health Organization (WHO) attributes 80% of the deaths in undeveloped nations to be due to lack of pure water and sanitation. When I was in South Korea as a visiting scientist in 1974, Seoul had conventional sewers, but human stool was routinely used as fertilizer for the rice fields, and country women washed their clothes in the cold icy streams. As we boated up a klong in Thailand within sight of Wat Arun, the Temple of Dawn, a boy was urinating from the porch of a shack, another man was standing in the water cleaning his teeth, and a third was taking a bath in the water. No wonder it is survival of the fittest in the undeveloped areas of the world.

KIDNEY DIALYSIS

John Jacob Abel (1857–1938) earned a PhD in Physiology at the University of Michigan in 1883 and an MD degree at Strasbourg in 1888, but never practiced as a clinician. He was very interested in physiology and drugs and became Professor of Pharmacology at Johns Hopkins in 1893. He has been called the Father of Pharmacology in America (7, p. 154). Dr. Abel, working with physiologist H. H. Turner, PhD, at Johns Hopkins University, built and demonstrated, using a dog, the world's first kidney dialysis unit at the International Congress of Physiology in London in 1912. Dr. Abel made the collodion membranes and hirudin from the heads and necks of leeches (an anticoagulant). Dr. Turner built the mechanical unit to wash the dog's red blood cells of urea nitrogen, a process called plasmapheresis. At the demonstration, Dr. Turner made the first announcement in history of the presence of free amino acids in circulating blood (7).

Clinically, the removal of the toxins urea and creatinine from the blood is called hemodialysis. It relies on the diffusion of these waste products across a semipermeable dialysis membrane, usually collodion, into a chemically prepared bath of dialysis fluid. Patients with kidney failure required repeated dialysis, done in the hospital, because the connections were made with glass tubing. In the fall of 1950, urologists (kidney specialists) from Mt. Sinai Hospital in Baltimore brought their revolving drum unit to a seminar for the freshmen medical students at the University of Maryland, which I attended. As I recall, the unit consisted of a cylindrical revolving drum of mesh wire (about 3 feet in diameter and 8- to 10-foot long) covered with collodion tubing mounted on a large wooden frame through which the patient's blood flowed, a very cumbersome affair.

Belding H. Scribner, MD (1921–2003), of Spokane, Washington, was haunted by the death of a patient from repeated dialysis and developed, in 1982, a U-shaped plastic shunt (probably made of polyethylene tubing) that could be used for long periods of dialysis and converted hemodialysis to a practical treatment. Although some diabetics die from congestive heart failure, most diabetics die from end-stage renal disease due to their high blood glucose glycosylating (attaching glucose by mass action; that is, blood glucose greater than about 150 mg/dL) to body proteins, particularly in the kidneys, reducing their capacity to less than 10% of normal. The November

2004 Johns Hopkins Medical Letter, describes two available dialysis procedures and states that about 400,000 Americans have end-stage renal disease (12). Most of those who need kidney dialysis choose hemodialysis, which requires getting to a dialysis center three times a week and remaining tethered to an artificial kidney machine for 3–5 hours. However, peritoneal dialysis employs the lining of the abdomen (peritoneal membrane) as a filter and can be done at home. It requires the surgical implantation of a catheter in the abdomen, which allows dialysis solution, called dialysate, to pass into the abdominal cavity. The dialysate draws wastes and excess fluid from the blood through the peritoneum membrane via osmosis. The used dialysis solution is drained through the catheter, flushed down the toilet, and replaced with new solution. This procedure, called an exchange, takes about 30–40 minutes.

OTHER SIGNIFICANT CONTRIBUTIONS

Theobald Smith, MD (1859–1934), was a microbiologist and pathologist whose discovery that Texas cattle fever is caused by a parasite transmitted by ticks helped the scientific community accept the role of mosquitoes in the transmission of malaria and yellow fever. He was also the first to identify the organism that causes tuberculosis (TB) in cattle and humans and to notice anaphylaxis, the human body allergic response when the tubercular organism is reintroduced after a time lapse (2).

Sigmund Freud, MD (1856–1939), was an Austrian neuropsychologist, the founder of psychoanalysis, and one of the major intellectual figures of the 20th century. Dr. Freud studied in Paris in 1885 with J. M. Charcot, whose work on hysteria led Freud to conclude that mental disorders might be caused purely by psychological factors, without the patient having any organic disease (2). Between 1899 and 1930, he published several classic works on mental health.

Alfred Ernest Jones, MD (1879–1958), was a Welsh psychoanalyst who became a member of London's Royal College of Physicians and later specialized in psychiatry. Dr. Jones was instrumental in introducing psychoanalysis to Great Britain and North America. His three-volume biography of Freud, published between 1953 and 1957, was for many years the world standard. He also helped Freud and his family escape Nazi Austria in 1939.

NOBEL PRIZES

Alfred Bernhard Nobel (1833–1896) of Sweden patented 355 discoveries during his lifetime, but the most important one was dynamite, which he named from the Greek word meaning power. He left most of his estate of \$9,200,000 to a foundation, from which the interest supports awards in five fields—physics, chemistry, physiology/medicine, literature, and peace (13). Nobel Prizes have become the world's preeminent award and have increased in value from about \$42,000 in 1901 to \$1,271,000 in 2003. The awardee(s) must be living, and each receives a leather-bound illuminated diploma, a gold medal, and

monetary funds, which are split among multiple awardees in Physiology or Medicine, as chosen by the Karolinska Institute of Stockholm, or in Physics and in Chemistry, as selected by the Royal Swedish Academy of Sciences. Because there have been annual Nobel Prizes in Physics, in Chemistry, and in Physiology/Medicine since 1900, I have arbitrarily included only a select few of special interest. I have been aided by the librarian of the Chemical Heritage Foundation in Philadelphia in finding birth and death dates of Nobel Prize winners (14) and by my local Catonsville Public Library and the librarians at the Health Science Library of St. Agnes Hospital in Baltimore, where I am a member of the Institutional Review Board, for information on other famous scientists.

In a letter written by Alfred Nobel in 1896, he stated, "My heart trouble will keep me here in Paris for another few days at least... Isn't it the irony of fate that I have been prescribed nitroglycerin, to be taken internally! They call it Trinitrin, so as not to scare the pharmacist and the public." Equally ironic is that just over 100 years later, in 1998, three biochemists, Robert Furchott, PhD, Louis Ignarro, PhD, and Ferid Murad, PhD, were awarded the Nobel Prize in Physiology/Medicine for their work in establishing the mechanism of how nitroglycerin relieves angina (15, p. 20). It acts by releasing nitric oxide gas into the bloodstream, which in turn signals blood vessels to relax and expand. Recent research suggests this may be a normal physiological process.

Wilhelm Roentgen, PhD (1845–1923), was a German physicist who in 1895 discovered rays that, unlike light rays, did not exhibit properties such as reflection or refraction and which he mistakenly thought were unrelated to light. Because of their mysterious nature, he called them x-rays. Later Roentgen produced the first x-ray photographs, showing the interiors of metal objects and the bones in his wife's hand. In 1901, Dr. Roentgen was awarded the first Nobel Prize in Physics.

Madame Curie (1867–1934) discovered and isolated pure radium and also distinguished alpha, beta, and gamma radiation. In 1903, she shared the Nobel Prize in Medicine with her husband, Pierre, who had assisted her, and Antoine H. Becquerel, who had discovered spontaneous radiation from uranium salts. Madame Curie died in 1934 of leukemia, caused by her long exposure to radioactivity. Her motto was, "Nothing in life is to be feared. It is only to be understood."

Alexis Carrel, MD (1873–1944), a brilliant experimental surgeon who was born in France, joined the newly established Rockefeller Institute in New York in 1905. There, using very fine needles and thread, he developed vascular suture techniques and the transplantation of blood vessels and organs from one area of an animal to another of the same species. In 1912, Dr. Carrel received the Nobel Prize in Medicine for his pioneering work in organ transplantation.

THE FLEXNER BROTHERS

Simon Flexner, MD (1863–1946), a distinguished pathologist, was invited in 1903 to organize and direct the Rockefeller

Institute for Medical Research in New York City, a position from which he retired in 1935. His appointment became a tremendous catalyst to medical research, which was clearly separated from medical education. The Institute's PhD or MD post-doctoral training program trained dozens of medical researchers who went on to become research scientists or head research organizations and chair clinical and basic science departments in medical schools. His brother Abraham Flexner, PhD, an academic professor and reformer at Johns Hopkins University, had an equally tremendous catalytic effect on medical education when his report on medical education in the United States and Canada recommended half of the medical schools existing in 1909 be closed and standards be instituted (6, p. 162). The public outcry that resulted brought about the closing of a number of proprietary medical schools, raised admission and graduation standards, and resulted in the introduction of intensive laboratory and clinical teaching of medicine based on science.

JOHNS HOPKINS MEDICINE

Benefactor Johns Hopkins (1795–1873) made a tremendous contribution to medicine. In 1819, he established Hopkins Brothers Wholesalers with his brothers. In 1836, he purchased a 166-acre estate in the country and at a cost of \$15,800 built a large mansion in northeast Baltimore City, known as Clifton, in what is today Clifton Park. He retired as a wealthy man in 1847 and continued investing in Baltimore real estate and in the Baltimore and Ohio Railroad. At Johns Hopkins' death in 1873, he left Clifton to the city of Baltimore, endowed an orphanage for black children, and left \$1,000,000 to his relatives and friends, \$4,000,000 to found Johns Hopkins University, and \$3,000,000 to fund Johns Hopkins Hospital. Johns Hopkins Hospital opened its doors in 1889, followed by the Johns Hopkins School of Medicine in 1893. The "big four" physicians associated with the founding of the very distinguished institution are William Henry Welch, William Osler, William S. Halstead, and Howard A. Kelly. For the past 15 years, Johns Hopkins Hospital has been rated as the number one hospital in the United States (16).

William Henry Welch, MD (1850–1934), was an American pathologist who studied pathology in Germany before returning to open the first pathology laboratory at Bellevue Hospital Medical College in 1879. In 1893, he developed the first true American university department of pathology at Johns Hopkins University, where he recruited William Osler and William S. Halsted. From 1893–1898, Dr. Welch served as the first dean of the medical school. Dr. Welch demanded that students study the physical sciences and be actively involved in clinical duties and laboratory work. He also demonstrated the effects of diphtheria toxin and discovered that bacteria are involved in wound fever and gas gangrene. From 1898–1922, he was president of the Maryland State Board of Health and continued as a member until 1929. He was the first director of the Johns Hopkins School of Hygiene & Public Health from 1916–1926. The Welch Library

at Johns Hopkins Medical School is named in honor of this very distinguished pathologist.

William Osler, MD (1849–1919), a Canadian with the title Baronet, received his MD from McGill University in Canada in 1872. Most intriguing is that he was a worrywart as a first-year medical student at McGill and lived in great fear of failing. However, a short passage from Thomas Carlyle, a British essayist and historian, inspired his confidence, after which his manner and personality changed and all fear and doubts left him forever. Carlyle's words were, "Do not try to see the future but what's ahead of you today; fear and stress is the worry about tomorrow." Henceforth, he lived one day at a time. After graduation, Dr. Osler trained for two years at Montreal General Hospital and then for two more years in Europe (2). He was appointed Professor of the Institutes of Medicine (largely physiology and pathology) at McGill University upon his return from Europe. In May 1884, he became William Pepper Professor of Clinical Medicine at the University of Pennsylvania (6). He was only 35 years old at the time, which was considered very young for such a position at the oldest medical school in the United States. In addition, he was provided with a salary, which made it possible for him to devote his time to teaching and research, without having to practice medicine, a very unusual situation. In 1889, Dr. Osler was invited to be the first physician in chief at the new Johns Hopkins Hospital and Medical School, where among many endeavors he organized a chief residency program and senior medical student clerkships, which became the standard protocol for medical education throughout the United States. In 1905, at age 56, Dr. Osler was named Emeritus and moved to England, where he became Regius Professor of Medicine at Oxford University, and was knighted. He died at age 70 in England on December 29, 1919 (6). Sir William Osler is generally considered to have been the leading physician of his day worldwide and possibly the greatest physician who ever lived. He is also remembered for being a humanitarian.

William S. Halstead, MD (1852–1922), was a student assistant in physiology and graduated at the head of his class from the College of Physicians and Surgeons of Columbia University in 1877. Following graduation, he served a surgical internship, took two years of training in Vienna, and returned to demonstrate anatomy at Columbia. As a visiting physician at several New York hospitals, he was one of the first to employ cocaine for regional anesthesia, nerve blocking, and as a spinal anesthetic. However, he used himself as an experimental subject and became addicted to cocaine in 1885, which brought an end to his clinical career in New York. After two periods of hospitalization in the struggle to end his addiction, he was persuaded to come to Johns Hopkins in Baltimore and work temporarily in Dr. William Welch's laboratory. In 1892, he assumed the position of chief of surgery at Johns Hopkins Hospital and professor of surgery at the Johns Hopkins University School of Medicine, where he developed many surgical techniques and introduced the use of rubber gloves in the surgical amphitheater (2, pp. 1022–1025). Among his contributions are the earliest surgery for breast cancer and the repair of hernias, the first successful ligation of the first portion of the

subclavian artery (in the shoulder) for an aneurysm, and the treatment of carbon monoxide poisoning by withdrawing blood, which was then defibrinated, reoxygenated, and returned to the patient. Most carbon monoxide cases today result from defective kerosene heaters and are often fatal, as carbon monoxide has over 200 times the affinity for hemoglobin as oxygen. Patients with severe exposure to carbon monoxide must be treated promptly with oxygen.

Howard A. Kelly, MD (1858–1943), is the fourth illustrious physician who built Johns Hopkins into an institution with great accomplishments. He completed his undergraduate and medical education at the University of Pennsylvania in 1882 and a residency in surgery at Episcopal Hospital in the Kensington area of Philadelphia. Interested in gynecology and obstetrics, Dr. Kelly established a women's hospital in Kensington in 1887, the sixth such clinic in the United States (2). He was barely 31 years old when President Gilman of Johns Hopkins University invited him in 1889 to head the department of obstetrics and gynecology at Johns Hopkins Hospital. Dr. Kelly believed that a gynecologist should be a well-trained abdominal surgeon first, as born out in a journal article he published in 1905 (2, p. 1025). He knew Madame Curie, pioneered radium treatment for cancer, and published over 600 scientific articles, including a two-volume treatise on operative surgery. Dr. Kelly had a summer home in Harford County, Maryland—the magnificent mansion, Liriodendron, the Latin name for tulip poplar trees, which are abundant on the 200-acre estate.

Alfred Blalock, MD (1899–1964), joined Johns Hopkins in 1941, and his research on the effectiveness of blood transfusion in traumatic and surgical shock due to blood loss saved many lives in World War II. However, he is best known for his research with Helen Brooke Taussig, MD (1898–1986), a pediatric cardiologist at Johns Hopkins, in the development of a surgical treatment for heart malformations (blue babies), which he first performed in 1944. A lesser known fact is that a black man, Vivien T. Thomas (1910–1985), was a key player in anastomosis of the subclavian artery to the pulmonary artery. His assistance with the surgery and his design of the surgical shunt used paved the way for the successful outcome of the Blalock-Taussig shunt. This major contribution was not recognized publicly until 1976, when he was awarded an honorary Doctorate of Laws by Johns Hopkins University.

Johns Hopkins Medicine has contributed more than 100 years of “firsts” including the first use of x-rays in surgery in 1897, the first model for renal dialysis in 1912, and the first salaried department chairmen in 1914. More recently, Johns Hopkins Medicine pioneered work in bone marrow transplantation in 1960, the first use of a laser to prevent blindness in 1969, the first nerve-sparing surgery for prostate cancer in 1982, and the first use of genetically engineered t-PA to treat a heart attack in 1984.

In April 2003, another first occurred at Johns Hopkins when a woman, Julie Freischlag, MD, Chief of Vascular Surgery at the University of California at Los Angeles (UCLA), was selected as the best candidate and became Surgeon in Chief of Johns Hopkins Hospital and Chairman

and Professor of the Department of Surgery at Johns Hopkins School of Medicine.

Harvey Williams Cushing, MD (1869–1946), was born in Cleveland and worked in Dr. Halstead's Department of Surgery at Johns Hopkins from 1896 to 1912. Subsequently, Dr. Cushing spent his career at Harvard, where he became a world-famous brain neurosurgeon in the early 20th century and greatly reduced the mortality (death rate). He also became the leading expert in the diagnosis and treatment of intracranial tumors and was first to ascribe pituitary-gland (master gland near the midbrain) malfunction to a condition now known as Cushing's disease or Cushing's syndrome. The disease is characterized by a large, round, moon-shaped face, truncle (waistline) obesity, hypertension (increased blood pressure), edema (swelling of body tissue), and osteoporosis (bones become more brittle and break easily) from the oversecretion of adrenal cortical hormones. The adrenal cortical hormones include cortisone and hydrocortisone, which were discovered in 1954.

Walter E. Dandy, MD (1886–1946), was trained under Dr. Harvey Cushing at Johns Hopkins and also became a dominant figure in early American neurosurgery. However, Dandy and his mentor, Dr. Cushing, clashed furiously over the treatment of tumors in the posterior fossa, near the fragile cerebellum and brain stem at the rear of the skull, and how fatalities would result (17). Nevertheless, Dr. Dandy kept experimenting, resulting in the deaths of 13 patients, before he had perfected, by 1921, a relatively safe procedure to remove such tumors. The procedure, which he described in the *Bulletin of Johns Hopkins Hospital*, was reviewed recently by Dr. Ben Carson, the famous pediatric neurosurgeon at Hopkins.

INTERNATIONALLY PROMINENT CLINICS

William Wornall Mayo, MD (1819–1911), was born and educated in England and came to America in 1845. In 1863, he opened a surgical practice in Rochester, Minnesota, about 60 miles southeast of Minneapolis-St Paul. In 1889, he founded St. Mary's Hospital with his two physician sons and the Sisters of St. Francis. The elder son, William James Mayo (1861–1939), specialized in surgery of the abdomen, pelvis, and kidney. The younger son, Charles Horace Mayo, MD, (1865–1939), originated modern procedures for goiter surgery (enlarged thyroid), neurosurgery, and orthopedic (bone) surgery. In 1910, their partnership became a voluntary association of physicians and surgeons, which later became the Mayo Clinic. In 1915, they also founded the Mayo Foundation for Medical Education and Research at the graduate level (students who already have MD degrees) (6). Dr. Charles Horace Mayo died of pneumonia on May 26, 1939, and his older brother, Dr. William James Mayo, died in his sleep at age 78 on July 28, 1939. Currently, the Mayo Clinic includes about 500 physicians and treats over 200,000 patients a year. Over 21,000 physicians worldwide have received training there. In February 1990, it was my privilege, along with a professional colleague, to perform an accreditation inspection of the Mayo Clinic post-doctorate program (PhD or MD) in clinical chemistry.

Fortunately, all of the affiliated hospitals, clinics, and teaching and research facilities are interconnected by underground tunnels to facilitate travel between buildings in the winter. In the early 1990's, Mayo Clinics were established in Scottsdale, Arizona, and in Jacksonville, Florida.

In 1920 in Topeka, Kansas, Charles Frederick Menninger (1862–1953) and his sons, Carl and William, founded the Menninger Diagnostic Clinic for general medicine and the Menninger Sanitarium and Psychopathic Hospital for psychiatric care, which became world famous institutions.

VITAMINS AND NUTRITION

In 1914, Casimir Funk, PhD (1884–1967), discovered thiamin (vitamin B1), a water-soluble compound and the first known vitamin, which has been shown to function as a cofactor needed for muscle cell decarboxylation and the movement of muscles. Thus, pigeons are unable to hold their heads up when they are vitamin B1 deficient, but the condition is corrected within minutes by giving them drinking water containing vitamin B1.

Sir Frederick Gowland Hopkins, PhD (1861–1947), discovered the essential amino acid, tryptophan, one of 21 essential amino acids, which are found in the common foods we eat and are required by our bodies to synthesize our various body proteins. Hopkins was the first to suggest that the effectiveness of water-soluble substances, such as thiamin (vitamin B1), must be due to the fact that they participate as catalysts (promoters) in our body. Each vitamin is part of an enzyme active center, which brings about a specific chemical reaction, changing compound A to compound B at body temperature. When we have a fever, our body metabolism speeds up, and when our body temperature is lowered by submersion in an ice bath, the circulation of blood slows down remarkably, permitting the first open heart surgery in 1948 by the use of hypothermia. By the early 1940s, all of the water-soluble vitamins were known, including riboflavin (B2), pyridoxyl (B6), niacin, pantothenic acid, lipoic acid, and biotin. The role of folic acid and vitamin B12 or cobalamin in pernicious anemia was also defined in the 1940s. A deficiency of vitamin C, ascorbic acid, leads to scurvy, explaining why sailors have known for centuries that, when obtainable at port, they needed fresh fruits and vegetables.

About the turn of the century, Graham Lusk, PhD (1866–1932), founded the science of nutrition, which includes the study of carbohydrates, protein, fats, vitamins, and other nutrients that we eat. Today, most of the emphasis related to nutrition is on taking our vitamins daily and examining the caloric content of the food we eat as it relates to obesity and weight loss.

THE FIRST CLINICAL CHEMIST

Otto Folin, PhD (1867–1934), Professor of Biological Chemistry at Harvard, was the first scientist to develop procedures for the measurement of blood sugar (glucose), which is altered in diabetes, and urea, which is altered in kidney disease—the two most

common disease entities. Dr. Folin developed a technique for making a clear protein filtrate of whole blood, which by the addition of chemicals, permitted either glucose or urea to form a colored clear solution. The amount of color produced depended on the quantity of glucose or urea in the blood sample. Hence, a blood sample from a patient could be compared with a glucose solution of known concentration in an instrument called a comparator or DuBoscque colorimeter, which I learned to use in college chemistry in 1943. Dr. Folin developed techniques for other constituents in the blood, such as uric acid in gout, a painful disease characterized by deposits of crystalline uric acid in the lower legs and feet, or in just one foot as depicted in historic pictures.

INBORN ERRORS OF METABOLISM

Sir Archibald Garrod (1857–1936), a visionary, saw biochemistry as being dynamic, which led him to think about metabolic pathways and, without any knowledge of genes, to recognize that a variation in Mendelian heredity could explain an alteration. He also coined the phrase “inborn error of metabolism.” An astute Norwegian mother recognized that her blue-eyed, blond-haired child was not developing normally and took the child to physician after physician, only to be told “nothing was wrong with the child.” However, Asjborn Folling, a 46-year-old Norwegian MD pediatrician and PhD biochemist, detected a strange odor in the child's urine that he identified, in 1934, as phenylketonuria (PKU), a condition that results in mental retardation. Children with this disease are deficient in the enzyme that converts the amino acid phenylalanine to tyrosine. In 1962, Robert “Bob” Guthrie, MD, a pediatrician in Buffalo, New York, developed a test for detecting excess phenylalanine in a drop of blood from a newborn's heel and collected on filter paper. The condition, which occurs about once in every 10,000 births, is correctable by placing the child on a low phenylalanine diet. New York State soon passed legislation requiring that all newborns be tested as of July 1, 1964. The state also provided the lophenylac diet to parents at no cost because it was not only the humanitarian thing to do, but it prevented expensive mental institutional care. Today, most states screen newborns for PKU, galactosemia, and sickle cell disease, and often other inherited conditions, most of which can be prevented or treated. Between 1965 and 1977, under my direction as Director of Clinical Chemistry and Toxicology at the Division of Laboratories and Research of the New York State Department of Health in Albany, New York State pioneered in the implementation of these screening procedures.

PH AND BODY ACID BALANCE

In 1909, Soren P. L. Sorensen (1868–1939), a chemist at the Carlsberg Breweries in Denmark, discovered the importance of hydrogen ion concentration, that is, pH, or degree of acidity, in the brewing of beer. He developed the pH scale relationship of 0,

the most acid, to 14, most basic (hydroxyl groups predominate), with a solution at pH 7 being neutral. Hydrochloric acid (HCl), produced by the stomach, is a strong acid and causes many clinical problems; whereas lye or strong sodium hydroxide (NaOH), a base, is likely to be fatal when ingested because it destroys tissue.

Donald D. Van Slyke, PhD (1883–1971), grew up in Geneva, New York, received his PhD from the University of Michigan in 1907, and became the first clinical chemist at the Rockefeller Institute in New York City, where he pioneered in developing many analytical methods. While there, he met John P. Peters, MD (1887–1955), a clinician at the Rockefeller Hospital, who had spent most of his career at Yale as a clinician interested in metabolic disease. Drs. Van Slyke and Peters forged the earliest alliance between chemistry and clinical medicine. Their comprehensive two volumes, *Quantitative Clinical Chemistry and Clinical Interpretations*, were first published in the 1930s and revised in the 1940s, and, for a generation, became “the Bible” for hundreds of newly developed hospital.

Dr. Van Slyke’s fundamental studies on acid/base balance in relation to lung and kidney function led to the Henderson-Hasselbach equation, which defines the mathematical–chemical relationship of acid/base balance in the body in terms of blood pH, normally maintained at 7.40, through control of the carbon dioxide/bicarbonate blood buffer system by the lungs and kidneys. It is one of the most difficult concepts in clinical medicine for medical students to understand and for clinicians to work with, but having been thoroughly schooled in it, I taught it most of my career. In 1988, while on the faculty of Hahnemann University, I had the opportunity during Grand Medical Rounds to explain to three full Professors of Medicine, among others, why they were incorrect in their interpretation of the clinical aspects of the Henderson-Hasselbach equation. It had been my good fortune to have Peters’ and Van Slyke’s two volumes as mainstays in my graduate education in Biochemistry and Physiology at the Syracuse University College of Medicine from 1946–1950. In about 1948, my mentor, W. W. Westerfeld, PhD, had also written a manual on the subject. In May 1969, Dr. Donald Van Slyke attended a symposium on acid/base balance, sponsored by our Upstate New York Section for Clinical Chemistry, and at that time, at age 86, he and his second wife were active tennis players and played on the available clay courts.

BLOOD COAGULATION (CLOTTING)

Jay McLean, MD (1890–1957), as a medical student at Harvard in 1916, isolated a crude preparation of brain tissue called cephalin, which had thromboplastic (blood clotting) activity. His finding led to the discovery of heparin in 1959, a blood anticoagulant (prevents blood clotting) that is in wide usage, mainly for hospitalized patients. A more commonly used anticoagulant is coumadin, which was isolated from spoiled sweet clover in 1940 by Karl Paul Link, PhD, and his associates at the University of Wisconsin after a farmer brought in two buckets of unclotted blood and complained his cattle were bleeding to

death. Their publication in 1941 suggested coumadin’s use as an anticoagulant should be considered by physiologists and hematologists (6, p. 470), and a few days later, they received a request from the Mayo Clinic for a supply. Within several months, Drs. Butt, Allen, and Bollman published a report on the clinical use of this new oral anticoagulant. Coumadin is the same as the rat poison, Warfarin. Warfarin stands for Wisconsin Alumni Research Foundation, which patented it. When I joined the faculty at the University of Maryland School of Medicine in 1950, a PhD physiologist, at a clinic he directed at Mercy Hospital in Baltimore, was measuring prothrombin times to control coumadin levels in patients who had suffered heart attacks. Although oral coumadin is the most common anticoagulant in current usage, it requires the monitoring of prothrombin levels.

Edward A. Doisy, Sr., PhD (1893–1986), at St. Louis University, identified the chemical nature of vitamin K and shared the Nobel Prize in Medicine in 1943 with Hendrik Dam (1895–1976), who studied its functional aspects in blood clotting. Centrifugation permits pouring off the clear liquid serum, leaving the clot behind. The separation of red cells from whole blood results in plasma that still has clotting capability.

Dr. Edward A. Doisy, Sr., also contributed much to the chemistry of the estrogens and the role of progesterone in the menstrual cycle. Two of his PhD trainees at St. Louis University, W. W. “Weste” Westerfeld and Daniel “Dan” Richert, who received some of the vitamin K Nobel Prize money, both former Harvard University faculty, were mentors for my graduate studies from 1946 to 1950 at the Syracuse University College of Medicine. Edward “Ed” Doisy, Jr., MD, became a professor of biochemistry at Harvard and Richard “Dick” Doisy, the youngest son, took his PhD with Dr. W. W. “Weste” Westerfeld at Syracuse and was a colleague there after I returned to Syracuse in 1957. Unfortunately, Dick passed away from cancer in the 1970’s.

PERNICIOUS ANEMIA

George R. Minot, MD (1885–1950), with his associate, William Murphy, MD (1892–1987), won the Nobel Prize in Medicine in 1934 for their clinical studies that had shown, in the 1920s, that the feeding of raw whole liver to patients affected the regeneration of red blood cells and brought about a marked improvement in patients suffering from pernicious anemia. In this disease, which can occur at any age but is most common in older individuals, the red cells are larger than usual and deficient in hemoglobin, the pigment that carries oxygen to our body cells, and when untreated can lead to serious consequences and death. In my view, the development and understanding of the intricate biochemistry, physiology, and pathology of pernicious anemia, including discovery of the vitamin complex of folic acid and cyanocobalamin (vitamin B12), is one of the leading accomplishments of 20th century medicine.

In the 1920s, at the Peter Bent Brigham Hospital in Boston, a part of Harvard, Dr. Minot fed nauseating quantities

of cooked calf or beef liver, low in fat, to 45 of his patients who had pernicious anemia. As a result, the patients promptly experienced a remarkable and consistent improvement in their critically low red blood cell levels (2). He also prescribed bed rest for them and gave them hydrochloric acid (HCl), which was absent from the gastric juice of most of his patients. In 1926, Dr. Minot published the results of his study. The next year, he evolved a better understanding of the reticulocyte rate increase (measures the rate of formation of new red blood cells). In patients with pernicious anemia, Dr. Minot found either liver or kidney corrected their deficiency, but when liver was fed to patients with secondary anemia, it did not correct their condition. This implied that a secondary or intrinsic factor was missing from patients who had achlorhydria (no HCl in their stomachs) (6). In his Nobel lecture, Dr. Minot noted that others had found diets rich in protein and iron to be helpful in various types of anemia in patients. George H. Whipple, MD (1878–1976), who shared the Nobel Prize with Drs. Minot and Murphy, found this to be especially true in dogs. Dr. Whipple later became Dean of the University of Rochester School of Medicine and Dentistry, and in the summer of 1944 he thought I might be eligible for a scholarship to medical school. At that time, I saw a showcase with his Nobel Prize award, but was too young and naive to appreciate what I was viewing and never made application to medical school, partially because my parents didn't feel they could help me financially.

William B. Castle, MD (1897–1990), was the pupil of, collaborator with, and successor to Dr. Minot as head of the Thorndike Memorial Laboratory at Harvard. He demonstrated that an "intrinsic factor" secreted by mucosal cells in the stomach wall, when fed with an extrinsic factor such as beef, produced a red cell stimulating effect in pernicious anemia patients similar to that produced by patients fed liver or kidney. In 1948, this was a very major and key discovery in the identification of the complex vitamin factor. Because I studied at Syracuse University College of Medicine under three young former faculty members from Harvard, from 1946–1950, I became acquainted with many of the Harvard staff, especially in Biochemistry, who told the following story about Bill Castle: As Distinguished Professor of Medicine at Harvard Medical School, he would often have to pick up visiting dignitaries. However, to their great surprise, he would arrive at the train station or airport in Boston in his 20-year-old 1928 Model A Ford roadster using an open rumble seat for their luggage.

In December 1947, Karl Folkers, PhD (1906–1997), and his colleagues at Merck, Sharp & Dohme, and, almost simultaneously, E. Lester-Smith, PhD, of Great Britain, working independently, isolated the active principle, that is, the intrinsic factor, from mammalian liver, and identified it as vitamin B12 (or cyanocobalamin). B12 (or cyanocobalamin) contains a cyanide group and a molecule of the rare trace mineral, cobalt, and acts with the vitamin folic acid as a cofactor to handle single carbon units in the body. Because the intrinsic factor consists of the vitamin B12 complex, acting in conjunction with folic acid, patients devoid of either one of these factors cannot make normal red blood cells and they develop pernicious anemia. Thus, the disease can result from a diet lacking in vitamin

B12 or when intrinsic factor is not produced by stomach cells or is unable to bind to the vitamin. Pernicious anemia causes weakness, waxy pallor, a shiny tongue, and stomach, intestinal, and neurological problems. It can be treated by monthly B12 injections into muscle tissue, but the injections must be continued for the rest of the patient's life (6). Although Dr. Folkers and Dr. Lester-Smith isolated the active principle, hundreds of other research scientists were involved in working out the other biochemical, physiological, and clinical aspects of these factors. Perhaps for this reason, no additional Nobel Prize was ever awarded in this area. However, in 1972, the brilliant organic chemist, Robert B. Woodward, PhD, of Harvard University, and his colleague, Albert Eschenmoser, PhD, achieved the total synthesis of vitamin B12. Recently, TriVita Sublingual B-12, vitamin B12 tablets that can be taken sublingually (under the tongue absorption), became available from a patented commercial source.

DISCOVERY OF INSULIN

Oskar Minkowski, MD (1858–1931), was a German physiologist and pathologist who researched diabetes mellitus, detected by sweet-tasting urine. In 1884, he discovered the presence of beta-hydroxybutyric acid in the urine of diabetic patients, and later detected a decrease in blood bicarbonate in diabetic coma, which causes diabetic acidosis (low blood pH). He also discovered that the resulting coma can be treated by alkaline therapy. This was a remarkable biochemical accomplishment at the time. Later experiments with Joseph von Mering (1849–1908), performed on dogs, led Minkowski, who must have been a scientific genius, to propose that the pancreas is the source of an antidiabetic substance, which we now know as insulin.

Frederick Grant Banting, MD (1891–1941), a Canadian orthopedic surgeon, worked in 1920 with a colleague, Charles H. Best, PhD, a physiologist. They became interested in the active principle (hormone) that lowered blood sugar in the pancreas. Their joint efforts under Professor J. J. R. McCleod, PhD (1876–1935), Chairman of Physiology at the University of Toronto, were begun in May 1921. As a source of pancreatic fluid, they ligated (tied off) the pancreatic ducts of dogs, and in just eight months they succeeded in the chemical purification of a potent extract for clinical trial, whereas others had labored for years (2). The need for a biochemist in the chemical purification and processing resulted in the addition of J. B. Collip, PhD, to the group. They succeeded because ligating the pancreatic ducts resulted in destroying the acinar cells (alpha cells), the source of digestive enzymes, but left intact the insular cells (beta cells), which are the source of insulin. The potent extract they isolated corrected the diabetes mellitus of a 14-year-old boy. After the Nobel Prize in Medicine was awarded to Banting and McCleod in 1923, Banting shared his award with Best, and MacLeod shared his with Professor Collip.

The first commercial animal insulin available in the United States was manufactured early in 1922 by the Connaught Laboratories of the University of Toronto, followed in October 1922 by the Eli Lilly & Company of Indianapolis, Indiana.

On August 7, 1922, Elliot Joslin, MD, founder of the world-famous Joslin Clinic in Boston, a part of Harvard, began using insulin from Canada for patients in his diabetic clinic, its first usage in the United States. Commercial injectable preparations of short- and long-acting beef and pork insulin have been available for many years to treat juvenile and adult diabetics and have been extremely important in diabetic care for 80 years. However, just recently, the application of new recombinant DNA technology has resulted in a modified bacterium, which produces human insulin that has been marketed with FDA approval. An amazing development! Over the past few years, Joslin Diabetic Centers have been established at many medical centers and large hospitals throughout the United States, including the University of Maryland Medical Center.

PENICILLIN

In 1928, Sir Alexander Fleming, MB, BS (1881–1955), a microbiologist, discovered that a crude broth containing an antibiotic, penicillin, inhibited bacteria, and he shared the Nobel Prize in 1945 with Sir Howard Florey (1898–1968) and Ernst Chain (1906–1979), who purified and crystallized it. The USDA Regional Lab in Peoria, Illinois, developed vat technology for its production. The availability of penicillin saved thousands of lives during World War II. It was manufactured mainly by Bristol Labs in Syracuse, New York and, after 1943, by three other pharmaceutical companies including, Pfizer, which greatly improved vat production. From 1947–1949, I was funded as a research fellow at the Syracuse University College of Medicine by a grant from Bristol Laboratories to W. W. Westerfeld, PhD, my thesis advisor. Dr. Westerfeld received his PhD at age 23 at St. Louis University under Nobel Prize winner, Edward A. Doisy Sr., PhD, and became a Rhodes Scholar at Oxford University. While there, he met and married Sir Alexander Fleming's niece, Nora, in 1938. Their oldest daughter, Mary Westerfeld Rakow, who was born in Oxford, England, in spring 1939, currently lives in Maryland, and I recently had the pleasure of renewing my acquaintance with her over the phone.

INSTRUMENTATION

Theodor Svedberg, PhD (1884–1971), a Swedish scientist, made many contributions to the chemistry of colloids (solids dispersed in solutions), for which he received the Nobel Prize in 1926. In 1940, he invented the ultracentrifuge for the separation of large molecules in solution such as proteins, carbohydrates, and polymers. Commercial ultracentrifuges became available after World War II and greatly advanced the field of biochemistry.

Arnold O. Beckman (1900–2004) founded Beckman Instruments in 1935 after developing a pH meter, in his garage, as a favor for a friend who worked in a citrus processing plant in California and wanted to measure the acidity of the fruit. The Beckman pH meter has been said to be one of the most important inventions of the 20th century. This forerunner of modern

electrochemical instrumentation was followed by the DU spectrophotometer in 1940. Both instruments revolutionized biochemical research. Quartz cells in the DU permit the measurement of clear liquids in both the visible and ultraviolet range. The \$4,000 instrument was an essential piece of equipment during my graduate research studies at the Syracuse University College of Medicine from 1946 to 1950. The company later became Beckman Coulter, Inc., of Fullerton, California.

In 1940, William "Bill" H. Summerson, PhD (1906–1986), a chemist/toxicologist and nerve gas expert at the Edgewood Chemical Arsenal in Edgewood, Maryland, invented an inexpensive, sophisticated, light-measuring instrument, the Klett Summerson Photometer. It was manufactured by the Klett Company of New York, New York, read in Klett units, and simplified chemical measurements of colored solutions by providing a direct relationship between the standard and the unknown. When I joined the University of Maryland Medical School in Baltimore in 1950, our medical student laboratory had both DuBosque colorimeters from the 1930s, which required the manual match of the colors of a known and an unknown (patient) solution and the newer Klett Summerson photoelectric colorimeters. Our students learned how to determine blood glucose on finger-stick blood and carried out glucose tolerance tests on themselves. We also injected them in the arm with phenolsulfophthalein dye as a kidney function test. Bill Summerson presented two lectures on nerve gases as part of our Biochemistry course for medical students.

Arne Tiselius, PhD (1902–1971), of Sweden did his PhD thesis in 1930 on the chemical properties of serum proteins and, in 1937, developed moving-boundary electrophoresis, apparatus to separate serum proteins into a profile according to their molecular weight. In 1939, the Klett Manufacturing Company of New York City began manufacturing electrophoretic apparatus, which was about 10 feet long and sat on two concrete pillars. William R. "Bill" Amberson, PhD, Chairman of Physiology at University of Maryland School of Medicine, had such a unit in his laboratory when I joined the faculty in Biochemistry in 1950. Three years later, I followed published directions by Durrum et al. and assembled a simple plastic unit with platinum wire electrodes using paper strips that produced similar results and allowed identification of the serum proteins by staining the strips. Within a few years, electrophoresis on paper and/or gel medium became a routine clinical laboratory test for separating serum proteins into albumin and alpha, beta, and gamma globulins. Although other media are often used today, the technique can be used to identify the spike peak of a paraprotein in the serum, which is characteristic of multiple myeloma (bone cancer). The technique is used currently as an adjunct test in detecting the creatine kinase (CK) isoenzymes released in myocardial infarction (MI).

OTHER FAMOUS SCIENTISTS AND PHYSICIANS

In 1946, Benjamin M. Spock (1903–1998), an American pediatrician trained in psychiatry and child development, published

The Common Sense Book of Baby and Child Care. In his book, he urged parental flexibility and reliance on common sense and discouraged corporal punishment. His book has influenced generations of parents and has sold over 50 million copies in 39 languages, after being revised to include new social and medical issues. The seventh and last edition was published in 1998 as *Dr. Spock's Baby and Child Care (4)*.

Carl F. Cori, PhD (1896–1984), of Washington University in St. Louis, shared one half the Nobel Prize in 1947 with his wife, Gerty T. Cori, MD (1896–1957), for their work on the biochemical conversion of liver glycogen (storage form of glucose) to glucose; the other half of the Nobel Prize went to Bernardo Houssay, MD (1887–1971), an Argentinian, for his research on the hormones produced by the anterior pituitary gland.

William “Bill” Sunderman, Sr., MD, PhD, (1899–2003), physician, pathologist, author, teacher, photographer, professional musician, and the outstanding clinical laboratory scientist of the 20th century, was the medical director for the Manhattan Project (atomic bomb) during World War II and founder of the Association of Clinical Laboratory Scientists. His umbrella organization incorporated pathologists, microbiologists, biochemists, physiologists, clinical chemists, blood bankers, hematologists, clinical pathologists, and a few clinicians in comprehensive, three-day, disease-oriented annual seminars. From about 1963 to 1990, it was my privilege to participate in and present papers at these seminars. I also coauthored, with Bill Sr. and Bill Jr., their monthly Proficiency Test Sample Program from 1978 until 1983, when Bill Sr. turned it over to the ASCP (American Association of Clinical Pathologists).

CARDIAC SURGERY

In June 1948, Charles Philamore Bailey, MD (1910–1993), of Hahnemann Medical College and Hospital in Philadelphia, carried out the first open heart surgery in the world for mitral valve disease, caused by rheumatic fever, by cooling the patient in an ice bath (hypothermia). He named the procedure a commissurotomy. Dr. Bailey founded the American College for Chest Surgery and had his picture on the cover of *Time* magazine in 1958 (18). After joining the faculty at Hahnemann in 1977, I had the unique experience of attending a seminar at which Dr. Bailey described the procedure using a woman's corset, with four attached garters representing the four main heart vessels.

In 1953, John H. Gibbon, Jr., MD (1903–1973), later chairman and professor of surgery (1967–1978) at Jefferson Medical College in Philadelphia, along with others, developed a prototype heart–lung machine. The same year, he was the first to successfully perform “open heart surgery” using his heart–lung machine on a young woman with a septal defect; that is, the closing of a hole between the upper chambers of her heart. However, his rudimentary machine had a number of problems and was far from being adequate for routine usage.

R. Adams Cowley, MD (1917–1991), performed the University of Maryland Hospital's first heart catheterization on a 12-year-old girl in August 1953. The surgery was carried out using hypothermia, a full-body ice bath to markedly slow down the

patient's heart and circulation. It was my good fortune to have observed the operation from a seat in the operating room amphitheater, along with a senior medical student, Bill Headley, class of 1954, who was working on a summer research project with me. A big cheer went up from the surgical table as Dr. Cowley's probe opened the closed cardiac blood vessel. Bill Headley's first wife, Jane, was the EKG technician and also recalls the surgery as a heart catheterization. Anthony Hammond, MD, FACS, a local ENT surgeon, informed me that in his senior year as a medical student at the University of Maryland (1956–1957), it was his task to have the hypothermia bath filled with ice by 7 a.m. for subsequent cardiac surgeries performed by Dr. Cowley.

In 1958, Mason Sones, Jr., MD (1918–1985), a graduate of the University of Maryland School of Medicine in the accelerated wartime class of 1943, who became a cardiac surgeon at the Cleveland Clinic, was the first to link heart catheterization, fluoroscopy, and cinematography. Also, he was the first cardiologist to thread a flexible catheter from a leg artery into the mouth of a coronary artery and obtain x-ray pictures of the heart in motion (19). When the probe was inserted into the patient's heart, it stopped, and Dr. Sones was able to induce the patient to cough three times, which restarted the patient's heart.

Paul Dudley White, MD (1886–1973), of Harvard, is considered to be the “Father of American Cardiology.” After his sister died from rheumatic fever, he embarked upon a lifelong study of the heart and circulatory system, and became a distinguished clinician. Although Dr. White was a founder of the American Heart Association, he is probably best known to the older public as the heart consultant caring for President Dwight D. Eisenhower after his heart attack in 1955.

Michael DeBakey, MD (1908–), is an American surgeon who is known for his techniques, including coronary bypass surgery, to replace damaged blood vessels. In 1967, Drs. DeBakey and Adrian Kantrowitz implanted the first artificial heart, which helped a weak heart pump blood until either the heart recovered or the surgeons could transplant another person's heart. Also Dr. DeBakey became the first surgeon to repair an aneurysm, a condition in which an artery balloons out, and is replaced with a blood vessel, such as a leg vein, or with Dacron, a synthetic compound.

Christiaan N. Barnard, MD (1922–2001), a South African surgeon, showed that intestinal atresia is caused by a deficient fetal blood supply, which led to the development of a surgical procedure to correct the formerly fatal defect. In 1967, Dr. Barnard's team performed the first human heart transplant, replacing the heart of Louis Waskansky with one from an accident victim. The transplant was successful, but Washansky, even with immunosuppressing drugs to prevent rejection of the heart, died 18 days later from pneumonia.

Morton M. Mower (University of Maryland, class of 1959), Chief of Cardiology at Sinai Hospital in Baltimore, whom I taught as a medical student, started development of a heart defibrillator in 1969, but it was not until 1980 that his first unit was implanted into a human. It was marketed in 1985 by drug and device maker, Eli Lilly and Co. Today, defibrillators are found at airports and in many public and large private meeting places for quick emergency purposes.

Raymond Bahr, a young Baltimore pharmacist (whom I taught in biochemistry), became traumatized by the sudden death of a close friend in the 1950s. Subsequently, in 1961, he earned an MD degree from the University of Maryland at Baltimore (UMB), became a cardiologist, and battled uphill for 15 years to finally establish, in 1981, the first Early Heart Attack Center (EHAC) at St. Agnes Hospital in Baltimore, Maryland (20). It proved to be so successful that today more than 2,500 hospitals throughout the United States, and 200 internationally, have followed the St. Agnes model (21). In the United States, acute myocardial infarction (MI) has remained the leading cause of death since 1900, presently resulting in more than 500,000 deaths annually (22). It has long been known that excess dietary salt leads to hypertension. Recently, Mordecai P. Blaustein, MD, professor of physiology and medicine at the University of Maryland School of Medicine, has shown that ouabain, a known drug, is secreted by the adrenal cortex. Also Dr. Blaustein and his associates have demonstrated that eating too much salt leads to the excess production of ouabain, which in turn has a dramatic effect on two other proteins that regulate the amount of sodium and calcium within the smooth muscle cells of the arteries (23).

CONN'S SYNDROME

Jerome W. Conn, MD (1907–1981), first described Conn's syndrome (primary aldosteronism), in 1955, in a patient at the University of Michigan who had hypertension, neuromuscular symptoms, renal potassium wasting, and elevated blood levels of aldosterone due to an adrenocortical adenoma (tumor). Potassium is the main body intracellular cation (positively charged ion), whereas sodium is the main cation in the blood vascular compartment. The secretion of excess aldosterone, which is a steroidal hormone with a unique aldehyde group at position 21, results in the kidneys excreting too much potassium and too little sodium.

KIDNEY TRANSPLANTS

On December 23, 1954, Joseph Murray, MD (1919–), and his team of surgeons at Peter Bent Brigham Hospital, a part of Harvard Medical School in Boston, performed the first successful organ transplantation, which involved the transplanting of a kidney from one twin brother to the other (24). In 1990, Dr. Murray was awarded the Nobel Prize in Medicine. Tissue "typing," developed in 1964, has revolutionized transplantation surgery. According to the United Network for Organ Sharing, more than 400,000 transplants have been performed in the United States since the first successful one in 1954 (24).

FIRST SEPARATION OF SIAMESE TWINS

William "Bill" Headley, MD, FACS, (Maryland, class of 1954), with whom I saw Dr. Cowley perform the University of Maryland Hospital's first heart catheterization, became a resident in

neurosurgery at the National Institutes of Health Clinical Center, and while there, in 1956, he assisted in the first separation of Siamese twins in the world. Subsequently, the hairlines of the separated twins were adjusted by a plastic surgeon at Johns Hopkins, where Dr. Headley had served his internship. I recently spoke with Bill, who is a vascular surgeon in Milledgeville, Georgia, and he informed me that the twin adult ladies, who are in their early 50s, are still alive and doing well.

HIP AND KNEE REPLACEMENT

In the 1940s, Austin Moore, MD (1899–1963), an ingenious orthopedic surgeon in Columbia, South Carolina, devised an artificial hip ball to replace fractured and arthritic joints, the first in the world. In 1948, he established the Apothecaries Sundries Manufacturing Company to sell the Austin Moore Hip Prosthesis-Excel and other surgical and hospital equipment. His accomplishment is not well recognized by the scientific community because he turned it into a commercial venture.

In 1962, Sir John Charnley (1911–1982), of England, was the first surgeon to perform a total knee replacement. In the 1960s, orthopedic surgeons at UCLA and the University of Kentucky, among others, established successful programs in knee-replacement surgery. The FDA approval, in 1972, of methyl methacrylate as a bone cement was a significant forward step for replacement surgery. A very distinguished East Coast American leader in hip- and knee-replacement surgery is David Hungerford, MD, FACS (1938–) who took his training in hip and knee replacement at Oxford in England in 1967, which included two lectures by Sir John Charnley. In 1971, Dr. Hungerford first applied the principles of carpentry to orthopedic surgery, and in 1978 he developed surgical tools to assure correct alignment of the prosthesis and the limb, a major contribution to the field. Recent technology, however, permits alignment by computer. Dr. Hungerford routinely performs up to seven knee and hip replacements a day at Good Samaritan Hospital in Baltimore, and is Professor of Orthopedics at Johns Hopkins University. His anesthesiologist for many years at Good Samaritan Hospital was my daughter-in-law's father, George Friskey (1926–2000), who received his MD at the University of Maryland in 1955 and whom I taught as a first year medical student. As an anesthesiologist, George had a wonderful bedside manner and was endeared by his patients for his relaxing sayings, nicknamed "Friskyisms."

SHOCK AND TRAUMA

R. Adams Cowley, MD, (1917–1991), who performed the University of Maryland Hospital's first heart catheterization in 1954, over the next ten years developed reliable heart–lung bypass equipment and in 1965 performed the first "open heart surgical procedure" carried out on a patient at the University of Maryland and in the state of Maryland. However, Dr. Cowley is best known for his leadership in founding, in 1968, the first Shock Trauma Center in the world, a specialized facility for "the treatment of seriously and critically ill patients suffering

from traumatic injuries and medical shock” (25). Helicopter service became available in 1970, and the R. A. Cowley Shock Trauma Center at the University of Maryland was the first of over 800 such centers around the world. The dramatic true story of a pioneering hospital conquering the most lethal killer of all, *Shock Trauma*, was published in 1980 (26). Dr. Cowley, a native of Utah who received his MD in 1944 from the University of Maryland, saw numerous battlefield deaths near the end of World War II that were due to shock. Many years of emergency room experience, working almost around the clock, and following “hopeless ER patients” and dying patients with perseverance, gave him breakthrough insight in understanding shock and trauma and the importance of heart beat and breathing. The fruits of his arduous endeavor enabled him to define, as the “Golden Hour,” the 60 minutes that exist to get emergency medical intervention to accident victims if they are to survive. It was my privilege to tour the R. A. Cowley Shock and Trauma Center in 1994 as part of the 40th reunion of the class of 1954, to whom I taught Biochemistry.

The length of stay in shock trauma decreased from 17 days in 1986 to five days in 1996 by referring patients to alternate sites such as rehabilitation facilities and home health services. Today, Shock Trauma at the University of Maryland is a free-standing hospital where 98% of accident victims that enter, be they from auto, farm, or industrial related accidents, survive; a truly remarkable success rate. On June 3, 2003, a gathering was held on the grounds of the Navy-Marine Corps Memorial Stadium to mark the 100,000th MedEvac transport since 1970 from the state of Maryland’s eight heliports.

LIVER TRANSPLANTS

Thomas Starzl, MD, PhD, (1926–), began attempting liver transplants in 1963 at the University of Colorado School of Medicine and had “ghastly results” when only 12 of the first 130 liver recipients were long-term survivors, with his first surviving patient in 1967. Dr. Starzl subsequently became Professor and Chairman of Surgery at Colorado, where he continued his investigations developing safer techniques and more effective immunosuppressant agents until 1980. Mr. Harry S. Dorsey, MBA, Life Fellow-American College of Health Care Executives, and former head of an army hospital during World War II, became head of Western Psychiatric Hospital in Pittsburgh after World War II and managed and obtained funding for its development into the University of Pittsburgh Medical Center (UPMC). His accomplishments included the building of a new hospital and very extensive new outpatient clinical facilities. In 1980, Harry S. Dorsey persuaded Dr. Starzl to join the University of Pittsburgh Medical Center, which soon became world famous for its success in performing liver transplants. Later, it was named the UPMC Thomas E. Starzl Transplant Institute, and for many years has been recognized internationally as the world’s leader in transplantation. Dr. Starzl is still active and has received more than 175 awards and honors for his pioneering work, including development of many of the currently used immunosuppressants and surgical transplant techniques.

In 1992, Harry and his wife Janet moved to our Charlestown Retirement Community, where both have since passed away. As an elected member of our Residents’ Council and chairman for six years of the Committee on Health Care, Harry provided the leadership for the White Paper, submitted in 1996, making recommendations for the future of Charlestown’s Medical Center. The innovative Harry S. Dorsey Center, built on the first floor of our care center, is a fitting tribute to his memory and his creative mind, as he first suggested such a unit but died shortly before it opened in September 1999 (27). It provides post-acute, short-term medical care, including intravenous fluids and/or physical, occupational, and speech rehabilitation to residents who are too ill to return to their home after a hospital stay or who need specific care in lieu of hospitalization. After a three-day hospital stay, Medicare pays for care at the Dorsey Center. I fondly recall serving with Harry for six years on our resident Health Committee, the most knowledgeable and brilliant person in healthcare affairs I ever met. During these early years, we spent many mornings together from 10 to 12, over hot tea, discussing healthcare issues ranging from health delivery, to Medicare, to the financial aspects—where he sparkled.

OPHTHALMOLOGY

Charles Kelman, MD (1930–2004), was the ophthalmologist who in 1967 developed the outpatient cataract operation known as phacoemulsification that has helped 100 million people worldwide improve their vision. He passed away in Boca Raton, Florida, in June 2004.

In 1981, Steven B. Siepser, MD, Director of Research of the Wills Eye Hospital in Philadelphia, Pennsylvania, became a pioneer in expansile lens technology. He developed a new surgical technique for cataract surgery called the Siepser Radial Transverse Incision (SRTI) in which a horizontal incision, instead of a vertical one, is made. The primary benefit to the patient of this new technique is that it is completely sutureless, further reducing the risk of infection and complications after surgery (28). Dr. Siepser’s expansile lens, made from a special polymer, can be inserted into the eye in a dehydrated state through a tiny, 3-mm incision, considerably smaller than the 7-mm incisions previously used in cataract surgery (29). Once implanted in the wet environment of the eye, the expansile lens will swell to a normal size of 6 mm and retain all of its optical qualities (29). Dr. Siepser managed my eye corrective needs so perfectly at surgery on September 2, 1988 (right eye), and on November 5, 1992 (left eye), in his FDA Experimental Program that I was issued a new Maryland State driver’s license through 2011, and can drive without wearing glasses.

MAGNETIC RESONANCE IMAGING

In April 2004, Raymond V. Damadian, MD (1936–), received the Franklin Institute’s Bower Award for Business Leadership in the Field of Brain Research for his development and

commercialization of magnetic resonance imaging (MRI) used in clinical applications (30). Dr. Damadian published on the concept in 1969; detected a patient's tumor in 1971; patented the invention, and founded the Fonar Corporation in 1978 for its manufacture. The company's first commercially available MRI unit was approved by the FDA in 1984. Today, more than 60,000,000 MRIs are performed around the world annually. It is a truly remarkable and astonishing accomplishment by one research medical scientist.

NUCLEAR MAGNETIC RESONANCE

Paul Lauterburg (1929–), of the University of Illinois, and Peter Mansfield (1933–), of the University of Nottingham in England, received the 2003 Nobel Prize Award for their pioneering work in the application of nuclear magnetic resonance (NMR) spectroscopy to medicine. In 1973, the two researchers took a technique used by chemists to study solutions and applied it to a method for making images of the human body, which is mostly water (over 90%). Unlike CT-scan machines, which use radiation, magnetic imaging probes the body only with magnetic fields and pulses of radio waves. NMR has replaced invasive techniques for examining joints, the brain, and other vital organs. The technique is so sensitive that it can locate where different mental tasks are performed in the living brain by the extra flow of blood that is present. More recently, it has been claimed to be able to detect whether or not people are telling the truth.

IN VITRO FERTILIZATION

In June 1978, Georgeanna Seegar Jones, MD (1913–2005), retired at age 65 as Distinguished Professor of Gynecology at Johns Hopkins School of Medicine. She and her husband Howard, who also was a gynecologist, arrived in Norfolk, Virginia, in July, which coincided with the birth in England of the world's so-called first test-tube baby (31). A newspaper reporter called and asked her if test-tube babies could be done in Norfolk, which she thought was a little flip, and she replied that "All it would take is a little money." Her comment was published and a former infertility patient of Georgeanna's called and asked. "How much would it cost?" Although the couple had planned to work leisurely in retirement at the new Eastern Virginia Medical School, they soon found themselves in the first in vitro fertilization program in the United States in which a woman's eggs are united with a man's sperm in a glass dish in a laboratory and later implanted in the uterus of the infertile wife. By the end of 1982, they had helped ten couples bring their pregnancies to fruition. After an article in *Life* magazine, their waiting list jumped to 10,000 names. I am intrigued by this article because in May 1953, I presented a seminar to Dr. Seegar's staff at Johns Hopkins on the 157 acetate that I had isolated, which stimulated the production of luteinizing hormone (LH) in rats and was a possible fertility agent. Even though she was a prolific publisher on infertility (350 manuscripts) and had

discovered human chorionic gonadotropin (hCG) in the 1940's, her laboratories were undergoing a "dry spell" at that time and she was looking for new ideas for research. I remember vividly being shown the memorials to Johns Hopkins "Four Greats" just inside the entrance to the old hospital on Broadway. A November 2005 article published in the journal *Obstetrics & Gynecology* states, "Fertility treatments found unlikely to result in birth defects or chromosomal abnormalities," but it is well documented that they increase the chances of multiple births, which are "associated with poor infant outcome, low birth weight and prematurity."

COCHLEAR IMPLANTATION

In 1984, Herbert Silverstein, MD, (1935–) of the University of Pennsylvania, performed the first cochlear implant, restoring hearing to a 12-year-old boy. Later, he founded the Florida Eye and Ear Clinic and Foundation in Sarasota, Florida, where he teaches the technique to ENT surgeons the world over and practices as a clinician. Since 1991, he has taken care of my open ear canal treatment during our stays in Florida, and early on took me through his teaching facility.

COMPUTERIZED TOMOGRAPHY

The concept of computed tomography (CT) was developed in 1972 by British engineer Godfrey Hounsfield of EMI Laboratories in England, and independently by South African-born physicist Allan Cormack of Tufts University in Massachusetts. Hounsfield's original unit took several hours to process the signal and he was later awarded the Nobel Prize. The first clinical CT scanners were installed between 1974 and 1976 and were dedicated to head imaging only. After 1976, manufacturers could combine a linear accelerator with a real-time signal, and systems for full-body scans became widely available by 1980. Over 6,000 scanners are in use in the U.S. today, with millions of scans performed annually.

POSITRON EMISSION TOMOGRAPHY

Positron emission tomography (PET) depends on the concept of short-acting labeled glucose distributing itself evenly throughout the body vascular compartment, except in tumor tissue where it concentrates as a hot spot due to its more active metabolism. It thereby pinpoints the localization and the size of tumor masses. The equipment is very expensive and one huge trailer with the necessary facilities for patient injection and radioisotope measurement serves the Baltimore area. Currently, it is located adjacent to the Seton Professional Building at 4334 Wilkens Avenue, where the Department of Radiology of St. Agnes Hospital is located. It is my impression that Johns Hopkins Medicine and the University of Maryland Medical System now have their own units. St. Agnes Hospital is the first hospital in the area to have the latest computerized tomography

unit, which combines pinpoint location with radiation treatment of cancer cells, a remarkable achievement. St. Agnes Hospital's full-time PhD physicist, Timothy Holmes, was involved in the design of the unit.

RECENT NOBEL PRIZE WINNERS

In 2003, the Nobel Prize in Medicine was awarded to Peter Agre, MD, Professor of Biochemistry at Johns Hopkins University School of Medicine, who discovered the first water-transportation tunnels in the walls of cells (32). When he took the podium at the press conference the day the award was made, the first thing Dr. Agre, a very self-effacing person, did was to acknowledge the 15 postdocs, grad students, and techs who work in his now-famous lab. In his words: "I didn't do this work: the young people in the lab did it. I just made the coffee and sharpened the pencils."

The Nobel Prize in Physiology or Medicine in 2004 was awarded to Dr. Richard Axel of the Howard Hughes Institute and Columbia University and to Dr. Linda B. Buck of The Fred Hutchinson Cancer Center in Seattle, Washington, "for their discoveries of odorant receptors and the organization of the olfactory system," which give us a sense of smell and add to the taste of food (33).

In 2005, two Australians won the Nobel Prize in Medicine for a discovery, which defied decades of medical dogma, showing that bacterial infection, not stress, caused ulcers in the stomach and intestine (34). The 1982 discovery by Drs. Barry Marshall and Robin Warren has transformed peptic ulcer disease from a chronic, frequent, disabling condition to one that can be cured by short-term antibiotics and other medicines.

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Chapter 3

Pharmacy, Dentistry, Nursing, and Hospital Development

Pharmacy, an ancient trade, long related to both science and magic, took its biggest step toward professionalism in 1821 when the first college of pharmacy was established in Philadelphia (1, p. 91). Although other pharmacy colleges subsequently emerged in Boston and New York, the very historic Philadelphia College of Pharmacy expanded in the 1990's into The University of the Sciences in Philadelphia (USP), with programs in pharmacy, biochemistry, biotechnology, computer science, and bioinformatics.

PHARMACY

An early 1800's apothecary shop was a dark murky room, heated by a fireplace, that had its walls lined with a myriad of large and small bottles of potions, herbs, extracts, and crude drugs, along with an identifying globe of colored red liquid. If the proprietor was a taxidermist, then a stuffed bird or animal might hang from the ceiling (1, p. 92). Purgatives, such as calomel, rhubarb, castor oil, and Epsom salts, as well as stimulants such as anise, pepper, cinnamon, cloves, dill, sage, ginger, horseradish, nutmeg, horehound, marjoram, and spearmint were sold. Other medications included quinine-containing bark for ague (malaria), blackberry wine, and elix asthmaticum (opium, honey, licorice, benzoic acid, camphor, oil of anise, potassium carbonate, and alcohol), known to contain paregoric and taken for dysentery. Emetics such as tartar emetic, ipecac, or warm water and honey were used for the treatment of bilious attacks, jaundice, and digestive problems. For muscular spasms and relaxation, opium, wine, and ardent spirits were freely available. Early medicine shops competed with early physicians who provided their own potions, herbs, extracts, and crude drugs to their patients. After the first homeopathic physicians arrived in the early 1800's, and David Stewart, MD, in 1844, taught the first practical course in the United States on weights and measures, medicine shops came to have scales, grinders, filters, and sieves, as well as mortars and pestles. About 1850, some enterprising druggists began distilling mineral water and manufacturing medicated candies, a big business, which paved the way for the soda fountain and destroyed the old apothecary shop. After the Civil War, numerous patent medicines, laced with addictive drugs in alcohol, became one of the main offerings of both drugstores and rural peddlers.

John Pemberton, a pharmacist, prepared the original Coca-Cola in his backyard in Atlanta, Georgia, on May 8, 1886. The drink was used as a nerve and brain tonic and a medical elixir. It contained various ingredients including lime, citric acid, cinnamon, vanilla, citrate caffeine from the caffeine-rich kola nut, and an extract of the leaves of the coca tree from South America that produces cocaine (2). The original drink contained about 1 in 400 parts cocaine, which was removed in 1905, and other modifications were made including the substitution of phosphoric acid for citric acid and decreasing the caffeine content, resulting in a product for which the formula is a Coca-Cola Company secret. Also, alcohol-based patent medicines, hard liquor, and imported pipes with pots for smoking opium were readily available. Although most trained pharmacists agreed not to sell adulterated drugs, patent medicines were socially acceptable and in such common usage that there were thousands of alcohol and narcotic addicts in America by the time Congress passed the first drug safety law in 1906. The next major law regulating drugs was not enacted by Congress until June 25, 1938, when the Food and Drug Administration (FDA) was created, a law that converted pharmacy from a cottage industry controlled by local pharmacists to mass production by large pharmaceutical houses.

In 1837, a convention of physicians meeting in Easton on Maryland's Eastern Shore passed a resolution asking the Maryland General Assembly to establish a School of Pharmacy. The Maryland College of Pharmacy was incorporated on January 27, 1841, as the fourth such college in the United States (2). Unlike its predecessors, the Maryland College emerged under the aegis of a university and established its program in an academic framework (1, p. 91). Elisha Butts, University of Maryland's School of Medicine Professor of Chemistry, was one of six scholars who drew up the original "U.S. Dispensatory," an index of drugs that is still used as a basic handbook for pharmacists. Professor Butts with the assistance of Pharmacist Thomas G. MacKenzie, who had been elected President of the recently organized Guild for Pharmacists, set up the school and held classes in the back of MacKenzie's drugstore at the corner of Gay and Baltimore Streets. Lectures were free and there were no admission requirements to the one-term (November–February) degree program where University of Maryland School of Medicine graduate, David Stewart, MD, lectured in chemistry. At that

time, bitter rivalry existed between druggists and physicians as both often made on-the-spot diagnoses and prescribed patent medicines. Of the College's first six students, only three graduated in 1842, but they included Frederick A. Cochrane, who became one of the most successful druggists in the state of Maryland; Alpheus P. Sharpe, who with a later graduate, Louis Dohme, founded Sharpe & Dohme Chemical Corporation, which later became Merck, Sharpe and Dohme; and William S. Thompson, who became a nationally renowned pharmaceutical professor and author. No lectures were given the second year and only one student was enrolled the third year.

In April 1844, the Maryland College of Pharmacy agreed to give lectures in pharmacy to medical students and, in return, pharmacy students were allowed to attend chemistry lectures at the medical school and were given a small room for College of Pharmacy meetings (3). Dr. Stewart was appointed Professor of Theory and Practice of Pharmacy, which was the first separate chair of Pharmacy in the United States. His course was practical and concentrated on weights and measures and other "pharmaceutical manipulations." Students were charged \$10 for the three lecture courses offered, and although there were 15 students enrolled in 1845–1846, only three graduated in 1847. There were no more graduates over the next nine years. However, under the leadership of Baltimore druggist Israel Graham, over 50 druggists joined the state pharmacy association and the college was revived with a band and enthusiastic speeches in fall 1856 for the 20 entering students. Graham became professor of pharmacy, Dr. Charles Frick assumed the professorship in materia medica, and Dr. Lewis H. Steiner, who later was the first librarian at the world-famous Enoch Pratt Library in Baltimore, became professor of chemistry (1, p. 95). Following the pattern of the Medical College, the druggists accepted the proprietary system and transferred the costs and responsibility for pharmacy education to the students. In 1858, the prospering school raised its standards sharply by requiring graduates to be 21 years of age, to have served a four-year apprenticeship, have attended two annual terms of college, written a thesis, passed an examination given by the faculty, and taken an oral examination offered by the state pharmacy association. Except for lower fees, the standards had become equal to those for medical graduates but physicians were not allowed to join the pharmacy association (1, p. 95). About ten men, both in and out of state, graduated each year, even during the Civil War.

By 1864, a half century before the other University of Maryland colleges in Baltimore could do likewise, the pharmacists were strong enough to deposit all tuition fees in a central treasury and place all members of the faculty of the Maryland College of Pharmacy on salaries of \$300 per year. In the decade after the Civil War, relationships between pharmacists, physicians, and drug companies were probably closer than in any other state, allowing the pharmacists, like the physicians and dentists, to provide national leadership (1, p. 221). In 1870, the pharmacists of Maryland persuaded the Maryland legislature to pass the first effective laws in the nation to regulate the sale of drugs and, in 1876, when the college needed a new laboratory building, both physicians and the drug industry helped finance it. The new 1870 regulations required all practicing pharmacists to pass an examination given by the College of Pharmacy.

Violators were fined \$50, half of which was paid to the informer of the violation (1, p. 221).

Also, in 1870, the pharmacists of Maryland, in cooperation with the College of Pharmacy, held a convention in Baltimore with the seven other American schools of pharmacy, which resulted in the creation of the American Association of Colleges of Pharmacy. The new Association immediately established national standards for pharmacists, including a four-year apprenticeship, a two-year pharmacy course, and a 21-year age minimum for all graduates. On the other hand, there were no national standards for medical schools until after 1910, some 40 years later.

The Maryland College of Pharmacy graduated about 15 students each year in the 1870's, about 30 students in the 1880's, and about 40 students in the 1890's, by which time the job market for pharmacists had been exceeded. Also, the pharmacists in 1886 had torn down their small building on Aisquith Street, borrowed \$35,000, and overextended the college by building a huge three-story structure, probably the finest pharmacy school building in the United States (1, p. 223). All of the proprietary professional schools at the University of Maryland in Baltimore similarly overextended and borrowed large sums of money. By 1920, when the state took over, the University had total assets of \$800,000 with crushing debt of more than half that amount.

The Maryland Pharmacists Association and Museum of Pharmacy has been located in its own building at 650 West Lombard since 1953. From 1924 to the late 1960's, the Pharmacy School was located in the northern half of a building shared with the dental school at the southwest corner of Greene and Lombard, now the Gudelsky Tower of University Hospital.

In the 1950's, pharmacy students were required to have work experience in a pharmacy, and I recall being greeted by name no matter what drugstore I walked into when we lived in the Baltimore area from 1950 to 1957. Most students were able to meet the one-year experience requirement by the time they graduated (2). In 1970, Maryland became the first state to eliminate their unstructured pharmacy internship program and replace it with a professional experience program. This advancement resulted from an agreement between the School of Pharmacy and the Maryland Board of Pharmacy to enact major changes in the traditional pharmacy curriculum, extending it to five years, and formalizing the internship program. Four-week experience rotations were required at a variety of sites such as a community pharmacy, an independent pharmacy, a chain pharmacy, a hospital pharmacy, or a long-term care pharmacy, etc. At that time, a six-year PharmD (Doctor of Pharmacy) option became available for those wishing to work on clinical units in hospitals, where, as numerous drugs require tight control to maintain maximum effectiveness, they became experts in drug interactions and the monitoring of drug levels in patients. In 1982, a new ten-story College of Pharmacy building was constructed at the northwest corner of Baltimore and Pine Streets, thereby extending the University of Maryland at Baltimore (UMAB) campus to Martin Luther King Boulevard. In about 1993, the six-year Doctorate in Clinical Pharmacy program became the base requirement for all new pharmacist graduates

in the United States (2). Today, many large hospitals employ PharmD's as part of their clinical services because many hospitalized patients are on 10 or 12 medications and drug interaction has become a serious medical problem. Unfortunately, this is true for much of the American public as people go to multiple physicians and obtain prescriptions without a responsible coordinating gatekeeper's knowledge. This situation is even more serious for the large, over-65 elderly population whose tolerance for drugs is often markedly decreased due to the physiological changes of aging.

DENTISTRY

In early America, professional dentists were unknown and various people worked on teeth, including physicians, barbers, and blacksmiths, who made forceps for pulling teeth. The first well-known American dental surgeon was John Baker, who had practiced in various cities in Europe before he established a practice in Boston in 1752. There, he taught Paul Revere, a craftsman, the art of constructing and repairing artificial dentures, and Benjamin Fendell, the earliest Baltimore-Washington dentist, who practiced from 1773 to 1808 (3). George Washington was one of the first Americans to wear dentures, which, it has been said, "gave him a grandmotherly look" and made it difficult for him to be thought of as the forceful general he was (1, p. 84). An ivory and gold set of his false teeth, one of four sets, are on display in the Dr. Samuel D. Harris National Museum of Dentistry at 31 South Greene Street, adjacent to historic Davidge Hall, in Baltimore. During the 1830's, ivory dentures became very fashionable, and "ignorant tooth drawers" toured rural areas supplying this very profitable item, sometimes even touring with a brass band (1, p. 84).

The most prominent advocate of dentistry as a profession was Horace Hayden of Baltimore, who had been an apprentice of George Washington's dentist, John Greenwood, the most famous and distinguished dentist of the late 1700's. Hayden taught dentistry at the University of Maryland in 1819 and from 1823 to 1825, when he ceased due to what he felt was insufficient focus by the medical school on dental education. Subsequently, Hayden studied medicine on his own, was accepted into the Maryland Medical Society, and became not only a well-respected dentist in Baltimore for 45 years but recognized by his colleagues as the foremost dentist in the nation. Chapin A. Harris had one year of medical training under his physician brother, and after training by Hayden, proceeded to claim he had an MD degree. After practicing excellent dentistry throughout the South for ten years, Dr. Harris returned to Baltimore and published, in 1838, the first textbook on dentistry, *The Dental Art*, which included Hayden's and many other dentists' "trade secrets" (1, p. 85). It was not only the first book on dentistry, but was so comprehensive that it went through 12 editions by 1900 and was translated into several languages. In 1839, Dr. Harris founded the pioneering *American Journal of Dental Surgery*, which he edited and supported financially for 40 years, eventually dying a pauper. Harris and his former teacher, Hayden, who had been irritated by the publication of his

trade secrets, got back together in 1840 and created the American Society of Dental Surgeons, a forerunner of the American Dental Association.

Also, in 1840, the General Assembly of Maryland passed a bill establishing the Baltimore College of Dental Surgery, the first dental college in the world (1, p. 89; 4, p. 11). Trying to avoid the pitfalls in faculty autonomy that had occurred with the School of Medicine, the legislature created a Board of Trustees consisting of nine physicians, four ministers, and two dentists, and the Board had absolute control over establishing standards and salaries. Dr. Horace H. Hayden became President and Professor of Dental Pathology; Dr. Chapin A. Harris became Dean and Professor of Practical Dentistry; Dr. Thomas E. Bond, son of one of the founders of the Medical College, became Professor of Special Dental Pathology and Therapeutics; and Dr. Henry Willis Baxley became Professor of Special Dental Anatomy.

On November 3, 1840, five students began classes in a beautiful three-room three-story building on Hopkins Place in Baltimore, one room being used as a classroom, another as a dental workshop, and the third as a dental museum. There were no formal entrance requirements and a Doctor of Dental Surgery degree was earned in two years, the same as for the medical college. The charter of the college authorized the faculty to confer the honorary degree of Doctor of Dental Surgery "on any Dentist who may have rendered service to the science or distinguished himself in his profession" (4, p. 12). At the second commencement on February 18, 1842, honorary degrees were conferred upon 22 dentists. Later, degrees were granted to highly qualified dentists in Canada, England, Scotland, and France.

After the Civil War, 22 new dental schools opened in the United States, including the Maryland Dental College in Baltimore in 1873, which was absorbed by the Baltimore College of Dental Surgery in 1878. In 1882, the General Assembly chartered the Dental Department of the University of Maryland, which had the advantage of academic affiliation with the School of Medicine. In 1913, the Baltimore College of Dental Surgery merged with the privately held Dental Department of the University of Maryland School of Medicine, which was located in the old General Hospital. In 1920, the merger became official when the State of Maryland took over the private University, but it was not until state aid became forthcoming in 1923 that the merger of the two dental schools was completed. At that time, a new dental school building was designed in Roman Renaissance-revival style by Baltimore architect, George Haskell (5). The main level of the 20,000-square-foot, three-and-one-half-story building at 31 South Greene Street was entered by a flight of bidirectional steps and served as the University of Maryland Dental School until 1929. Subsequently, the building became known as the Pathology Building and housed the medical school Pathology Department on the first floor, Microbiology on the second, and the Biological Chemistry Department on the third floor. In the late 1960's, a new School of Pharmacy building was constructed at 20 North Pine Street near Baltimore Street.

In 1920, the private University of Maryland in Baltimore was merged with Maryland State College at College Park to

create the University of Maryland at Baltimore (UMB, 1807) and the University of Maryland at College Park (UMCP, 1856); the great seal of the University of Maryland bears the dates 1807–1856–1920. Thus in 1920, the oldest dental college in the world, the Baltimore College of Dental Surgery, which was founded in 1840, became officially the University of Maryland School of Dentistry. In 1929, the academic part of the dental school moved into a new building at the southwest corner of Greene and Lombard Streets, shared with the School of Pharmacy on the north side. The dental clinics, so located when I was on the medical school faculty at UMB from 1950 to 1957, were in the part of the dental school that extended west on Lombard Street. I was never directly involved with the Dental School, which had its own small Biochemistry Department under Dr. VandenBosch. However, Charles B. Leonard, Jr., who took his masters degree in Biochemistry with me in 1957 and later his PhD with my successor, joined Dr. VandenBosch as his assistant, subsequently replaced him, and retired in 1993 as Professor of Biochemistry after 38 years on the faculty of the Dental School. Charles was very helpful to me by loaning me his copy of the history of the Dental School, which was published in 1982 (4).

In 1970, the University of Maryland School of Dentistry moved into a new, ultramodern, six-story building at 666 West Baltimore Street, which was named Hayden Harris Hall after the school's founding fathers. In 1990, the dental clinical facilities were renovated to make provisions for individual waiting rooms for each dentist. However, these facilities are already outmoded and with asbestos abundant in the 1970 facility, which does not meet environmental requirements, it was found to be cheaper to build a new, adjacent ten-story University of Maryland Dental Building, which opened in January 2006.

In 1994, the Pathology Building, which had been built originally as the Dental School and occupied as such from 1923 to 1929, was restored to its original grandeur and became, in 1996, the home of the Dr. Samuel D. Harris National Museum of Dentistry, the only national museum dedicated to the history of dentistry (5). Although my old office and laboratory and the adjacent structures were removed as part of the restoration in order to build a new side entrance to the Dental Museum, I was able to tour the intact Department of Biochemistry facilities after moving to Baltimore in 1993.

Joseph Volker, PhD, a Professor of Chemistry at Indiana University, demonstrated in the late 1930's that, when treated with sodium fluoride, isolated powdered tooth enamel is less soluble in acid than untreated enamel and hypothesized that fluoride might inhibit tooth decay. In 1940, Harry G. Day, who had just received his PhD in nutrition and biochemistry at Johns Hopkins University under famous nutritionist E. V. McCollum, PhD, joined the faculty of Indiana University. His first assignment was to teach biochemistry to first-year dental students and he emphasized to the students how important knowledge of biochemistry and sound nutrition were in improving dental health. Over the next several years, Dr. Day, assisted by several dental students, including Joseph C. Mueller and Grant Van Huysen, demonstrated, by 1947, the insolubility of enamel protected by sodium fluoride. Subsequently, Dr. Day developed toothpaste containing

stannous fluoride, which was first marketed by Proctor and Gamble in 1955 (6). An ad by Norman Rockwell pictures a tube of Crest, labeled "Fluorostan," with a freckled-faced young boy saying, "Look, Mom—no cavities." Although stannous fluoride toothpastes still have specialized uses, over-the-counter toothpastes are now formulated with sodium fluoride (6).

Although fluoridation of drinking water was accepted by many cities and states, it was voted down by the provincial residential population of Cumberland, Maryland, where I was director of clinical laboratories at Memorial Hospital from 1962 to 1965. Since its introduction, fluoridation has resulted in markedly reduced cavities in both children and adults. However, a scientific journal article, Fluoride Concerns Surface Once Again (7), published in August 2003, describes research linking fluoride in drinking water to skeletal fluorosis (bone degeneration). As a result, the EPA Protection Committee requested that the National Research Council review the problems associated with the fluoridation of drinking water.

The Paffenberger Research Center, named for its first director from 1929 to 1974, is and has been a prime mover of dental materials research. It is a \$4,000,000 operation funded by the National Institute of Standards and Technology, the American Dental Association Health Foundation (ADAHF), the National Institute of Dental Research, and the dental materials industry; it accepts visiting scientists as research associates from the Navy Dental Corp and from domestic and foreign universities in the dental field. About 30 research associates are employed full time by ADAHF (8).

My parents were 10 and 9 years old in 1900, and are the last generation to have false teeth (dentures) due to unavailable, limited, or unaffordable dental care.

NURSING AND HOSPITAL DEVELOPMENT

The Maryland Hospital at Baltimore, which became a state insane asylum for the poor in 1828, was one of four hospitals in the United States that accepted mentally ill patients in 1800 (9, p. 8). These patients were treated in spacious, well-lit rooms with good food and by physicians enlightened in the moral treatment movement, where "moral" meant psychological or nonorganic. The profession of nursing, however, was unknown at this time.

In 1823, Professor Granville Sharp Pattison of the University of Maryland School of Medicine persuaded the faculty of the private university to build a teaching hospital on Lombard Street, a half block west of Greene Street. It was a handsome four-story building in the Federalist style and cost \$14,109 for construction, plus \$2,520 for beds and furnishings (1, p. 43). A semicircular operating theater with seats for student observation was located at the rear of the 60-bed hospital. Since, at that time, hospitals were pesthouses and where people went to die, Pattison's magnificent solution to the problem was to turn to Roman Catholic nuns who had served so heroically in European hospitals and were beginning to work as nurses in America. Thus, the Sisters of Charity from nearby

Emmitsburg, Maryland, responded with eagerness to his invitation. "I can hardly express the joy they felt," wrote a priest after the arrangements were made (1, p. 43). Sister Superior Joanna Smith soon arrived as the first manager of the hospital and brought four Sisters to help her.

Elizabeth Blackwell became the first woman physician in the United States when she graduated from Geneva Medical College in Geneva, New York, in 1849. In 1857, Dr. Blackwell and her sister, Emily, founded a hospital in New York City staffed entirely by women, which was the first nursing school in the United States. Later, Dr. Blackwell returned to her native England and founded an Infirmary and the London School of Medicine for Women for which Emily served as dean and professor.

In England in 1854, Florence Nightingale founded nursing as a profession, which transformed nursing from service by a religious order to a scientific discipline and from menial servitude to eminent respectability (1, p. 205). Thus, in 1889, by mutual agreement, the nuns and the physicians at the University of Maryland terminated their 66-year association. With the thought of cheap labor in mind, the physicians hired Miss Louisa Parsons to develop a Nurses Training School, but they had greatly underestimated her capabilities (1, p. 224). Louisa Parsons was a stern, authoritarian person who had graduated from the St. Thomas Hospital nursing program in London, England, under Florence Nightingale and had served as a nurse with the British troops in Egypt. She demanded intense training, high academic standards with firm discipline, supervisors who were women, and rigid separation of nursing duties from those of a physician. She met all of the doctors' provisions but demanded a separate new \$10,000 building for her students to live in, which was built behind the hospital. After investing in the construction of the new three-story building, the proprietary physicians became obliged to respond to her persistent demands on behalf of the nursing program.

The nursing school opened in December 1889 with students working 12-hour days, which were very common at the time, for two years, with four weeks of vacation each year. Seven days a week, they served as charwomen, did the cooking, and took care of patients, and, in return, they received free board, had two hours off for church on Sundays and two hours off on Wednesdays for exercise, and were paid \$8 per month. They also made their own distinctive uniforms. At this time in American history, male laborers worked 12 hours per day for six days per week and were paid as little as \$1 per day, and some factories operated on two 12-hour shifts. In addition, the physicians gave one or two lectures a week to off-duty nurses. Beginning in 1892, those who completed the two-year program were authorized to call themselves "Graduates of the University of Maryland Faculty of Physic Training School for Nurses." By 1895, there were 32 students enrolled, and in 1905 some 55 students. Since the nursing students at Maryland had their own class colors, songs, traditions, and uniforms, they possessed a greater sense of unity than existed in any of the other University colleges (1, p. 226). Although Miss Parsons returned to England after only two years, she left most of her estate of about \$10,000 to the University of Maryland Nurses Alumnae Association after her death in 1916.

The Sisters of Charity of St. Joseph's in Emmitsburg, Maryland, opened St. Joseph Hospital in Baltimore City in 1862, the first Catholic Hospital in Baltimore City, which was renamed St. Agnes Hospital in 1863. Only two years after St. Agnes was founded, the Sisters of Mercy opened Mercy Hospital in 1864. The extension of Lanvale Street in 1876 forced St. Agnes Hospital to move to its present site at Caton and Wilkins Avenues at the southwestern edge of Baltimore City. St. Agnes Hospital established a nursing school in 1895 and graduated its first nursing students in 1898. In 1906, after Dr. Joseph Colt Bloodgood became Chief of Staff, serving until 1935, St. Agnes Hospital was recognized as a general hospital, and Dr. Bloodgood established an internship program and the second oldest surgical residency in the United States (10). In 1907, the first Women's Hospital Auxiliary in the United States was formed, and in 1910, the 210-bed hospital opened an Out-Patient Department, a free Dispensary for the surrounding poor living in the area, and the Jenkins family donated \$2,000 to build a new children's wing. In 1971, 50 student nurses graduated, marking an end to the St. Agnes School of Nursing after 76 years of operation and the training of over 1,500 nurses. In 1995, St. Agnes Hospital of the City of Baltimore, Inc, became St. Agnes HealthCare, Inc., reflecting its growth of services into the community. Today, its Department of Human Resources sponsors three different work study programs in nursing education and provides the full-time services of two clinical nurse instructors to the Howard County Community College Nursing Program. In December 2005, officials announced a \$160,000,000 renovation and expansion program. According to signs posted in their visitor elevators, St. Agnes Hospital is one of 25 hospitals in the United States participating in the Vocera Voice Program, a very sophisticated wireless program that uses voice messaging.

Because of changed socioeconomic influences after the Civil War and the need for expansion, the Baltimore City almshouse was moved in 1866 to the eastern edge of Baltimore City and developed into the Bayview Asylum. Medical student teaching by both the University of Maryland and Johns Hopkins started there in 1891, and the same year it became a major center for treating tuberculosis (TB) in a separate ward, a first in the nation. Also, it had a large surgical/medical ward. A nurses' training school opened at Bayview in 1911, and in 1915, Bayview had 1,500 patients. It continued as a large general hospital serving the training needs of both medical schools until the early 1990's, when the 1,000-bed Bay View Hospital, one of the largest in the world, became the Francis Scott Key Medical Center. More recently, it was renamed the Johns Hopkins Bayview Medical Center, a second large medical campus facility meeting Johns Hopkins' expanding needs and serving the residents in Eastern Baltimore City as well as those who find it more convenient.

The nursing profession in Maryland relied on organization at the state level until the Association of Collegiate Schools of Nursing was organized in 1935. In 1941, the faculty and alumnae of the University of Maryland School of Nursing joined with the Schools of Medicine, Dentistry, and Pharmacy in raising two 500-bed units to serve in the Pacific Theater of operations during World War II.

In 1950, a *McCready v. Byrd* ruling paved the way for the entrance of the first black students to the School of Nursing. I joined the faculty of the University of Maryland School of Medicine on September 1, 1950, and started giving four lectures in Biochemistry to the nursing students in the summer of 1951. At that time, Ann Virginia "Ginny" Brown taught the balance of the course and Miss Florence N. Gipe was Dean of the Nursing School, which, as I recall, was a three-year program leading to an associate degree and eligibility to take the RN examination. In 1951, University Hospital installed a new communication system that enabled patients to speak to a central desk nurse, which was expected to save 25% of nursing time. In 1952, a four-year Bachelor of Science (BS) degree nursing program was instituted, and in 1955 Nursing became part of the Graduate School and was granted authority to grant a Master of Science in Nursing. The University of Maryland at Baltimore (UMB) became authorized to grant PhD's in Nursing in 1979, the 16th university in the United States to do so, and granted the first PhD in Nursing in 1984.

In 1993, a new Veterans Administration Hospital with sophisticated computerization of patient records at the bedside was completed with a walkway to the 990-bed University Hospital. The VA Hospital of 291 beds is the designated center for veterans with multiple sclerosis and carries on over 30 major VA-funded research projects in conjunction with the University of Maryland Medical System. Today, computerization of patient records is routine at all medical centers, teaching hospitals, and large hospitals including St. Agnes Hospital, which is the closest hospital to our retirement community.

The famous 90-bed James Lawrence Kernan Hospital for orthopaedics and rehabilitation was founded in 1895 and became a part of the University of Maryland Medical System in 1986. Kernan's 2,700 admissions each year make it the largest provider of orthopedic services in the state of Maryland, services that include total joint replacement, spine surgery, sports medicine, hand and upper extremity surgery, and pediatric orthopedics. I had my right knee replacement there in May 1997, and after my two seizures on September 23, 2006 and spending 10 days in St. Agnes Hospital, I spent three additional weeks in Kernan Hospital. There, I received cognitive therapy (includes speech), occupational therapy, and physical therapy up to three times a day.

In the 1990's, many other new projects were developed as part of the University of Maryland Medical System, including a Biomedical Research Facility in 1992, the Gudelsky Tower and front lobby area at the Hospital and a Health Sciences Facility, both in 1995, a new Nursing School in 1998, and a new hospital tower as part of the Weinberg Building in 2003. The Greenbaum Cancer Center is also located in the new tower. The Division of Transplantation is one of the largest in the world and provides kidney and pancreas transplants with the latest advances in immunosuppressive medication and conducts state-of-the-art research to improve patient outcomes and quality of life. Among the institution's newer treatment programs are virtual colonoscopy, achieving weight management in obesity with bariatric surgery for the removal of fatty tissue instead of the

common Roux-en-y gastric bypass, and selective internal radiation therapy (SIRT) for inoperable liver cancer.

In 1983, the Medical System moved toward self governance on a road to financial soundness and with a focus on patient care. About 1984, hospital reimbursement systems were initiated based on one of 450 Diagnostic Related Groups (DRGs); therefore, care delivery was designed by disease, not by department, and the hospital's commitment to the patient was renewed and strengthened. The institution then shifted into a qualitative phase to meet "customer" expectations. By 1992, the Medical System moved into a strategic phase, adopting a data-based, action-oriented consensus strategic plan that established the institution's vision, mission, goals, and values (3). Today, the University of Maryland Medical System (UMMS) has 1,907 licensed beds and more than 9,000 employees. In 2004, Morton Rapaport, MD (class of 1960; the last class I taught), retired as Chief Executive Officer of the private self-sustaining System, which now occupies a 56-acre downtown campus. In the 2004–2005 budget year, the Medical System, including the Medical School, received less than 6% of its funding from the State of Maryland (11). It is a world leader in providing newer cutting-edge diagnostic and treatment programs, and its goal is to become a standard-setting academic hospital. A new Biotechnology Research Park opened in 2005, new dental clinics and a new School of Dentistry building in January 2006, and a new rehabilitation facility combining Montebello (183 beds) and Kernan (69 beds) Hospitals is expected to be built in 2007.

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Chapter 4

Drug Discovery

PHARMACOPEIAS

For centuries, physicians and apothecarians, the earliest pharmacists, vied for the right to define and compile drugs. A pharmacopeia (or pharmacopoeia) is simply a list of drugs, ranging, historically, from herbal preparations and recipes used by the earliest apothecaries to modern formularies, along with information about how to prepare them. The Greco-Roman military physician Dioscorides produced *De Materia Medica* in 79 AD, one of the earliest pharmacopeias, which described hundreds of pharmaceutical preparations made from animal, vegetable, and mineral sources (1). In the second century, Galen (131–201 AD), a physician to gladiators and emperors, shaped medieval medicine and pharmaceutical practice for several centuries with his pharmacopeia of hundreds of animal and vegetable ingredients. A medieval nun, Hildegard of Binben (1098–1179), an Abbess of the Benedictine convent in Rupertsburg, Germany, compiled and organized information about the pharmaceutical uses of plants and kept records of efficacious formulae (1).

In the mid-13th century, Gilbertus Anglicus' *Compendium* relied on an array of 400 ingredients for making numerous drug preparations and also provided guides to diagnosis and prognosis. Although early medicine continued to be conducted in Latin as an academic pursuit, Anglicus' *Compendium* was translated into English for the apothecaries in the early 1500's. "Apothecary" comes from the Latin *apotheca*, a place where herbs, spices, and wines were sold during the Middle Ages in England, and came to describe the shop or stall where herbs and drugs were sold. The apothecarians achieved separate status from grocers on December 6, 1617, when James I granted a royal charter permitting them to incorporate (1). Although several other European cities and political entities established some formulations for drugs, the first truly national pharmacopeia was the *London Pharmacopeia* of 1618, which contained 1,028 single-ingredient drugs and almost as many preparations and compounds. In retrospect, many of these were worthless or actually poisonous, but some may have had a placebo effect, which is psychological. The sixth edition, published in 1788, was the first authorized English language edition; the last *London Pharmacopeia* was published in 1851.

The first college of pharmacy was established in Philadelphia in 1821, followed by pharmacy colleges in Boston and New York, and on January 27, 1841, the Maryland College

of Pharmacy in Baltimore, Maryland. However, unlike its predecessors, the Maryland College emerged under the aegis of a university and established its program in an academic framework (2). Elisha Butts, Professor of Chemistry at the University of Maryland School of Medicine (founded in 1807) and cofounder of the Maryland College of Pharmacy in 1841, was one of six scholars who had drawn up the *United States Pharmacopeia* (USP) in 1821, an index of drugs that is still used as a basic handbook for pharmacists nationally. It contained 217 drug names divided into two groups according to the level of general acceptance and usage. A group of five early physicians, joined by Dr. Butts, sought uniformity in the drugs and medicines they used to treat their patients—those prepared and sold by them, as well as those mostly prepared by the early American apothecarians. In 1889, the American Pharmaceutical Association started publishing the *National Formulary* (NF), a guide to drugs and medicines. The USP and the NF existed in parallel for almost a century, but the USP was considered by some to be more influential (3). Over the years, the drug listings of the USP and NF converged and overlapped so much that they merged on January 2, 1975 (1). Today, the USP is an independent non-profit organization supported by groups such as the American Medical Association (AMA), the American Nurses Association (ANA), the American Dental Association (ADA), the American Pharmaceutical Association (APA), and various governmental groups, including the FDA. It has no binding legal status or federal authority, although some local jurisdictions and states have adopted its standards. The USP publishes *The United States Pharmacopeia–National Formulary* (USP–NF) annually; it is of the utmost value and usage to practitioners of medicine and dentistry as it contains details on the clinical usage of drugs.

VACCINE DEVELOPMENT

Louis Pasteur (1822–1895) was a French chemist who, in 1861, demonstrated the "Pasteur effect," that is, the fermentation of alcohol and the souring of milk taking place without oxygen. In 1881, he developed a way to isolate and weaken germs and, following Edward Jenner's example, went on to develop vaccines against anthrax in sheep and cholera in chickens. Next, Pasteur turned his attention to rabies, and in 1885 saved the life of a young boy by inoculating him with a weakened rabies virus

after he had been bitten by a rabid dog (4). In Paris in 1888, he founded the Pasteur Institute for rabies research, prevention, and treatment.

Also in 1888, Emile Roux and Alexandre Yersin, of the Pasteur Institute, first isolated the deadly toxin that causes diphtheria's lethal effects. In 1894, Hermann M. Biggs, MD, working at the New York City Department of Health Laboratories, prepared a diphtheria antitoxin, which was subsequently manufactured by the Bender Laboratory in Albany, New York, under the supervision of its first director, Joseph J. Kinyoun, MD, and was certified for sale by the New York State Health Department in 1897 (5). This was the first of many vaccines to be produced under New York State auspices, but they were produced by the State Laboratory in Albany after 1910. The first commercial diphtheria antitoxin was produced by H. K. Mulford Company of Philadelphia, which merged into Sharpe & Dohm when they moved their pharmaceutical company from Baltimore to Philadelphia in 1929 (6).

PATENT MEDICINES

One of the most flamboyant manifestations of the entrepreneurial spirit of 19th century America was the "patent medicine" industry, which was rooted in a lack of competent physicians and affordable medical care for most Americans. Routine healthcare was provided by the mother of the family, relying on home remedies and herbal medicines, for which recipes could often be found in cookbooks. Patent medicines were not medicines that had been patented, but were proprietary (secret formula) and unproved remedies that were widely advertised and sold door-to-door by traveling salesmen and often contained a very high alcohol content. They carried names such as Mrs. Winslow's Soothing Syrup (alcohol and opiates), Brown's Iron Bitters and True Tonic, and Dr. E. Rowell's Invigorating Tonic and Family Medicine. Many were sold for "dyspepsia" (indigestion), the 19th century's major disease complaint. It was 1906 before the federal government enacted the first Pure Food and Drug Act, which also established the United States Department of Agriculture Bureau of Chemistry as the regulatory agency, but with only limited powers of inspection and control over the industry (4). It attempted to do away with the sale of contaminated food and it required bottles to be labeled with their specific content of alcohol and narcotics, but did not prohibit the sale of patent medicines, a powerful \$80,000,000 industry. Not only were patent medicines loaded with alcohol, but numerous other addictive drugs were widely available from drug stores, and the smoking of opium was introduced during the last half of the 19th century. Beer, wine, and hard liquors were also available for picnics, games, and social activities. No wonder the social period of the late 1800's was referred to as the "Gay Nineties" and, like today, America at the time had its share of alcoholics and drug addicts.

INFECTIOUS DISEASES

At the national level, the National Immigration Act of 1891 mandated the physical inspection of immigrants for diseases,

any number of which could be considered cause for quarantine or exclusion from entrance. (It is not widely recognized, but the taxation of immigrants at ports of entry was the main source of federal government funding prior to 1912 when a constitutional amendment led to the taxation of income.) Also in 1891, a National Hygienic Laboratory, founded as an inspection unit at Ellis Island in 1887, was moved to Washington, DC, and evolved into the National Institutes of Health (NIH) (4). It was the same year in which an International Sanitary Convention was established, which initially restricted its efforts to cholera. In 1902, the International Sanitary Convention evolved into the Pan American Sanitary Organization in Washington, DC, the forerunner of the World Health Organization's (WHO) Regional Office for the Americas. Also in 1902, Congress passed legislation for the development of the Biological Controls Group to regulate the interstate sale of viruses, serums, antitoxins, and similar products, which later became the Biologics Division of the FDA and, beginning after World War II, included the regulation of blood and blood products.

In 1892, Hoeschst Pharmaceuticals in Germany developed an antitoxin to tuberculosis (TB), a leading cause of death both in Europe and the U.S., which formed the basis for the development of a new pharmaceutical industry manufacturing vaccines and antitoxins both in Europe and in America (6).

In 1904, the National Tuberculosis Society was founded to promote research and social change in tuberculosis (consumption) (4, p. 27), which continued to be a leading cause of death in the first half of the 20th century. My father survived surgery in 1917 for TB of the left parotid (salivary) glands (7, pp. 79-80). My first cousin, Edwin Vanderlinde died in 1936, at age 23, from TB, and his brother, Army Captain Robert "Bob" Vanderlinde, MD, acquired it in 1946 after returning from the European Theater of Operations during World War II. He was treated for it by the surgical removal of part of one lung and with bed rest and isoniazid at the New York State Sanitarium at Saranac Lake, New York, where we visited him in summer 1947. Although streptomycin was discovered in 1944 and provided the first cure for TB, it had very serious side effects. An improved drug, isoniazid, was first marketed in early 1947. Bob, who had received the third highest score on the National Boards in Medicine in the United States upon his graduation from Duke School of Medicine in 1943, said to his younger sister, Marian, some years before his demise, "It's bad when your body goes but it's something else when this goes," as he pointed to his head (7, p. 67). About 10 years later, at age 75, Bob died of Alzheimer's. This brilliant clinician, who had been Senior Officer for Clinical Affairs at the Dartmouth Mary Hitchcock Clinical Center and Professor of Medicine at Dartmouth Medical School, recognized his developing condition early on. This unfortunate disease is very stressful on the caregiver and, not surprisingly, his wife Margaret passed away about three years later.

GOVERNMENT REGULATION

Prohibition came in 1919, leading to speakeasies and bathtub gin, the fur coat age, and "booze" on college campuses during

the “Roaring Twenties,” but this era had faded by 1933 when prohibition was repealed. In 1938, the Food, Drug and Cosmetic Act was passed, which greatly enhanced the powers of the federal Food and Drug Administration (FDA) (4). Subsequently, the government assumed increasing responsibility for maintaining the quality and efficacy of drugs and the marketing of new drugs. America largely escaped the thalidomide tragedy of some 10,000 children born with congenital abnormalities, mainly in Europe and Australia, with some in Canada, due to the vigilance of Dr. Francis Kelsey, an FDA medical officer, who delayed the drug’s market approval in the United States (8).

New York City founded a Department of Health in 1873 and New York State founded a Board of Health in Albany, the state capital, in 1881. The Board of Health was responsible for a new Act to Prevent the Adulteration of Food and Drugs and established a Sanitary Committee to carry out the law (5). Subsequent bacteriological studies within New York State involved Dr. Theobald Smith of Washington, DC, who used his new fermentation tube technique for the detection of *Bacillus coli*, later renamed *Escherichia coli* or *E. coli* after Theodor Escherich, who had discovered it in 1879. Dr. Smith showed the Mohawk and Hudson Rivers to be polluted with bacterial-causing diseases, including typhoid fever, and to be unsafe as a source of drinking water. Although the state had a contract, from 1896–1906, with Bender Laboratory—a private Albany laboratory founded in 1895—to examine drinking water and pathological specimens for disease and to instruct county health officers in techniques for bacteriological and pathological examination, in 1907 it developed a small State Hygienic Laboratory on Yates Street (preceded as a state lab only by the Commonwealth of Massachusetts).

In 1914, the State Hygienic Laboratory was reorganized as the Division of Laboratories and Research. By 1929, at its peak, it had grown into the largest public health laboratory complex in the world, with a complex of 19 buildings and up to 1,500 staff and visiting scientists. New York State began supplying rabies antitoxin in 1897, and by 1914 was supplying antisera for pneumococcus, meningococcus, dysentery, and typhoid, and was the sole source of antitoxins for the Army in World War I (5). The antigen of the Wasserman complement-fixation test, used routinely since 1922 to detect individuals with syphilis, was identified as cardiolipin in 1941 by Mary C. Pangborn, PhD, who became the senior author of the World Health Organization (WHO) Report on Cardiolipin Antigens in 1951.

DRUG AND VACCINE DEVELOPMENT

In 1950, two antifungal agents were isolated from soil by mycologists Rachel Brown, PhD, and Elizabeth L. Hazen, PhD, one of which became Nystatin [NY (for New York) plus statin]. Nystatin was the first broadly effective antifungal agent available to the medical profession and is still in use today. Drs. Brown and Hazen placed their share of the royalties in a trust fund, which later provided the funds for Kent Miller, PhD, and

Sally Kelly, PhD, to attend Albany Medical College. The trust also provided funds for Robert Rej, my young protégé, to earn his PhD degree in Biochemistry there in 1976.

Developing simultaneously with the golden age of vaccines and antitoxins for many newly identified diseases—which can be designated as the first “immunologics”—was the chemical and drug golden age, which the American Chemical Society has chosen to call *The Pharmaceutical Century; Ten Decades of Drug Discovery* (4). Drug discovery has involved hundreds of thousands of chemists and other scientists in the purification, structural identification, and testing of substances for bioactivity in their natural and purified form, as well as in their synthesis and their commercial production by the pharmaceutical industry, about which many hundreds of books have been written. *The Johns Hopkins Complete Home Encyclopedia of Drugs* (9) and the *Physicians Desk Reference* (10) are representative of the current state of the art, and are books that I keep on my bookshelf for personal usage.

Felix Hoffman hated to see his father suffering from arthritis and the severe side effects of the sodium salicylate used to treat it, but unlike most sons, he had the capability to do something about it. As a chemist at *Farbenfabriken Friedrich Bayer* in Germany, he modified salicylic acid in the hope of preserving its inflammation-fighting properties while easing the harsh effects it had on the stomach. The resulting compound was acetylsalicylic acid, a universal pain reliever through its anti-inflammatory activity, which the company began marketing in 1899 under the trade name Bayer Aspirin (4). However, as I was taught in medical school pharmacology in 1948, “No drug is given without some attendant hazard,” and in the 1980’s, it was determined that there is a strong association between Reyes disease, a very serious viral condition, and children who have taken aspirin.

Cortisone and its more active reduced form, hydrocortisone, were discovered in 1954 as natural steroidal compounds produced from cholesterol by the outer cortex of the adrenal gland, with marked anti-inflammatory activity. Aspirin has been referred to as the “poor man’s cortisone” because, among other effects, it stimulates the adrenal glands. Over the past 50 years, a throng of non-steroidal anti-inflammatory drugs (NSAIDs) have emerged. However, aspirin remains the most widely consumed drug in the world, with Americans gulping down over 29 billion pills per year (11). Many of these billions of doses of aspirin are to ward off heart attack and coronary artery disease, which my wife and I have been doing since about 1975 when a clinical pharmacologist friend, employed by Sterling Winthrop Laboratories in Albany (makers of Bayer Aspirin, for which the patents expired eons ago), told me about Sterling Winthrop’s studies during a Rotary Club luncheon. While on the faculty at Hahnemann in the 1980’s, I learned from a hematology colleague that it is necessary to take only a baby aspirin (81 mg) a day to maintain prevention; of course, one must stop taking aspirin 10 days before any surgery. Today, a significant percentage of the adult population takes aspirin to prevent heart attack, and it is commonly recommended that one quickly take two aspirin if one develops, acutely, what appears to be a heart attack.

Since 1900, there has been an explosion in our medical knowledge of not only infectious and communicable diseases, cancer, and inherited metabolic diseases, but of the underlying nature of many disease processes. Even in the past 30 years, we have learned about new viruses and rickettsia, such as Rocky Mountain spotted fever and Legionnaires' disease, and have seen a serious worldwide spread in AIDS. Shortly after I retired on June 30, 1990, I worked two hours in our garden and developed swollen finger joints; this led to me being tested for Lyme disease, which is born by deer ticks. Nearby Valley Forge Park was overpopulated with deer and they often invaded our garden. In the past five years, we have seen the Asian flu and West Nile virus arrive, and "mad cow disease" or basal cell spongiform disease in cattle has entered the human food chain. Previously, the latter type of disease was known only among cannibals who eat human flesh and develop fatal Creutzfeldt-Jakob disease.

Although many of the responsibilities of the FDA in respect to food production, manufacturing, and purity, including the slaughter of animals for meat production, were taken over by the United States Department of Agriculture (USDA) just before World War II, there are a few food discoveries that overlap with drug discovery. In 1869, the J. S. Young Company on Boston Street in Baltimore was the first candy company to produce licorice. Licorice is a perennial herb of the legume family cultivated for its roots which, when dry, provide a product used as a flavoring in medicine, candy, and tobacco (12). In 1879, saccharin, the first sugar substitute, was developed by Ira Remsen and Constantine Fahlberg, chemists at Johns Hopkins University in Baltimore.

Rise of Drug Companies

In 1872, John Wyeth & Brother of Philadelphia pioneered in the production of tablets, which they trademarked, in 1877, as "compressed tablets." Their company evolved into Wyeth-Ayerst Laboratories, one of the major pharmaceutical companies in the United States (6).

In 1880, the Lambert Pharmacal Company was founded in St. Louis, Missouri. It is best known as the manufacturer of Listerine, which is available today, under various names, as an over-the-counter mouthwash.

In 1885, James, Edward, and Robert Wood Johnson, who were early advocates of Joseph Lister's controversial theory regarding air-borne germs, started a surgical supply company in New Brunswick, New Jersey, which was incorporated two years later as Johnson & Johnson. In the 1890's, they added Johnson's Baby Powder (talc) to their growing list of antiseptical surgical dressings, plus catgut sutures made from sheep intestines, and gauze, and cotton. In 1901, they published *Johnson's First Aid Manual*, the first complete manual written on the subject (6). Band-Aid adhesive bandages and an expanded line of baby products followed in 1921. Today, it is a leading corporate giant in the healthcare field, and the Robert Johnson Foundation is a leading funder of medical education and research.

In Baltimore in 1891, Bromo Seltzer, the first commercial antacid for dyspepsia (indigestion), the leading disease

complaint of the 19th century, was developed by Isaac Emerson. The city of Baltimore is famous for the Bromo Seltzer Tower. Also in Baltimore in 1892, Crown Cork and Seal developed and manufactured the first disposable glass vial with a rubber cap, which became very important in vaccine and anti-toxin development and utilization. The hypodermic needle syringe with its hollow-point needle had been invented independently in 1853 by Charles Gabriel Pravaz, MD (1791–1853), a French surgeon, and Alexander Wood, MD (1817–1884), a Scottish physician, and was available for the administration of vaccines (13).

In 1891, Smith, Kline & Company in Philadelphia absorbed French, Richard & Company, another drug wholesaler, which then became Smith, Kline and French (6). Bzedrine was first developed in 1929 as an amphetamine inhalor used to treat colds, hay fever, and other upper respiratory illnesses. It was marketed originally in a glass tube, but was switched to an aluminum tube in 1932 and is sold today as a plastic inhaler. In 1944, they developed Dexedrine (phenylpropanolamine), used as an appetite suppressant and also to treat depression and narcolepsy. Dexedrine was developed in 1952 as a time-release capsule called a spansule. Since about 1970, we have recognized that these types of drugs are stimulants that are subject to abuse.

Also in 1891, hypothyroidism was first treated with sheep-thyroid injections—the first proof that animal-gland solutions (hormones) could benefit humans. In 1896, Addison's disease (hypoadrenalism) was treated with chopped up adrenal glands from a pig. These treatments initiated hormone research, which became known as endocrinology.

After 1900, biochemical, metabolic, and nutritional research took off with the discovery by Landsteiner in 1901 of the blood groups O, A, and B. The same year, several other discoveries were made, including the essential amino acid tryptophan by Sir Frederick Hopkins; the first artificial hydrogenation of fats to produce saturated fats, as in oleomargarine (which causes so many health problems today); the discovery by E. L. Opie that the islets of Langerhans in the pancreas relate to diabetes; and the isolation of the first vitamin, thiamin. In 1909, Harvey Cushing, MD, demonstrated the link between the production of growth hormone by the anterior pituitary gland and gigantism (abnormally tall people).

Birth of Chemotherapy

In 1906, August von Wasserman (1866–1925), a German bacteriologist, developed an antibody to the spirochete that causes syphilis. His test, along with other procedures, is still used to diagnose syphilis. He is also noted for developing a test for tuberculosis and, with Wilhelm Kolle, published a six-volume work in 1903–1909 entitled *Handbook of Pathogenic Microorganisms* (4).

Also in 1906, Paul Ehrlich (1854–1915), a German medical scientist, came up with the concept of a "magic bullet" drug to knock out disease-producing organisms. Its first application—marking the birth of chemotherapy—was in 1910 when Ehrlich and Sahachiro Hata (1837–1938) developed arsenic compound

606, marketed by Hoesch of Germany as Salvarsan, the first effective drug for syphilis (4). Ehrlich also developed a stain slide test on sputum for the diagnosis of tuberculosis (TB), and his studies of cell nutrition showed the rate of oxygen utilization reflected the intensity of cell processes. His method of increasing the production of antitoxins in animals was crucial to the creation of a diphtheria antitoxin. He shared the Nobel Prize in 1908 in Physiology with Elie Metchnikoff, a Russian microbiologist and director of the Pasteur Institute in Paris, who discovered that phagocytes in the bloodstream of mammals, including humans, engulf foreign bodies such as bacteria. This process is called phagocytosis and is a basic concept of immunology.

Vaccine Development

In 1909, the U.S. Army began a mass vaccination against typhoid, making it available before World War I. The Charmerlain-Kahn Act of 1918 provided the first federal funding for controlling venereal disease, just in time for America's soldiers in World War I. However, there were problems with the administration of Salvarsan, as it had to be delivered into the blood stream through a glass syringe or a rubber tube. The toxicity and dangers associated with its administration became its downfall (4).

World War I brought with it an influenza epidemic in 1918, attacking not just the old and frail but the young and strong. Fortunately, the New York State Health Department Division of Labs and Research had produced sufficient vaccine to treat most of our soldiers before they went overseas. My Uncle Archie, as a young 18-year-old recruit during World War I, wrote a postcard saying he had passed out upon receiving an inoculation for influenza and "Albert and another fellow carried me back to the barracks where I was sick for the rest of the day" (7, p. 32). The influenza epidemic of 1918–1920 killed over 20,000,000 people worldwide. Virologists recently have discovered it was so very devastating because it was an avian (bird) virus that had mutated to a virus that attacked humans.

Mercurochrome, an early antiseptic drug for scratches and small cuts, was developed in Baltimore in 1919 and became a very widely used medication because it did not sting like tincture of iodine.

Insulin and Diabetes Treatment

Frederick Grant Banting, MD, (1891–1941), a Canadian orthopedic surgeon, worked in 1920 with a colleague physiologist, Charles H. Best, PhD, on the active principle in the pancreas that lowered blood sugar. Their joint efforts were begun in May 1921 under the auspices of Professor J. J. R. McCleod, PhD (1876–1935), Chairman of Physiology at the University of Toronto. The need for a biochemist in the chemical purification and processing resulted in the addition of J. B. Collip, PhD, to the group. After the Nobel Prize in Medicine was awarded only to Banting and McCleod in 1923, Banting shared his honorarium with Best, and McCleod shared his award with Professor Collip.

On August 7, 1922, Elliot Joslin, MD, founder of the world-famous Joslin Clinic, a part of Harvard in Boston, began using insulin from Canada for patients in his diabetic clinic, its first usage in the United States. The first commercially available animal insulin in the United States was manufactured by Eli Lilly & Company of Indianapolis, Indiana. Commercial injectable preparations of short- and long-acting beef and pork insulin have been available for many years to treat juvenile and adult diabetics and have been extremely important in diabetic care for over 80 years. However, just recently, the application of new recombinant DNA technology has resulted in a modified bacterium, which produces human insulin that has been marketed with FDA approval. An amazing development!

Baxter Laboratories was founded in 1931 in Deerfield, Illinois. Today, Baxter International is a global healthcare giant that manufactures, among its many products, drugs for treating blood diseases, medication delivery systems, and kidney dialysis devices.

VITAMIN SYNTHESIS

In 1933, Tadeus Reichstein synthesized ascorbic acid (vitamin C), creating the whole new field of commercial vitamins, which many people take today on a daily basis. We now know vitamin C stimulates the human immunologic system (increases our resistance to disease). As early as 1946, the nutrition group at Harvard School of Public Health knew that extra ascorbic acid prevented colds. Later, Nobel Prize winner, Linus Pauling, PhD, carried this concept to an extreme.

ANTIBIOTIC DEVELOPMENT

A major breakthrough in the treatment of bacterial infections took place in 1935 when Gerhard Domagk, PhD, at I. G. Farben in Germany, discovered Prontosil, the first of several sulpha drugs (4). Its clinical effectiveness was documented in London by the curing of life-threatening bacterial infections in 26 newborns. The active part of the drug turned out to be sulfanilamide. Domagk received the 1939 Nobel Prize in medicine. Later, it was found that sulfa drugs or sulphonamides do not kill bacteria but halt their growth and multiplication, permitting the body's defenses to take over. Many people today are allergic to sulpha drugs.

In 1937, an American pharmaceutical company marketed, without any clinical testing, an elixir of sulfanilamide using the automotive antifreeze diethylene glycol as a solvent. Diethylene glycol is metabolized to poisonous oxalic acid and over 100 people died, many of whom were children (14, p. 44). As a result, the federal government enacted the Food, Drug and Cosmetic Act of 1938, which banned drugs that were dangerous, required new drugs to be tested for safety before government approval, and made prescriptions mandatory for most drugs, whereas none were required previously. A regulatory division of the FDA was given enforcement authority. As a result of this Act, pharmacy moved from a "cottage industry to mass production" (14, p. 13). In the 1940's, the Federal Trade

Commission (FTC) began requiring drug manufacturers to substantiate claims (4).

In 1938, lysergic acid diethylamide (LSD), a powerful and dangerous hallucinogenic drug, was discovered. In the 1970's, Timothy O'Leary, MD, of Boston, touted this dangerous drug, which resulted in many youths becoming drug addicts with damaged brains.

In 1928, Sir Alexander Fleming (1881–1955) noted that bacteria were inhibited by a crude mold broth that he named penicillin. Penicillin was later purified by Howard Florey's group, leading to Fleming and Florey sharing the Nobel Prize for Physiology or Medicine in 1945. Although discovered in 1928, it was not until early 1941, and shortly before the United States became involved in World War II, that the commercial production of penicillin was developed using huge vats at the USDA's Northern Regional Research Laboratory in Peoria, Illinois. It was subsequently manufactured by several pharmaceutical companies. Penicillin was exceedingly valuable against battle-wound infections and saved thousands of our servicemen's lives in World War II. It was also effective against venereal diseases that have always infected armies, and acted principally upon gram negative staining bacteria. In 2001, on the 60th anniversary of the Antibiotic Age, the United States Department of Agriculture's National Center for Agricultural Research in Peoria, Illinois, was designated as an International Historic Chemical Landmark.

Unfortunately, penicillin turned out to be ineffective against malaria resulting from mosquito bites and contracted by a very high percentage (80–90%) of our South Pacific troops beginning in Guadalcanal in 1942. Although Atabrine was readily available, it had numerous side effects and lacked the efficacy of quinine, a drug isolated from cinchona bark. In 1944, William E. Doering, PhD, and Robert B. Woodward, PhD, of Harvard University synthesized quinine, a very complex compound, from coal tar, for which they received the Nobel Prize in 1965. However, chloroquine, discovered by the Germans in 1934, was rediscovered in the mid-1940's, and is still the primary drug used to treat malaria (4).

After Rene DuBos, MD, presented his results with tyrothricin at the Third International Congress of Microbiology in New York City in 1939, Selman Waksman, PhD, and his associates isolated streptomycin, the first of 18 aminoglycoside antibiotics that were found to target gram positive staining bacteria (4). After streptomycin was discovered to be effective against tuberculosis in guinea pigs, the first human patient was cured of tuberculosis in November 1944, a discovery for which Dr. Waksman received the Nobel Prize for Medicine in 1952. Streptomycin, which has serious side effects, was replaced in 1951 by isoniazid, which has fewer side effects. Subsequently, TB was brought under control, and by about 1970, the New York State Department of Health, where I was employed, was able to close down its three TB sanitariums.

In 1948, Professor Benjamin Duggar, PhD, of the University of Wisconsin isolated the first tetracycline antibiotic, chlorotetracycline, which was found to be a broad spectrum antibiotic and active against an estimated 50 disease organisms by blocking protein synthesis. Other antibiotics with

inhibitory effects on bacterial cell wall synthesis were discovered during the 1940's and include cephalosporin (a beta-lactam) and bacitracin, useful for skin infections. Erythromycin, which treats a broad spectrum of gram positive bacteria, was introduced in 1952.

CANCER DRUGS

Methotrexate, an extremely potent anticancer drug, which requires therapeutic monitoring, was also discovered in 1948. Initially, it was the mainstay of early treatment for leukemia. It is used today for the treatment of immunological diseases such as severe rheumatoid arthritis and lupus erythematosus, but has not been shown to be beneficial in multiple sclerosis. Because it is such a potent drug, my laboratory at Hahnemann (1977–1991) monitored the levels of the drug.

The Humphrey-Durham Amendments of 1951 fully differentiated drugs into the categories of prescription and nonprescription, referred to officially as "legend" and "OTC" (over the counter), and required pharmaceutical companies to direct their advertising to physicians (4). The great increase in the prescription-only category shifted the doctor-patient relationship more toward the giving out of prescriptions. The same year also saw the introduction of mood-controlling drugs acting by inhibiting monamine oxidase (MAO type drugs). Unfortunately, a few years ago the FDA shifted its policy, and television and our news media are loaded with drug advertisements, which can be questioned on an ethical basis.

In 1952, reserpine was isolated from many tons of a weed from India, known as rauwolfia, which had a folklore curative background. This alkaloid was very effective in lowering blood pressure, and many of the hypotensive agents marketed since are chemically related to reserpine, an alkaloid, which was also found to have tranquilizer properties.

The adrenal cortex hormones cortisone and hydrocortisone (interconvertible in the body) were first isolated and their chemical structure defined in 1954. Injectable cortisone is widely used today for treating acute painful orthopedic problems. Various other more powerful fluorinated derivatives of cortisone, such as (methyl) prednisone, some of which can be taken orally, are used to treat various immunological diseases such as multiple sclerosis, rheumatoid arthritis, and lupus erythematosus, a disease seen most frequently in women. Other fluorinated steroids are used in salves or ointments to treat various skin rashes and problems.

In 1954, Smith, Kline & French marketed Thorazine (chlorpromazine), a drug licensed from the French drug house, Rhone-Poulenc, which became widely used in the treatment of mentally ill patients (6). Drugs of this type, which are phenothiazines, belong to the drug class "neuroleptics and antipsychotics" and revolutionized mental healthcare in America, freeing patients to open society instead of institutionalization.

McNeil Laboratories introduced Children's Elixir in 1955 as a prescription form of acetaminophen (Tylenol). In 1960, it was approved by the FDA for sale without a prescription. After it was discovered that aspirin given to young children increases

the likelihood of Reye's syndrome, a viral condition that results in cerebral edema and liver damage, acetaminophen (Tylenol) became the drug of choice for the young pediatric population.

Also in 1955, Milltown (meprobamate) was marketed as the first antianxiety or tranquilizer drug developed in the United States, but it is seldom used today. It was followed by Librium in 1961 and Valium in 1963. Intravenous Valium is often used today to relax patients before surgery. Subsequently, the benzodiazepine drugs permitted the discharge of millions of institutionalized patients from mental hospitals to outpatient treatment facilities.

Interferon, a protein produced by intact animal cells when infected with viruses, was first identified in 1957. Several types of human interferon are known today and are of some clinical value in treating hepatitis, some cancers, and sometimes self-destructing immunological diseases such as multiple sclerosis, in which the body nerves demyelinate (lose their surface sheath).

In 1958, Merck, Sharpe, and Dohm marketed Diuril (dichlorothiazide), a diuretic, used to control blood pressure in patients with modest to moderate hypertension. The patents have expired and it is available inexpensively today as a generic diuretic (15).

DRUG TOXICITY: THALIDOMIDE

A major world tragedy occurred in Europe and Australia between 1959 and 1963 when some 10,000 children were born with major deformities due to the drug thalidomide, which had been prescribed for their pregnant mothers. The United States registered only 17 cases due to the vigilance of Francis Kelsey, MD, a medical officer at the FDA, who repeatedly delayed market approval of the drug. Dr. Kelsey, who was born in July 1914, was still working for the FDA at age 87 in fall 2002 (16).

THE "PILL"

Enovid, "the pill," was marketed in 1960 by Searle as an oral contraceptive, which led to a new wave of social change the world over. Also, 1960 saw the election of the Kennedy/Johnson Administration, leading to federal intervention in previously unregulated areas of food and medicine. In 1962, the Kefauver-Harris amendments to the Food, Drug and Cosmetic Act of 1938 greatly expanded the FDA's control over food and pharmaceutical manufacturers and for the first time protected human "guinea pigs" from medical disasters like the one involving syphilis that occurred at Tuskegee, Alabama, during World War II under Public Health auspices (4). Today, the FDA requires all clinical facilities using experimental or limited approval drugs to have an Institutional Review Board (IRB) to review and monitor all projects involving either new experimental drugs or new experimental devices. Nevertheless, both the University of Pennsylvania and Johns Hopkins Universities have had fatalities occur recently because of violations of regulations.

I have been a member of the St. Agnes Hospital Institutional Review Board since June 2002 as a professional healthcare specialist who has no affiliation with the Institution.

In 1963, Merck developed Aldomet (methyldopa), an anti-hypertensive acting on the central nervous system, which causes blood vessels to relax and widen, which in turn lowers blood pressure. Parkinson's disease, a degenerative neurologic disorder, involves an imbalance between the brain neurotransmitters dopamine and acetylcholine. Dopamine-boosting agents such as methyldopa increase dopamine activity, help restore their natural balance with acetylcholine, and are of some value today in treating Parkinsonism.

In 1964, Smith, Kline & French developed Dyrenium, a diuretic, which spares potassium loss. Dyrenium was later marketed as Dyazide. Potassium loss is an important consideration, especially in elderly patients. Also in 1964, azidothymidine (AZT; brand name Retrovir) became available for the treatment of human immunodeficiency virus (HIV) in combination with other drugs (15).

In 1968, Wyeth Laboratories developed its first oral contraceptive, Ovral, which contains norgestrel and ethinyl estradiol (steroids).

TB THERAPY

After Rifampin (various brand names such as Rifadin, Rimactane) was found able to penetrate the thick lipid wall of the TB bacillus in 1970 and the FDA approved it in 1972, it was hoped it would stamp out tuberculosis (TB). Unfortunately, more resistant forms of the tuberculosis bacilli, which has a fatty lipid protective wall that is impervious to many drugs, have returned in the 1990's. Thus TB constitutes a serious public health problem, with 14,600 cases occurring in the United States in 2003 and an estimated 2 million people worldwide killed by it in 2002. In December 2004, the diarylquinoline, R207910, was announced as the first selective TB agent in 40 years to reach clinical trials (17). It was reported to act by inhibiting ATP synthase, a mechanism of action never before described for any antibiotic.

PARKINSON'S THERAPY

Merck's Sinemet, a combination of carbadopa and levodopa, was approved by the FDA in 1975 as a treatment for Parkinson's disease, a very significant development, as it is used today for other nerve-related diseases, including multiple sclerosis. It is available today as a generic drug or as a legend (brand name) drug, the latter being more expensive, but both requiring prescriptions.

PROTON PUMP INHIBITORS

In 1976, the SmithKline Corporation, formerly Smith, Kline and French, marketed Tagamet (cimetidine), which later

became the world's first billion-dollar drug. It blocks histamine, which in turn decreases the stomach's secretion of hydrochloric acid (HCl). Tagamet, along with several competing products, is widely used today as an over-the-counter (OTC) drug for gastrointestinal disorders (15). It is sometimes administered intravenously to decrease the likelihood of queasiness in patients undergoing anesthesia. However, Tums, introduced in 1928, remains the largest selling antacid on the market. Patients with severe gastrointestinal acid reflux often need to be treated with the newer proton pump inhibitors that directly block HCl production, such as Prilosec (now OTC) and its stronger prescription form, Nexium, or the Japanese-marketed Prevacid.

FURTHER VACCINE DEVELOPMENT

In 1978, Merck developed Pneumovax, a vaccine to prevent pneumococcal bacterial infections such as pneumonia, meningitis, and bacteremia. However, several other strains of bacteria can cause pneumonia, with the viral pneumonias being the most serious. I was hospitalized in Bryn Mawr Hospital in late August 1978 for 4–5 days with viral pneumonia after an earlier case of pneumonia in 1972. The vaccine has not been very effective for me, as I developed double pneumonia in April 1999, which returned in one lung in July 1999, and I had my fifth case of pneumonia in summer 2001. However, there have been several cases of TB in my close relatives, with some deaths, and I unfortunately inherited a disposition for lung disease. Although I have permanent lung damage, bronchiectasis, from the multiple pneumonias, with clinically observable ralls, I am able to work out at our on-campus health club 2–3 times per week. Also, I recently had an updated pneumonia vaccination as they only last for five years, and each fall flu vaccine is available for all of our residents who wish to receive it and are not allergic to eggs.

Centocor is an early biotechnology company that was incorporated in 1979 in Malvern, Pennsylvania, near where we lived from 1977–1993. Its first product was a diagnostic test to detect rabies, thereby permitting children or adults, who had been bitten by a dog, to have their serum tested for the presence or absence of the virus (9). This was a very significant contribution because rabies causes severe encephalitis, which is fatal, and the rabies vaccine is nasty “stuff” to have injected if one does not need it. In September 2005, a young girl in Wisconsin was bitten by a rabid bat and, because she was used to bats, she ignored the incident. Her survival is the first documented case of recovery from rabies.

In 1982, Merck developed Heptavax-B, a vaccine for hepatitis B, which was a major step toward eliminating the disease. It results in serious liver damage, which can be fatal, and is transmitted mainly by parenteral routes due to unclean needles and syringes, therefore occurring most frequently in drug addicts.

Also in 1982, A. H. Robbins Company of Richmond, Virginia, was licensed to market dextromethorphan, a cough suppressant, in their popular OTC Robitussin line of products for colds and other respiratory diseases (15). Such products

also often contain guaifenesin, an expectorant, which recently came on the over-the-counter market as Mucinex, an extended-release bi-layer tablet.

CLINICAL LABORATORY INSTRUMENTS

The SmithKline Corporation acquired, in 1982, Beckman Instruments, the large California-based instrument company, which had been founded in 1935 by Arnold O. Beckman (1900–2004) after he built the first pH meter. In 1982, newly merged SmithKline Beckman of Philadelphia built a 48 million dollar headquarters in Franklin Plaza in Center City, Pennsylvania, where I passed in view of it daily as I walked the three blocks from the Pennsylvania train station to Hahnemann University (1977–1991). By the late 1990's, it had merged with Beecham, the large British pharmaceutical company, and became SmithKline Beecham. Today it is GlaxoSmithKline.

NEW INSULIN THERAPY

The year 1982 also saw the introduction of several new injectable preparations of insulin, which could be short-, intermediary-, or long-acting depending upon the patient's need for control (15).

CONTINUING DRUG DEVELOPMENT

In 1983, Centocor of Malvern, Pennsylvania, developed a test to detect hepatitis B in patients, the first of its kind, which was soon approved by the FDA.

Prozac (fluoxetine hydrochloride) was introduced in 1987 as the first selective serotonin reuptake inhibitor (SSRI) antidepressant. It is used to treat major depression, obsessive compulsive disorders, panic disorder, and chronic pain. Its use in teenagers has been questioned recently, as it may lead to increased suicidal tendencies.

In 1988, with FDA approval, Rohrer marketed Monoclate, the first factor VIII clotting agent isolated and concentrated from pure blood plasma with the aid of monoclonal antibodies.

ReoPor was developed in 1994 by Centocor to reduce heart attacks and deaths after high-risk balloon angioplasty, and was soon approved by the FDA.

The ending of the 20th century brought the first cloning of an animal in 1996, the development of Viagra in 1998, and the development of a vaccine for malaria in 1999.

It has been estimated recently by GlaxoSmithKline (GSK), a corporate giant, that the 4 billion dollars they spend on research and development projects results in only a 10 percent success rate in producing new marketable drugs (18). However, this industry giant operates GSK Ventures, which invests in start-up companies following up on other promising leads for new drugs, for new manufacturing technologies, and for library resources and patents.

Ever since polymerase chain reaction (PCR) technology for the production of tailor-made synthetic drugs became available

in the 1980's, there has been a tremendous expansion of the biotechnology industry, often with teaching institutions leading the way. Both Johns Hopkins and University of Maryland have recently established large biotechnology parks in Baltimore that cover several acres.

In May 2006, Merck & Co. announced a major new type of drug, which they named platensimycin as it is produced by the soil bacterium *Streptomyces platensis*. It has proved effective in curing mice infected with antibiotic-resistant bacteria and the hope is it will be effective in man (19). Only time and much more research, followed by clinical trials—which may take 5–10 years—will tell its future.

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Chapter 5

Medical Education in the United States

By 1770, the population of the 13 U.S. colonies had reached 2,148,000, stretching from New Hampshire and Massachusetts to Georgia (1). It has been estimated that the life expectancy for Americans after the Revolution was only about 35 years, as one in three babies died before its 6th birthday and fewer than half reached the age of 16, with poor or no medical care available to the large rural populations (2). In 1770, some 37% of the Colonial population lived in Virginia, North Carolina, South Carolina, and Georgia (1), but the 3,000–4,000 available medical practitioners were concentrated in the urban areas of Boston, New York, Baltimore, and especially heavily in Philadelphia (3). Most of the practitioners had been trained in apprenticeships under other physicians and only 300–400 had college degrees, mostly from Edinburgh College in Scotland. During the late colonial period, two medical schools were established: the Medical Department of the College of Philadelphia in 1765 by prominent physicians Warren Shippen, MD (1736–1808), and John Morgan, MD (1735–1789), which became the University of Pennsylvania, and the Kings College in New York City in 1768, later Physicians and Surgeons Medical College of Columbia University (3). By 1776, when classes were suspended because of the Revolution, only 51 degrees had been issued by the two new medical schools.

The medical school course at the University of Pennsylvania was of two-years duration, running from November to June, with the first year consisting of pre-clinical subjects such as liberal arts, with mathematics, natural history, a working knowledge of Latin, and preferably French as well. The second year included anatomy, with dissection of a cadaver; materia medica; botany; chemistry; physics; pathology; and clinical medicine. Dr. Warren Shippen, one of the founders, became the instructor of anatomy, surgery, and obstetrics. At the end of the second year, an examination was given for a bachelor's degree. Class instruction was by lectures, demonstrations, and attendance upon patients at Pennsylvania Hospital, the oldest hospital in America, and still today an independent entity. Prior to 1750, hospital-type care had been provided through almshouses for the poor, an early New England town concept, and residents who were better off financially chose to be treated in their homes. However, Dr. Thomas Bond, aided by his friend Benjamin Franklin, created Pennsylvania Hospital in 1751, funded by voluntary contributions and patients' fees, as a public general hospital for "inhabitation by strangers." The new

concept of voluntary hospitals became an ingrained part of American culture, continuing to the present day. Those medical students who successfully completed the two-year program then received an additional three years of study and practice, culminating in a stiffer examination, which had to be written in Latin. They also had to complete a thesis to be defended before the faculty before they were allowed to practice. However, most practicing physicians in the colonies were trained by the apprentice system and were accorded the same privileges as those few who were college trained (3).

Benjamin Rush, MD (1745–1813), of Philadelphia received his medical degree from the University of Edinburgh in 1768 and served as Professor of Chemistry and later Medicine at the College of Philadelphia, which became the University of Pennsylvania, the oldest medical school in America (3, 4). During the late 1700's and early 1800's, medical teaching was dominated by his premise that "health was a natural balance of basic elements in the body, and disease was an imbalance that required correction." Some physicians felt the balance of elements was primarily chemical, although others felt it was affected by stimulants such as food, heat, exercise, and emotion. However, too much of either would cause a debility or excitement, transmitted through the blood, that would produce spasms in the vessels, which would erupt as a specific irritation or disease. Because nature by itself would not correct the imbalance, it was believed necessary to use medical therapy such as emetics and purgents to purify the stomach and generous blood-letting to purify the blood. Calomel, a white tasteless form of bichloride of mercury, a very poisonous compound, was used widely as a purgative. Because mercuric compounds were used in making leather hats, such tradesmen frequently developed what became known as "mad hatter's disease." The theory on bleeding was that a reduction of blood volume by a pint or two reduced fever and tension and often lessened pain. Sharper, more localized pain, such as that in appendicitis and gout, required "cupping" in which a small area near the pain was scarified and a suction cup applied to draw blood. Among other treatments were leeches applied for inflammation, and blistering for kidney ailments in which a coating of gunpowder was applied to the patient's back and then lit with a match. One physician said, "Every good doctor carries the lancet in one hand and calomel in the other."

Apprentice-trained physicians were almost universal in New England and one of these, John Warren, MD (1753–1815), who had graduated from Harvard College at age 18, founded Harvard Medical School on September 19, 1782, the third oldest medical school in the United States (3, 4). For the first 25 years of its existence, it had only three faculty members. Dartmouth Medical College in Hanover, New Hampshire, was founded in 1798 by Nathan Smith as a two-year medical school, which it continues to be, but its graduates attend Harvard for their two years of clinical training and to obtain their MD degrees.

In 1733, an almshouse for the poor, later City Hospital (and today the Johns Hopkins Bayview Medical Center), was founded three miles from the business area of the village of Baltimore. In 1755, Baltimore became a center for medicine when 36-year-old Charles F. Wiesenthal, MD, physician to Frederick the Great, arrived from Prussia (5, p. 17). Nobody knows why Dr. Wiesenthal, one of the ablest medical men in Europe, left for the hardships of a town on the American frontier. He became surgeon general of Maryland during the Revolution and founded a medical school in Baltimore in the 1760's, simultaneously with the establishment of the first medical schools at the University of Pennsylvania in 1765 and Kings College in New York in 1768. At that time, Baltimore had a population of less than a thousand people; hostile Indians were still murdering isolated colonists living within 50 miles of the city. In 1769, Dr. Wiesenthal built a small two-story brick laboratory building behind his house on Gay Street for teaching his 15–20 students, each paying \$10 for anatomical dissection of a human cadaver and attending his medical lectures. Even in Europe, human dissection was frowned upon and the idea terrified Americans. On a late afternoon in December 1788, an angry mob, supported by charlatan medical practitioners, stormed the school, destroyed the contents, and dragged the body through the streets. However, instead of destroying medical education in Baltimore, it suppressed quackery, caused the physicians of Baltimore to incorporate in 1799 as the Medical and Chirurgical (surgical) Society of Maryland, and paved the way for the founding of the University of Maryland School of Medicine eight years later. The Maryland General Assembly granted authority to the Medical and Chirurgical Society to license qualified physicians and to prosecute, in the courts, anyone practicing without a license (5, pp. 18–19). In 1796, Baltimore, with a population of 25,000, was incorporated as a city and was already assuming a prominent place in the development of the new nation.

The University of Maryland School of Medicine in Baltimore, founded in 1807, is the fifth oldest medical school in the United States and the oldest entity of the University of Maryland. Although Yale University, the third oldest university in the United States, was founded in 1701, its medical school was not added until 1810 and is the sixth oldest in the nation. William and Mary College was founded in Williamsburg, Virginia, in 1793, and although it is the second oldest college in the United States, a medical department was first founded at the University of Virginia in Charlottesville by Dr. Robley

Dunlison sometime in the late 1830's. In 1833, Dr. Dunlison offered the first course in the United States on hygiene (preventive medicine) at the University of Maryland, where he was Professor of Materia Medica and Therapeutics, Hygiene, and Medical Jurisprudence. New professions developing simultaneously with medicine in Colonial America, and often competing with it, were the druggists and apothecaries, since some physicians supplied their patients with medicinals.

After graduating from St. John's College in Annapolis, Maryland, with a Master of Arts degree, John B. Davidge went to Scotland and earned an MD degree at Glasgow University in Scotland in 1793 (5, pp. 19–20). Dr. Davidge was an early attending physician at the Baltimore General Dispensary, founded in 1801, and delivered the first oration before the Medical and Chirurgical Faculty of Maryland in 1803. By 1802, Dr. Davidge had sufficient students to offer regular lectures on midwifery, surgery, anatomy, and physiology (6, p. 3). In 1805, two other physicians arrived in Baltimore, Dr. James Cocke of Virginia, who offered lectures in physiology and anatomy, and James Shaw, a graduate of St. John's College in Annapolis, who had been a surgeon in the U.S. Navy and was knowledgeable in chemistry (5, p. 20). On November 21, 1807, under the leadership of James Shaw, application was made to the Maryland General Assembly for incorporation of a medical school. However, several times in October 1807, modest announcements appeared in the Baltimore newspapers stating that Dr. Davidge's private laboratory behind his house was almost complete and that the course in anatomy would be rendered more full and complete by study of the functions of some of the most important organs of the body (5, p. 20). Further, on November 17, 1807, a ruffian appeared with a body at the laboratory, which the townspeople must have heard about, and an angry mob attacked Davidge's laboratory and destroyed the building, the very day application for a medical college had been made to the legislature. Nevertheless, "An act for founding a medical college in the city or precincts of Baltimore for the instruction of students in the different branches of medicine" was incorporated by the Maryland General Assembly on December 12, 1807; the medical college was called the College of Medicine of Maryland (5, pp. 22–23). Dr. Davidge was named dean and took the chair of surgery, Dr. Cockey assumed the chair of anatomy and physiology, James Shaw the chair of chemistry, and Dr. Nathaniel Potter was named to the chair of the theory and practice of medicine. A fifth chair in materia medica (pharmacy), taught in Latin, was subsequently filled in 1809 by Dr. Samuel Baker. Later, the college became known as the University of Maryland School of Medicine and is the fifth oldest medical school in the United States.

In 1810, land was purchased from Colonel John Eager Howard on the outskirts of Baltimore, amid huge open fields extending westerly and southerly down to the Patapsco River (5, p. 26). Groundbreaking for the new medical school building on the 300-foot by 300-foot lot, now the corner of Lombard and Greene Streets, took place April 7, 1811. Although the anatomical and dissecting labs on the first floor were opened in October 1812, the beautiful, solid brick building with walls two to four feet thick, built at a cost of \$35,000, was not completed until

1813. Its classical design included a huge, round domed tower structure, modeled after the Pantheon in Rome, which towered over the two-story, 64-foot by 90-foot front, with a balanced stone, eight-pillared colonnade, patterned after the Parthenon in Greece, facing Lombard Street. The front section of the Medical College housed the college offices, classrooms, and dissecting laboratories, and the round tower housed two amphitheatres, 60-feet in diameter, one known as Chemical Hall and the one above it, Anatomical Hall. It had four entrances and was supplied with light from a sky dome (6, p. 6), which is still true today. The citizens of Baltimore were very proud of the building, it being among the largest buildings in the new young nation, with the benches in Anatomical Hall seating almost 1,500 people. Even though the building was extremely elegant, with heating by four charcoal-burning ceiling stoves and oil lamps for lighting, and with the students sitting on wooden benches for classes, it offered little comfort. In addition, smoke from the stoves and chemical experiments, the stench from poor embalming practices, and the poor air circulation added to their discomfort.

John Crawford, MD, was the first to introduce the small pox vaccination to Baltimore and taught two courses at the College in about 1811–1812. After he passed away in 1813, the College purchased his private collection of 568 books, from his wife for \$500, for the start of a medical library, which opened in 1815 at the southeast corner of Lombard and Greene Streets and many years later was named Davidge Hall.

The College was built in the countryside, several blocks from the residential, business, and commerce areas of Baltimore. However, the local townspeople disapproved of human dissection so strongly that there were occasional raids by mobs, who beat at the locked front doors, especially after a body or two disappeared from fresh graves in the historic Westminster Church Cemetery, two blocks north on Greene Street, where Edgar Allen Poe was later buried. On September 28, 1830, Dr. Nathan Ryno Smith, Professor of Surgery, informed faculty at Bowdoin College in Maine that he would have no problem shipping them two barrels, for \$50, with the bodies preserved in whiskey, as “Frank, our body-snatcher (a better man never lifted a spade)” could procure them (5, p. 114). Even Frank became greatly alarmed and fearful for his personal safety in 1831 (6, p. 7). Dr. Smith became known as “the Emperor” for the fear he instilled in the students, who were also amused by his habit of carefully washing his hands before surgery. During the Civil War, he developed the anterior leg splint, which was widely used for treating compound fractures.

H. L. Mencken, Baltimore’s famous journalist, wrote in his book, *Happy Days: 1880–1892*, that in the 1880’s, black residents like Reverend Wesley, a black preacher who, when he attended his Masonic Lodge in southwestern Baltimore, avoided the route past the University of Maryland Medical School at Lombard and Greene Streets by six or eight blocks (7, p. 284). This was because he “held it to be manifest that medical students were indistinguishable from demons.” “They lay in wait in dark Greene Street with their dreadful hooks, saws, lassos, and knives, and when they had roped a poor colored man, they dragged him into their den with hellish shrieks, sawed off his

legs and arms, scalped him and boiled down what remained of him to make medicine” (7, p. 284).

The University of Maryland became the first university established on the foundation of a private medical college when, on December 29, 1812, the General Assembly approved a charter submitted by the professors of the College entitled “An act for founding a University in the precincts of Baltimore, by the name of the University of Maryland” (6, p. 3). The new 1812 charter allowed the University of Maryland College of Medicine to annex to itself a College of Divinity (never built), a Faculty of Law, and a College of Liberal Arts. In addition, each college was authorized to appoint seven professors, who also served as a Board of Regents and were charged with setting academic rules and policies but provided with no state funding. Although the two-year University of Maryland School of Law was not founded until 1870, significant efforts were made to found a College of Arts and Sciences in 1814 and again in 1824. In 1830, the University of Maryland, by a new statute, took over Baltimore College but left intact their secondary education program. In 1840, the College of Arts and Sciences was turned over to the directorship of secondary school principal Horace Morrison, who served until 1854, when Episcopalian clergyman Edwin Dample was appointed. Although prior degrees may have been issued, the first known degree was issued to Isaac Brooks in June 1859 (5, p. 97). There were four graduates in 1860, two of whom served in the Confederate service and one in the Union service during the Civil War, but the war devastated the arts college. Subsequently, the College of Arts and Sciences catered to adult learning but had a very rocky history. What had been the Farmers Club in Baltimore became the Maryland State Agricultural Society, a very sophisticated group of gentleman farmers (plantation owners) who helped found the College of Agriculture in rural central Maryland in 1860, which developed into the University of Maryland at College Park (UMCP).

After an adulterous affair with a colleague’s wife in Scotland, charismatic, handsome, Scottish surgeon, Granville Sharp Pattison, MD, left Scotland and spent two years practicing surgery in Philadelphia. In 1821, he moved to Baltimore and became Professor of Surgery at the University of Maryland College of Medicine (5, p. 41). Students admired his charming manner and applauded his dynamic authoritarian lectures in surgery, and he soon became Dean of the Medical College. Dr. Pattison brought with him, and sold to the college for \$7,800, his magnificent collection of 1,000 pickled normal and diseased organs, an anatomical collection that became invaluable in teaching anatomy and later pathology. However, Dr. Pattison so impressed the wives and debutantes of Baltimore society who pursued him that 50 years after he left Maryland, his amours and exploitations of women were legendary. History records that he had taken so much calomel containing mercury for his venereal disease that he was afraid to take hold of a door bell for fear of electric shock (5, p. 41).

In October 1823, the University of Maryland became the first medical school in the United States to build its own hospital, the Baltimore Infirmary, for the clinical training of its medical students (5, p. 43). It was built on an open field on

Lombard Street, about a half block west of Greene Street. The 60-bed infirmary was four-stories tall and built under a 99-year renewable lease at a cost of \$16,690, funded by a loan of \$7,000 from the Bank of Baltimore, with the remainder subsidized by the seven primary faculty. Built in the federalist style, the stately Infirmary included a large operating theater seating several dozen students and had four wards, one of which was devoted to eye patients. Three physicians and four surgeons comprised the staff, and with its immediate proximity to the medical school, it gave the institution advantages not possessed by any other American school of its day. The facility was soon overtaxed and an additional four wards were added, raising the hospital's capacity to 90 beds.

The townspeople of Baltimore were not only proud of their new Medical College, but fondly remembered the Marquis de Lafayette, the French general and statesman, who had inspired the Revolutionary troops and had brought France in on the American side, thereby assuring the success of the Revolution. In October 1824, in the new Medical College Building, today called Davidge Hall, Colonel John Eager Howard, Revolutionary War hero and former governor of Maryland, presided over ceremonies at which the first honorary degree by the University of Maryland was awarded to the 67-year-old Marquis de Lafayette (5, p. 45). The main lecture hall of the medical building, which would seat almost 1,500 people and was the largest classroom in the world (6, p. 6), was fitted with green carpets and red cushions as more than one thousand state and national dignitaries listened to the Revolutionary War hero praise the University "as one of the illustrious flowers of American independence." In 1826, the two-year University had 300 students from many states and awarded 89 medical degrees, the largest class of the next half century.

In 1821, the state authorized the University to hold lotteries and provided a \$30,000 loan at 5% interest, backed by a personal bond from the faculty. By 1826, the privately owned University of Maryland was \$38,000 in debt and the privately owned University Hospital was in default to the Bank of Baltimore when the General Assembly passed the Act of 1826, literally confiscating the private institution and hospital (8, pp. 8–12). Unfortunately, the fight between the faculties of the Medical College and Law School in Baltimore and the governor and General Assembly involved much maneuvering on both sides, resulted in several failed compromises, and lasted 18 years. From 1837–1839, two University of Maryland Medical Schools existed simultaneously in Baltimore, with separate faculty and students, one private and, after its creation by the General Assembly, the other public. Owing to much high-level politicking, even at the Congressional and Supreme Court level (Roger B. Taney from Maryland was chief justice), the Maryland Court of Appeals failed to take action until April 4, 1839, when the Act of 1826, by which the State had the authority to take over private property, was declared unconstitutional. Finally, an act of restitution was passed by the General Assembly, and titles to the University and its Infirmary were transferred back to the Faculty Regents in Baltimore on April 10, 1839 (8, pp. 8–12). At that time, the Medical College was valued at \$150,000 and the Arts and Science building on Mulberry Street at \$87,000, with about

\$18,000 in cash and bonds that had been held by the state-appointed Trustees. Nevertheless, the long crisis and legal battle had taken its toll on the faculty, including Dr. John Davidge, who died in 1828, at the height of the crisis.

By 1850, the medical profession in America consisted basically of three groups: those who had studied at the medical schools in Boston, New York, Philadelphia, or Baltimore; those who were products of the preceptor system, whereby young men apprenticed with an established physician for usually three years; and those who simply took the title of doctor without any special training or credentials (2). However, the Board of Regents of the new University of Michigan, in the village of Ann Arbor, created a medical school in 1850, built around its Chemistry Building and Science Department, that had no hospital for 25 years, but involved local physicians and their patients for clinical training. Also in 1850, the first medical college for women, the Medical College of Pennsylvania, was founded in a three-story building on Arch Street in Philadelphia. Ann Preston, MD, of the class of 1852, became the first woman to hold a professorial chair in a medical school and the first woman dean of Women's Medical College. She also founded the Women's Hospital of Philadelphia to ensure that women physicians, who were barred from the city's other hospitals, had access to practice medicine. In 1992, the Medical College of Pennsylvania (MCP) became part of Hahnemann University, where I was on the faculty from 1977–1991. Because of irresponsible leadership, the medical school failed financially during the 1990's, and in 2002 became the Drexel University School of Medicine—in the tradition of MCP Hahnemann.

Elizabeth Blackwell (1821–1910) was the first woman in America to become a physician (9, 10). The graduation exercises of the Geneva Medical College, founded in 1836 but with predecessors dating back to 1809, were held in the Geneva Presbyterian Church in Geneva, New York, on January 23, 1849. After nearly 100 men had received their degrees, a self-possessed young lady of 28, who had been born in England, walked up the aisle to receive her diploma, the first medical degree in America to be awarded to a woman. Even after reading medical books and having private instruction, she had been refused admission by several medical colleges before being accepted by a vote of the students and faculty of the two-year Geneva Medical College. Though considered somewhat of a freak by the local residents, "her cool detached efficiency and independent spirit eventually won the respect of the men students and the faculty" and she graduated as the top student in her class (9). Dr. Blackwell became the first woman to intern at an American hospital, and with her sister, Emily (1826–1910), founded the first school of nursing in the United States. In 1857, despite much opposition, she established the New York Infirmary, which was staffed entirely by women, and added a program of medical education for women (9). In 1869, she moved to England, where she had been born, and became the first woman to enroll on the Medical Register of Great Britain. There, she founded an infirmary and the London School of Medicine for Women, for which Emily served as dean and professor.

Rebecca Lee became the first black woman to earn an American medical degree, which she received from the New England Female Medical College in Boston on March 1, 1864.

The successor to the Geneva Medical College, a part of Hobart College in Geneva, New York, was the Syracuse University College of Medicine in Syracuse, New York (10). In 1871, after the founding of Syracuse University in 1870 as a Methodist Church-related institution, five professors from Geneva Medical College approached the Onondaga Medical Society proposing the transfer of the medical library and pathological museum from the Geneva Medical College to the new Syracuse University for \$2,000 (11, p. 7). Most medical training at the time consisted of three years of working under a physician and attending three 16-week terms of lectures. However, the Syracuse-area physicians in the Medical Society felt the new medical college should be inaugurated on a modern and correct pedagogical basis, with high standards, including a general knowledge of all the sciences related to medicine and three years of college, such as those adopted in 1859 by Northwestern University and in 1871 by Harvard University (10). By 1911, Syracuse Medical College had achieved a national reputation due largely to the efforts of its voluntary part-time faculty who had helped with financial support for the college as it brought improved healthcare to their patients. Herman Weiskotten, MD, became dean in 1922, and the school flourished under his leadership from 1922 to 1951. Following the Hopkins model, the first step toward a modern medical center was taken in 1929 when Syracuse Memorial Hospital was built by public subscription as a voluntary hospital of 340 beds. In 1936, President Franklin D. Roosevelt, former governor of New York State, laid the cornerstone for a new Medical College building on Irving Avenue between Yates Castle, home of the Syracuse University College of Journalism, and the Syracuse Memorial Hospital. Major upgrading of the faculty, with an emphasis on research, took place in the early 1940's due to the addition of year-round accelerated classes to meet the physician needs of World War II.

On July 1, 1946, I enrolled as the first graduate student in the new Division of Medical Sciences of the Syracuse University College of Medicine and Graduate School and benefited greatly from its outstanding faculty. In late August 1950, I received the first and only PhD degree in Biochemistry and Physiology awarded through the College of Medicine and the Graduate Division of Syracuse University. The medical college was one of the two private medical schools purchased in 1949 by the new State University of New York (SUNY) educational system, which had been founded in 1948, and it became the SUNY Upstate Medical Center at Syracuse. The second, Long Island School of Medicine, became Stony Brook. However, during its initial year of operation, 1949–1950, it was operated under contract by Syracuse University, and I received \$2,700 as a Teaching Fellow in Biochemistry. Thus, my PhD degree in Biochemistry and Physiology, with minors in Endocrinology (hormones and steroids) and Nutrition, was granted, within about four years of my enrollment, at the end of August 1950 by Syracuse University; whereas all subsequent graduate students took five or more years and received their degrees from

the SUNY Upstate Medical Center. However, I kept a very rigorous schedule and studied from 8:30 am to 10:30 or 11 pm daily, and a half-day on Saturdays and on Sunday evenings.

The University of Maryland School of Medicine in Baltimore remained independent and privately operated until 1920 when it, along with the other professional schools in Baltimore, Pharmacy, Dentistry, Nursing, and Law, and the University of Maryland at College Park became part of the state-supported University of Maryland under one Board of Regents.

In 1875, the Medical Alumni Association was founded as an independent charitable organization dedicated to supporting the private University of Maryland School of Medicine and Davidge Hall. On January 10, 1929, Association President, Charles R. Edwards, MD, class of 1913, signed an agreement to purchase Davidge Hall from the State of Maryland for \$22,500; it was then the college library, at 519 West Lombard Street. The purchase was to be secured by 6% bonds issued to alumni, faculty, and friends (12). Books, supplies, and stationery were then ordered for a new University Bookstore. Subsequently, the Association entered into a lease agreement to open a cafeteria and lunch business in the basement and provide some student living quarters there also. William “Bill” Headley, class of 1954, a vascular surgeon in Milledgeville, Georgia, has commented that he roomed in the old college library basement and ate his meals at Carl’s Cafeteria.

On September 1, 1950, I joined the faculty of the University of Maryland School of Medicine in Baltimore, Maryland, as an Assistant Professor of Biological Chemistry. Public opposition to the dissection of dogs was still very active in Baltimore in November 1944 when Dr. Alfred Blalock, chief of surgery at Johns Hopkins, with Dr. Helen Taussig, a pediatric cardiologist, developed a surgical procedure on dogs for correcting a heart defect in newborn “blue babies,” with the first successful surgery taking place on a one-year-old child. One of the first stories I heard about, after joining the faculty at the University of Maryland, was how Dr. Blalock later on found it necessary to parade several surviving healthy children across the stage at a public meeting and state how these children would not be here today if he had not been able to develop the surgical technique on dogs.

In 1953, I was promoted to Associate Professor and became a member of the Medical Faculty Board, and additionally gave two lectures on “The Biochemistry of Pregnancy” to the junior medical students and lectured on “The Chemistry and Physiology of the Steroid Hormones” to Post Graduate Physicians. In 1957, after seven years of very extensive teaching involving over 60 hours of lectures each year and minimal research, I left to be closer to patient care, becoming Clinical Chemist and Director of Laboratories at Syracuse Memorial Hospital (340 beds), the larger of the two hospital units of the SUNY Upstate Medical Center (University Hospital had only 100 beds).

Shortly after I left the University of Maryland in 1957, the old library and University Bookstore building, with Carl’s Cafeteria and some student living quarters in the basement, was razed to make room for a new Health Sciences Library further south on Greene Street. At that time, the Board of Regents

transferred the name Davidge Hall to the original Medical College Building, built in 1811–1813, in honor of the School's founder and first dean, Dr. John B. Davidge.

It was recognized, as early as 1954, that the 140-year-old timber underpinnings of the original School of Medicine, renamed Davidge Hall in 1960, had deteriorated and needed restoration. In 1954, George Yeager, MD, class of 1929, Professor of Clinical Surgery, and William Triplett, MD, class of 1911, the first Executive Director of the Alumni Association, collaborated on a resolution urging the University of Maryland Board of Regents to take action and, failing that, to have the Alumni Association raise the money (12). Sixteen years later in 1970, a resolution by the Maryland House of Delegates charged the University of Maryland Medical Alumni Association to raise \$400,000 for the restoration of Davidge Hall. The work was started in 1977, but the tower required a new steel beam understructure and was not completed until 1982, at a cost of \$1,500,000. Restoration of the roof and skylight was completed recently and it was found that the original cedar roof had survived for a longer period of time than either of the two metal roofs added later. Today, Davidge Hall, fully restored to its original grandeur, serves as the home of the Medical Alumni Association. In April 2004 I attended the reunion of the class of 1954, the first class to which I had taught Biochemistry in 1950–1951. Of the 96 graduates in the class of '54, 60 of the 66 remaining graduates were present at their 50th reunion in Davidge Hall and the luncheon that followed at Westminster Church, which I attended on April 17, 2004. Today, the professional schools in Baltimore, dominated by the Medical Center, are referred to collectively as the University of Maryland at Baltimore (UMB) and cover 17 city blocks and 50 acres of land.

In May 1974, Davidge Hall was listed on the National Register of Historic Places and was declared a National Historic Landmark by the U.S. Department of Interior in fall 1997, exactly 185 years after it opened for classes (13). For almost 200 years, Davidge Hall was shaded by an English elm that had survived the Dutch elm disease plague that felled millions of east coast elm trees. However, the "Davidge Elm" finally succumbed to old age and disease, was deemed unsafe for neighboring buildings, the city traffic, and pedestrians, and was removed in December 2001 (14). Fortunately, cuttings had been taken and cultivated by a nursery in Virginia, some of which are now over 6- to 8-foot tall, and some day, one may be transplanted to the campus.

After World War I came the "roaring twenties"—with Prohibition and bathtub gin—and alumni returning to campuses, such as College Park, dressed in fur coats and in open model T Fords, and collegiate came to mean not education, but a way of life, "an ideal of insouciant gaiety" (5, p. 291). When I joined the faculty at the University of Maryland School of Medicine at Baltimore (UMB) in 1950, the University of Maryland at College Park (UMCP) had the reputation of being a party school and a university of bricks and mortar with an outstanding Physics Department and a top-notch football team. As a faculty member at UMB, I could purchase faculty tickets and we attended several basketball and football games at College Park. Fortunately, after World War II, a generation of serious, dedicated men and

women, who had spent up to five years fighting the war in Europe and the South Pacific, received their education under the GI bill. Because we taught a "briefer" Biochemistry course to the Pharmacy students in the fall, it made preparation easier for the 25 physiologically (clinically) oriented Biochemistry lectures I taught the medical students in the spring semester of 1951. We only had 96 medical students, and because each half of the class spent three hours in Biochem Labs two afternoons each week, I was able to learn all of their names by the end of the first week. The medical students were totally amazed and a little intimidated because they had hoped to stay anonymous, and if their grades were borderline, be given the benefit of any doubts. I also gave four lectures to the nursing students in the summer, and we had the graduate students year round, thus I was never able to carry out as much research as I would have liked. We had a number of graduate students who worked full-time at the Army Chemical Center in Edgewood, Maryland, and I directed one PhD and five master's degrees students during my tenure at Maryland. Also, I spent my month of vacation in August 1956 attending Radioisotope School at Oak Ridge, Tennessee, where we lived in a cabin at Norris Dam State Park. In the fall, I also taught a new graduate course in radioisotopes, but left the University of Maryland as of July 1, 1957.

Early in 1953, the Middle States Association of Colleges and Secondary Schools found five serious problems in the reaccreditation of the University of Maryland at College Park. Among the five critical issues, one involved central authority and another, the status and salaries of faculty, including those at the Medical School. Dean H. Boyd Wylie retired as of June 30, 1955, and William "Bill" Stone, MD, a recently retired Army colonel in charge of Walter Reed Army Medical Center, became Dean. The Faculty Board of the Medical School had been made up of departmental chairman, but departments could now elect additional members, proportional to their size, and I became an elected member of the Faculty Board as of July 1, 1955.

Although the University of Maryland had always lived in the shadow of Johns Hopkins, by 1953 the attitude of the general public toward the University of Maryland had become one of wanting excellence for their state institutions, as fostered by editorials in the *Baltimore Sun*. As a result, Harry Clifton "Curley" Byrd, the powerful bachelor's degree football coach, former Dean of the Agricultural College and President of the University of Maryland at College Park since 1935, was forced to resign in January 1954. The Board of Regents then asked Dr. Thomas B. Symons, recently retired Dean of Agriculture and Director of Extension, to take over temporarily. The Board, recognizing the need for a strong academic leader, but feeling the pressure by many alumni and Marylanders who strongly supported college sports, selected Wilson H. Elkins, PhD, as the new president. Dr. Elkins was the 45-year-old president of Texas Western College in El Paso, Texas, who had been an all-American football quarterback at the University of Texas, earned eight varsity letters in sports, served as president of the student body, was elected to Phi Beta Kappa, had earned both bachelor's and master's degrees in four years, and had been a Rhodes Scholar at Oxford—rather impeccable and outstanding credentials!

In 1950, Byrd's Democratic choice for governor, Preston Lane, lost to Theodore Roosevelt McKeldin, who had become the first Republican Governor of Maryland since 1895 (5, pp. 360–362). Thus, the reaccreditation reports became a major political issue in the election for the governorship of Maryland, where we had moved on September 1, 1950. Although Preston Lane won the Democratic nomination by a vote of 163,324 to 159,230, perennial candidate George Mahoney, a paving contractor whose slogan was "Your house is your castle," kept the election tied up in recounts and court litigation until the middle of October. As a result, the *Baltimore Sun* switched its support to the Republican Governor. Although the Democratic Party swept most offices in the election, Governor McKeldin was reelected by a vote of 381,000 to 319,033 for Lane (5, p. 363). Subsequently, both the University of Maryland at Baltimore (UMB) and University of Maryland at College Park (UMCP) received additional funding, with major academic reorganization and improvements.

After leaving Maryland in 1957, we did not live in the area again for 36 years. In 1993 we moved to the Charlestown Retirement Community in suburban Baltimore, where we have received extensive medical care through both the University of Maryland Medical System and Johns Hopkins Medicine.

By 2004–2005, the University of Maryland Medical System (UMMS) occupied 17 city blocks and had a \$530,000,000 budget of which only \$30,000,000 came from the state. This information was presented in 2004—in a talk to the alumni at the 50th reunion of the class of 1954—by Donald Wilson, MD, dean of the University of Maryland School of Medicine from September 1991 to September 2006, and the first black dean of an American medical college. Half the physicians in the State of Maryland are University of Maryland graduates. Frank Rapoport, MD, class of '60, whom I taught as a freshman medical student, retired as Executive Director of the University of Maryland Medical System in 2004. In November 2005, Dr. Timothy J. Babineau, formerly of the Boston Medical Center, was appointed senior vice president and chief medical officer, and Leonard Taylor, Jr., was appointed as vice president of facilities management for the downtown University Hospital and medical school, which has 655 beds.

The University of Maryland, with its affiliated institutions, which includes Kernan Hospital, the adjacent modern VA Hospital, built in 1992, the Maryland General Hospital, and Montebello Hospital, among others, as well as very large outpatient facilities and specialized treatment centers, has a total of 1,955 beds.

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Chapter 6

Faculty of the University of Maryland from 1950 to 1957

On September 1, 1950, I joined the faculty of the University of Maryland School of Medicine in Baltimore, Maryland, as an Assistant Professor of Biological Chemistry, where I taught the medical students (25 lectures and laboratory supervisor), the pharmacy students, nursing students, and graduate students.

The Dental College was built in 1923 as a three-story Roman Renaissance Revival building at 31 South Greene Street, but in 1929 a new academic building with attached clinical dental facilities was built at the southwest corner of South Greene and Lombard Streets. Thus, the six-year-old classical structure became the Pathology Building of the medical school (1). The Department of Biological Chemistry on the third floor had direct access by a six-foot steel bridge into Anatomic Hall where we held our laboratory conferences, but most lectures were given in the Administrative Hall, located to the east of the historic structure. Anatomic Hall on the upper level and Chemical Hall on the lower level of Davidge Hall were very large, each seating almost 1,500. Anatomic Hall had unusual acoustics and I used to say, "It is the only place where I ever heard my own lecture." Several years ago, I mentioned this to the executive director of the Medical Alumni Office, who said that students in corrective speech therapy come there to practice.

I started my academic duties as Assistant Professor of Biological Chemistry at the University of Maryland School of Medicine after Labor Day 1950. We parked our cars for \$52 per year on the Redwood Street Law School parking lot, where the School for Social Work now stands. Adjacent, on the east side of Greene Street, were the Bressler Building, the Pathology Building, now the Dental Museum, and the historic Davidge Hall at the northeast corner of Greene and Lombard. The Departments of Anatomy, Physiology, and Pharmacology were located in the Bressler Building, with an Animal Farm occupying the roof of the building. Pathology occupied the first floor of the Pathology Building, Microbiology the second, and Biochemistry the third floor, which included office research labs for the staff and a large teaching laboratory with adjacent stock room for glassware and biochemicals. The second-year medical school course in clinical pathology was taught at the University Hospital, as was a new first-year Introduction to Medicine course. Junior medical students did home deliveries of babies for the needy throughout the city of Baltimore.

Dr. Emil G. Schmidt, the Chairman and Professor of Biological Chemistry, had an office that opened to our Departmental Library, where we ate our brown bag lunches. A door at the south corner of the Library was connected by a short 6-foot steel bridge to an entrance door into the Anatomical Amphitheater in Davidge Hall, which made it very convenient for attending the discussion meetings for our laboratory sessions. The Biological Chemistry Department at Maryland was invited to present an educational program on television in the late fall 1950. I remember spending many hours working up and practicing a program to educate the public on the importance of diabetes. At that time, there were only two Baltimore TV channels, and it was 1953 before we purchased our first television set, which was black and white, as color TV didn't become available until the 1960's.

Dr. Schmidt had received his PhD in Biochemistry from the University of Wisconsin in 1924 and became a pioneer clinical chemist at Mercy Hospital in Baltimore. Starting in the middle 1920's, Dr. Schmidt published several papers on diabetes tying together the basic biochemistry of diabetes and the earliest treatment of patients with commercial insulin (Eli Lilly & Co in 1926) and described the biochemical aspects of hypo- and hyper-diabetic shock and coma. Later, he joined the Department of Biological Chemistry at the University of Maryland on a part-time basis, until he joined H. Boyd Wylie, MD, full time in the Department in the middle 1940's. After Dr. Wylie became Dean of the School of Medicine in 1949, Edward J. "Ed" Herbst, a PhD from the University of Wisconsin, joined the staff in 1949, and I joined the staff in 1950.

Biochemistry was taught during the spring semester, with a less concentrated course offered to the Pharmacy students in the fall. The five lectures per week for 15 weeks, a third of which I gave, were presented in East Hall, which was just to the east of Davidge Hall. Once while lecturing, I remember accidentally stepping off the foot-high platform and stepping back up without ever missing a word. I wrote out on the chalkboard the chemical structures of body constituents and related structure to physiological function. I never knew until a few years ago when my ear, nose, throat surgeon friend, Dr. Anthony Hammond [class of '57; Fellow of the American College of Surgery (FACS), which takes 7 years of training], told me that I was known as "the fastest lecturer in the college." Later on, I lectured from slides, but always followed an outline so that if a

student missed a point, he or she could maintain continuity. Although West and Todd was used as a text, no exam questions were asked on material not given in lecture. Some questions required essay answers, and I got to be very good at deciphering hand writing, which was often very poor, like many written prescriptions.

Virginia "Ginny" Brown, a bachelor's-degree instructor, prepared the reagents for the laboratory exercises with one-half of the medical students having biochemistry labs on Monday and Thursday from 1–4 and the other half on Tuesday and Friday 1–4. The groups were reversed for the afternoon Physiology Lab sessions, with the entire class having Wednesday afternoons free. I didn't have much to do during the first labs, so I conversed with each student about where he or she went to college or completed their pre-med requirements as many were World War II veterans up to 47 years of age who returned under the GI Bill. The preponderance of the class were males and we always had three or four excellent students from Utah and the Rocky Mountain states, where there were very few medical schools. These students were usually Mormon and had usually served as missionaries for two years between their sophomore and junior years. I learned recently that these students paid a higher tuition rate, as did all out of state students (\$750/yr instead of \$500) (2).

The distinguished psychiatrist, Dr. Jacob "Jake" Finesinger from Harvard, had arrived at Maryland in 1949, and a new innovative Institute for Psychiatry and Human Behavior of 185 beds was built on West Redwood Street, which opened in 1953 (3). The first-year medical students starting in fall 1950 took a two-hour-per-week Saturday morning course in Introductory Psychiatry.

Initially we had about 96–100 medical students per class, but later on the class size was enlarged to about 120. My 25 lectures to the medical students each spring semester included Spectrophotometry, Nutrition and Basal Metabolic Rate (BMR), Nucleoproteins, Steroids, Water and Electrolyte Balance, Acid–Base Balance, and two lectures on cancer, among others. The cancer lectures were the only ones I didn't have to update every year because little changed in cancer chemotherapy until more than 10 years after I left Maryland in 1957. In my lectures, I interrelated basic biochemical and physiological interrelationships and, where possible, pointed out their role and relevance in clinical medicine.

My mentor at the Syracuse University Medical College, W. W. Westerfeld, PhD, wrote and published a booklet in 1948 devoted to body electrolytes (sodium is the main cation in the vascular system and potassium within all body cells) and body acid–base balance as controlled by the lungs and kidneys, which I was required to become expert in. Dr. Schmidt had been teaching the concentration of the cations, sodium and potassium, in outmoded mg % units, which I was not familiar with. Hence, I talked to Fred Ferguson, PhD, Associate Professor of Physiology, and we agreed to switch to Gamble Diagrams and the expression of electrolytes in mEq/liter, as is done today. As a result, the clinical staff of the medical school and the hospital soon updated as well. We were aided and supported by the University Hospital clinical chemist, Associate

Professor Marie Andersch, PhD, and her chief, Milton Sacks, MD, PhD, Professor of Clinical Pathology and Director of Clinical Laboratories at University Hospital, who changed their hospital clinical laboratory patient reports. Dr. Sacks was a cofounder of the Rh Typing Laboratory at University of Maryland, which opened in 1945, one of the first in the nation.

I gave the initial lectures for the Biochemistry labs on the principles of spectrophotometry and the measurement of the colored end products developed by adding reagents to Folin Wu filtrates for measuring various constituents in blood, such as glucose, blood urea nitrogen (buns), and uric acid, etc. Our labs were equipped with about ten DuBoscq colorimeters for visually color matching an unknown with a standard and about ten Klett-Summerson photoelectric spectrophotometers, which used one of three glass filters to read the standard and the unknown solution at the proper wave length band. The latter instrument had been invented by William "Bill" Summerson, PhD, of the Army Chemical Center at Edgewood in northeast Maryland and was manufactured by the Klett Company of New York. The instrument read directly in Klett units and also, because of its reasonable cost of about \$400, became widely used by clinical laboratories after World War II ended in 1946. However, Bausch and Lomb spectrophotometers were also popular and eventually replaced our DuBoscqs. Bill Summerson was a guest lecturer in Biochemistry and gave two lectures on nerve gas poisons each year to the medical students. As I recall, the main poison gases were mustard gas, which attacked the lungs and was used by the Germans in World War I, phosgene (carbonyl chloride), which also attacks the lungs, and the nerve gas, diisopropyl fluorophosphate (DFP), which paralyzes the central nervous system. DFP acts by tying up the phosphate group on a molecule of serine that forms the active center of the enzyme, cholinesterase, and quickly produces death. A smaller molecular form of the gas is O-isopropylmethylphosphonofluoridate and thousands of tons of the gas, under the name Sarin, which had been stored in tanks since World War II at the Aberdeen Proving Grounds in northeast Maryland, were destroyed in March–April of 2005.

In the Biochemistry Laboratory, the students learned to perform routine urinalysis and utilize the basic principles of spectrophotometry for quantitating colored reactions to measure total nitrogen in urine; carry out two methods of blood glucose analysis and perform fingerstick glucose tolerance tests on themselves; measure blood urea nitrogen (buns), the main test for kidney disease, and the determination of blood NPN (non protein nitrogen); how to test for carbon monoxide poisoning; carry out two methods for measuring bilirubin; perform gastric analysis; measure a simulated BSP liver function specimen; and performed the phenolsulfophthalein (PSP) dye excretion test for kidney function on themselves. One year we forgot to forewarn the students we were going to inject them in the arm with PSP dye and we had several who got woozy. Thus, first-year medical students became familiar with all of the common clinical laboratory chemical tests and their applications. Junior and senior medical students, interns, and residents were required to perform urinalysis, specific tests for glucose and ketone bodies found in the urine of diabetics, and to stain

culture smears in small labs located on the large hospital wards. By the 1960's, Al and Helen Free had developed a commercial dipstick system (Ames Company) for measuring these constituents in urine. However, the microscopic examination of urine for sediment, crystals, cells, and etc., still required centrifugation of a 10-mL aliquot of urine and decantation of all except the last drop, which was placed on a microscope slide.

The distinguished John C. Krantz, Jr., PhD, who as a pharmacist, had discovered and patented several useful anesthetics, was Chairman and Professor of Pharmacology. Each year, he held a Christmas Party on campus to which all basic science faculty were invited, as well as selected clinical faculty. Even Governor McKeldin attended, with whom John had written a book on *The Art of Eloquence*. In December 1950, I sat across from Monte Edwards who was an MRCS (Member of the Royal College of Surgeons and had no MD degree), which he earned in 1917, and was a Clinical Professor of Surgery at Maryland. He turned to me and asked "Are you a DPh or a doctor?" The ironic part is surgeons in England are addressed as Mr. and you insult them if you call them "Doctor." As a matter of fact, British physicians receive a Bachelor of Medicine and a Bachelor of Surgery degree, and it requires an additional year with completion of a research thesis to earn the MD degree, which the PhD degree outranks academically. In 1950, Syracuse University awarded the Bachelors degrees, the Bachelor of Laws degrees, the MD degrees, the Masters degrees, and finally the ten or so PhD degrees, including mine, the ultimate academic doctoral degree. However, physicians have become so commonly referred to as "doctor" over the past half century that I gave up long ago trying to explain. In 1954, Henry J. L. Marriott, BA (Oxford), MA, BM, BCh 1944, who was an Associate Professor of Medicine at Maryland, wrote a book on physical medicine and asked the Medical Faculty Board, of which I was an elected member, to take steps toward granting him an honorary MD degree, but his request was refused by the Board.

Eduard Uhlenhuth, Professor and Chairman of Anatomy, who received his PhD from the University of Vienna in 1909, with his long, flowing white hair, was "the great white father" to the entire faculty, and everyone practically bowed down when they encountered him. Dr. Uhlenhuth retired shortly after I arrived, and Frank Figge, PhD, who had a major interest in porphyrins (red blood pigments in the urine), became the new Chairman of Anatomy. At that time, Maryland students were spending more credit hours in Anatomy than were students in any other medical school in the United States. John Wagner, MD, who was Professor of Neuroanatomy at Maryland, had a sign over the entrance doors to his laboratories which read, "The best brains in the University pass through these doors," which of course subsequently either got dissected or fixed in formaldehyde.

In the early hours of August 20, 1952, a black Chrysler sedan rolled down Taylor Avenue toward Bel Air Road and then suddenly veered off the road, hit a tree, and turned over on its right side (a stone had been placed on the accelerator of the car, which had an automatic transmission). Two nearby Baltimore County police officers, sitting in their patrol vehicle sipping

coffee, raced to the vehicle and discovered the body of Mrs. G. Edward Grammer jammed under the dashboard. How well I remember reading about the event and all of the subsequent news articles about it, one of which I retained. Dr. Russell "Russ" Fisher, the state of Maryland Medical Examiner, soon concluded that her wounds were inflicted before the accident and said, "Murder—no ifs, ands, or buts." Convicted of first-degree murder, G. Edward Grammer, a metals company executive, was executed on the gallows on June 11, 1953. In 1955, Russ Fisher and I were among the youngest departmental representatives on the Faculty Board of the School of Medicine. Prior to his early sudden death from a heart attack, at about the age of 65 in the 1980's, Dr. Fisher established himself as one of the leading medical examiners in the United States and trained a generation of pathologists in proper autopsy technique. He was one of five pathologists who investigated the murder of President John F. Kennedy, Jr., in 1962.

At the faculty evaluation of the lower division of medical students in June 1952, there was a lot of concern expressed by the faculty. Although most of the students had excellent academic records, there were about a half a dozen who were border line. Because some of these student were the same students we had penalized for skipping a lab session in Biochemistry to study for a Physiology examination, we felt somewhat intimidated and although the second-year faculty had concerns, the decision was made to promote them. This was a big mistake because in June 1953, six junior medical students were required by the clinical faculty to repeat their junior year. It should be pointed out that this took place about the time the accreditation of the University of Maryland at College Park, under its bachelor's degree president, the former governor, Harry "Curly" Byrd, became a political issue and academic standards were brought into question.

In the 1950's, I read *Chemical Abstracts* routinely to keep up on the literature and the latest developments. In 1953, I learned about the newly proposed Watson-Crick double helix three-dimensional structure for desoxyribonucleic acid (DNA), the most significant discovery of the 20th century since DNA is made up of chromosomes and transmits our hereditary traits and characteristics. However, the nucleoproteins making up DNA were first isolated, analyzed, and recognized as unique macromolecules in 1869 by Friedrich Miescher, MD, of Basel, Switzerland, and Victor Myers, PhD (1883–1948). In the 15 years of his scientific career devoted to this field, from 1910 to 1925, Dr. Myers described in great detail the chemical nature of the nucleoproteins and nucleotides. Because I was already lecturing to the medical students on the fundamental base pairings of the nucleotides making up DNA, I immediately had a slide made of the Watson-Crick double helix structure and required the medical students to learn the four fundamental nucleotide pairings, whose combinations into different sequences make us all different. The entire scientific community soon recognized the importance of this replication for understanding immunology as well as human genetics, and only 10 years later the double helix structure was pictured in my oldest daughter's 7th grade science book.

Rosalind Franklin, PhD (1920–1958), a young Britisher, in 1952 conceived of and captured the “B” form of DNA on x-ray film as “Photograph 51.” This three-dimensional photograph, acquired through 100 hours of x-ray exposure from equipment she had refined, revealed the structure of DNA and how all life on earth is passed down from generation to generation. Unfortunately, Dr. Franklin passed away at age 37 from ovarian cancer, which may or may not relate to her extensive x-ray exposure as a crystallographer. Because of her early death, she never participated in the Nobel Prize awarded in 1967 to her mentor at Kings College in London, Sir Maurice Wilkins.

In 1962, Sir Francis Crick (1916–2004), James Watson of Indiana University (1928–), and Britisher Maurice Wilkins (1916–2004) were awarded the Nobel Prize “for their discoveries concerning the molecular structure of nucleic acids and its significance for information transfer in living materials.” Thus, the new sciences of Molecular Biology and Molecular Genetics, as well as Immunology, began producing tremendous technological advances. These advances include DNA “fingerprinting,” which has revolutioned forensic science and criminal law, and an expanded array of new drugs including the manufacture of human insulin. In 1998, we learned of the artificial production of “Dolly,” a cloned sheep. In April 2003, American researchers produced the final sequence of the mapping of the human genome (genes), creating the “Genomics Revolution”. It has been hailed as “the first great technological triumph of the 21st century.” It is now entirely in the public domain, as the vested commercial interest, Celera Genomics Group, found by April 2005 that they could not sell their mappings because they also had been developed and made freely available to the public by the National Center for Biotechnology Information, a division of the National Institutes of Health (NIH). It is now estimated that there are only about 20,000–25,000 human genes, about the same number of genes as a small flowering plant or a tiny worm, and a significant drop from the 30,000–40,000 originally estimated. The next phase is for our scientists to make discoveries that will correct metabolic defects, create new drugs, and make new developments utilizing the information about the human genome. The National Institutes of Health, under their director, Elias S. Zerhouni, MD, former Vice President for Research of the Johns Hopkins University School of Medicine, are playing the lead role in this effort, both in terms of leadership and funding, with several new multimillion-dollar programs announced in December 2005.

During the 1940’s, Tadeus Reichstein, PhD, of Switzerland, and Edward C. Kendall, PhD, of the Mayo Clinic, isolated several adrenal cortical steroids and established their multi-carbon-ring (steroidal) basic structure as derivatives of cholesterol. During World War II, Merck and Company worked on synthesizing cortisone (compound E) from desoxycholic acid, which occurs in the bile of mammals. In 1948, Kendall received, from Merck, some of their small supply of compound E and with his clinical colleague, Phillip Hench, MD, found cortisone to have a profound effect on rheumatoid arthritis, the crippling form of the disease. In 1950, Drs. Reichstein, Kendall, and Hench received the Nobel Prize for their achievement, which was the first demonstration of its anti-inflammatory activity clinically.

However, it was 1954 before cortisone was actually isolated from adrenal tissue. Compound E (cortisone) and compound F (hydrocortisone) are interconvertible in the body, as the reaction involves purely a reduction of a ketone group at position 11 of the steroid nucleus to a hydroxyl group by adding two hydrogens. Compounds E and F are made in the adrenal cortex (outer layer of cells) from cholesterol and have been shown to increase blood glucose, increase protein catabolism (breakdown), and inhibit allergic and inflammatory reactions. Because aspirin releases cortisone, it has been called “the poor man’s cortisone.”

In my lectures to the medical students, I demonstrated cholesterol by use of a wooden ball and stick model (like a tinker toy), and labeled, on a blackboard, the positions of the steroid nucleus. I taught which functional groups were present on the steroid nucleus in which numbered positions for the adrenal and sex hormones and the role progesterone and the estrogens played in the menstrual cycle and pregnancy. Starting in 1955, I gave two lectures on “The Chemistry and Physiological Effects of the Steroid Hormones” as part of the Postgraduate Physician Continuing Education Program. About the same time, at the request of the new Chairman of Obstetrics, Arthur L. Haskins, MD, I also gave two lectures on the “Biochemistry of Pregnancy” to the third-year medical students.

In 1953, a unique steroid that contains an aldehyde group was isolated and named aldosterone; as a mineralocorticoid it was 300 times as active in its salt effect as cortisol (4). A tumor of the adrenal that produces excess aldosterone is called Conn’s Disease, after the clinician at the University of Michigan who reported the first case. Patients with this rare disorder have hyposmolality (decreased serum sodium) and hyponatremia (decreased urinary sodium), but increased total body sodium. Aldosterone acts by causing the reabsorption of sodium by the kidney, the main cation in the blood, and increases the loss of potassium, the main cation within cells. Because hypertension (high blood pressure) involves the retention of sodium ions, potassium chloride (for example, NuSalt) can be substituted as well as diuretic drugs since they increase urine flow.

The inner center or medulla of the adrenal gland secretes the catecholamines, epinephrine, and norepinephrine, which are responsible for the episodic physiological responses that are summarized by the well-known phrase “fright, flight, or fight.” Hans Selye, MD, of the University of Montreal first described this phenomenon in about 1955. Tumors of the medulla are extremely rare but constitute a type of intermittent high blood pressure that is corrected by surgery. The distinguished Maurice C. Pincoffs, MD, who was Chairman and Professor of Medicine at Maryland when I arrived in 1950, made, in 1929, the first clinical report of a patient with a pheochromocytoma, which was cured surgically by Dr. Arthur M. Shipley, Professor of Surgery. It is the only type of tumor and hypertension (intermittent) in which surgery results in a dramatic instantaneous cure. Dr. Pincoffs, who was the Editor of *Annals of Internal Medicine*, the foremost journal in medicine at the time, retired in 1954 as Chairman and Professor of Medicine. However, Dr. Pincoffs (1886–1960) stayed active by becoming Chairman and Professor of Preventive Medicine and Rehabilitation. He died

almost instantly on December 8, 1960, of a dissecting aneurysm of the heart while lecturing at age 74. It has been said that he diagnosed his cause of death as he died. Theodore E. "Ted" Woodward, MD (1914–2005; class of '38), who had a very impressive World War II record of accomplishments in infectious diseases, was selected as the new Chairman and Professor of Medicine. Ted served for 27 years (1954–1981), and while we renewed acquaintance at the University of Maryland Reunion Day in April of 2004, he passed away at age 90 on July 12, 2005.

In the early 1950's, two substances were isolated from the posterior pituitary gland, which sits under the rear brain area. Patients lacking vasopressin or antidiuretic hormone (ADH) have diabetes insipidus in which they put out tremendous volumes of very dilute urine. The second hormone produced is oxytocin, which plays a role in the contraction of uterine muscles in childbirth and can be administered to promote the process of childbirth. Both of these hormones are polypeptides (very small proteins), each made up of only 10–12 amino acids in a ring structure with a short tail. Vincent du Vigneaud, PhD, Professor of Biochemistry at Cornell University Medical College in New York City, synthesized these two unique structures and received the Nobel Prize in 1955. Proinsulin is a polypeptide of 81 amino acids with an attached C chain, which when activated splits into active insulin (A and B chains), plus a C chain that has no known function and is discarded. Both insulin and the C chain were degraded one amino acid at a time and characterized by Frederick Sanger, PhD, a Britisher. He received a Nobel Prize in 1958 for "his work on the structure of proteins, especially that of insulin" (5). In 1980, knighted Sir Frederick Sanger, became the recipient of a second Nobel Prize for his work with Walter Gilbert of Harvard University "concerning the determination of base sequences in nucleic acids" (6). Both Dr. du Vigneaud and Dr. Sanger were speakers at national meetings I have attended.

I recall vividly in fall 1955 a first-year student from West Virginia named Gregory D. who asked the difference in nutritional content between green olives and black olives. Later on, he dated a bar waitress on Baltimore Street, and after she was propositioned by an out-of-town engineer, he followed the 60-year-old engineer across the street to the lobby of the Hotel Baltimore and slugged him. Unfortunately, the engineer fell, struck his head, and died, and our student was charged with manslaughter. I recall my friend Lester "Les" Kiefer, MD, a Pathology resident, being one of several faculty who testified on his behalf. Gregory served time for manslaughter, but must have been exonerated by the governor as former felons cannot practice medicine and he graduated with an MD degree in 1961, two years after his original class.

I arrived for work one exceedingly cold morning in November 1955 and found Greene Street closed, with fire hoses and ice covering the street in front of the Pathology Building. According to a *Baltimore Sun* newspaper article, "The firefighters were credited with 'doing a wonderful job' in saving valuable scientific equipment, papers and books. Dr. Raymond Vanderlinde, associate professor of biochemistry, said tarpaulins spread over equipment by the firemen saved the material from

water damage." I learned later that the hospital had, the previous day, burned a huge bulk of old records in the incinerator at the rear of our building, resulting in the adjacent smokestack overheating and starting a fire at 12:45 a.m. in the wooden loft above our Biochemistry Department Library and some of our office labs. My only loss was my cardboard slide rule case. Also, I learned that the Salvage Corps, which is employed by the fire insurance companies, had come in and covered, with tarps, our research lab benches, which were filled with dangerous inflammable solvents. Even with state contracts involved, the damage was repaired by the late spring 1956.

The first black students were admitted to the University of Maryland Medical School in fall 1951. Although the faculty was concerned, these students turned out to be no different in their academic capability and background than any other students, and Donald W. Stewart, MD, and Elijah Saunders, MD, were among the first graduates; the latter is a full professor at Maryland today. However, the high schools in Baltimore were not integrated in 1954 and a big sit-down strike took place at Southern High School in 1954.

The University of Maryland was one of the ten sponsoring universities of the Radioisotope Training Program at Oak Ridge, Tennessee, and I spent my month of August vacation in 1956 at radioisotope school. We had reserved an apartment in nearby Kingsport, Tennessee, but upon entering the apartment and flicking on a light switch, the cockroaches scattered in all directions and my wife exclaimed, "I'm not staying here." Next, I talked to Ralph Overman, PhD, director of the program and learned that several couples with children were staying in cabins at Norris Dam State Park about 30 miles away and we car-pooled daily. Most intriguing was that we had to drive through Clinton, Tennessee, daily, where a huge strike was taking place over school integration that made the daily headlines of the nation's newspapers. We had 7 hours of lecture and movies the first day of radioisotope school to prepare us for the laboratory experience with radioisotopes that followed; I had to stand up and walk up and down the outer aisle during the long afternoon session. After receiving a certificate for completion of the four-week course, which qualified me for a radioisotope handling license, I taught courses on radioisotopes both semesters of 1956–1957 at Maryland to the 15–20 graduate students in the basic medical sciences, several of whom were employed at the Edgewood Army Chemical Center. From 1977 to July 1990, I held the radioisotope license for the Clinical Laboratories of Hahnemann University Hospital and provided clinical laboratory training (in vitro testing) for our residents in Radiology.

In addition to my teaching at University of Maryland, I directed five master's degree theses and the doctoral thesis of Frank Vasington, who joined our faculty in 1955. We published about 8–10 papers during this period, including Frank's and my joint chemical studies on the oxidation of stilbestrol in alkali in the *Journal of the American Chemical Society* (7). During my first fall at Maryland, I had continued the ether extractions, but had an accident. While redistilling the recovered ether in the proper manner, I made the mistake of refilling the container while it was hot, and it boiled up over the top of the flask and

water bath, striking the electric hot plate, and ignited. I proceeded to push the liter bottle of ether I was holding into the hood, where the flames shot up the exhaust hood, but all I suffered was a slightly singed finger. This is the only laboratory accident I ever had even though I worked with several very hazardous and explosive chemicals, including peroxides, in attempting to synthesize a structure similar to the incompletely identified compound I had isolated, which had promising biological activity. A major pharmaceutical company was interested in pursuing the compound but backed off after they learned my later studies had been supported by a grant from the National Cancer Institute.

Two of my master's degree students turned out to have very interesting careers. Charles B. Leonard, Jr., completed his PhD with my successor, and spent his career on the faculty of the Dental College. After retirement at age 55, Charles learned sign language and became a professor at Gallaudet University in Washington, DC, but commuted daily from his home in Ellicott, Maryland. He recently had lunch with us at Charlestown. Vincent J. Speckhart subsequently earned an MD degree from Flower City Medical College in New York City, which is today New York Medical College at Valhalla in Westchester County, and became an oncologist (cancer specialist) in Virginia Beach in Virginia, where we visited him several times during the 1960's and 1970's. Vincent and his nurse wife are very fine Christians and took care of four foster children in addition to five children of their own. They made their own children live on the same clothing budget as the foster children received from the State of Virginia. From 1966–1968, they served as a medical missionary team for Catholic Missions in Malawi, Central Africa, where Vincent became the Medical Superintendent of the Likuni Mission Hospital. Subsequently, he provided me with a published paper entitled "A Retrospective Study of Diseases at Likuni Mission Hospital." During his three years there, 44,653 patients were processed, with a detailed study of 5,407 patients. He performed over 2,000 surgeries, the most common procedures being cataract and other eye problems, the lancing of abscesses, and Cesarean sections. As one might guess, various types of amebiasis and other GI tract organisms including worms and anemia were the most common medical conditions and occurred in over 26% of the 10,000 patients seen on an annual basis. A very large percentage of the children showed pot bellies, which are characteristic of malnutrition. Triage (separation of the well from the sick) was done by a native assistant they trained so they could spend their time providing care to those needing treatment the most.

Frank Vasington, whose PhD thesis I directed, was my only doctoral level student and took two years of postdoctoral training at Johns Hopkins University, following which he joined the faculty of the Biochemistry Department of the University of Connecticut where he had received his bachelor's degree. He spent his career there near where he grew up.

My mentor from Syracuse, W. W. Westerfeld, PhD, was Acting Dean and Acting President of the SUNY Upstate Medical Center for several years. I had been in contact with him for two or three years about the possibility of returning as Clinical Chemist for the 340-bed Syracuse Memorial Hospital, the main teaching

hospital of the Upstate Medical Center. Two acute events precipitated the need for a qualified laboratory director; blood for laboratory tests was drawn from the jugular vein (neck) or the femoral vein (upper thigh) of infants, and by mistake the femoral nerve of an infant had been hit, resulting in the infant having a "congenital type hip" in which the child would never walk normally and, secondly, a Blood Bank error had resulted in a fatality. After seven years of academic teaching involving over 60 lectures per year, I was anxious to work in an environment where I could see my efforts directly benefit patient care. After negotiation with the hospital administration, I became Clinical Chemist and Laboratory Administrative Director in charge of all phases of laboratory operations, with William "Bill" Waters, MD, a research pediatrician, as a consultant in Hematology and Blood Banking.

My chief at Maryland, Dr. Schmidt, who had been a pioneer clinical chemist at Mercy Hospital from 1927 until the 1940's, before he joined the Biochemistry Department full time, told me I "was making the biggest mistake of my life and I was going to throw my life away." However, I have never regretted it and my 35-year career in Clinical Chemistry took place during the Golden Age of the profession, which was founded in New York City in 1948. Fortunately, Dr. Schmidt let me spend six weeks, of which four were my annual vacation, training at University Hospital under Marie Andersch, PhD, Clinical Chemist and Associate Professor of Clinical Pathology, who had made a similar switch some years before. In 1957, over half of clinical chemistry testing consisted of blood glucose determinations for detecting or treating diabetes and blood urea nitrogen for detecting and evaluating kidney disease. Marie taught me how to semi-automate the preparation of the Folin-Wu filtrate for these two analytes using Seligson semi-automatic pipettes, which were available commercially. She reviewed with me all the other routine tests and taught me how to trouble shoot them, but advised me "to innovate and be the first to try out the new and the last to give up the old." Secondly, she said, "No matter who enters your office door, they are your equal and address them by their first name whether it is the Chief and Professor of Medicine or a complaining staff physician." Her recommendations were worth their weight in gold and led to my having a very successful and rewarding career in Clinical Chemistry. I also became an Assistant Professor of Biochemistry in Dr. Westerfeld's Department in the adjacent Basic Science Building of the SUNY Upstate Medical Center where I lectured to the medical students and the two-year medical technician students and gave two lectures in each graduate course offered.

In 1949, H. Boyd Wiley, MD, the former chairman and professor of biochemistry, had become Dean of the University of Maryland School of Medicine. In honor of his retirement, as of June 30, 1955, a very large dinner party was held with a life-size oil painting of Dr. Wiley being unveiled at the special occasion. The new dean, Colonel William "Bill" Stone, MD, had been Commandant of the Graduate School at Walter Reed Medical Center. I served as an elected member of the Faculty Board from 1955 to 1957, which he headed, and he impressed me as a very democratic, not authoritarian leader. After I left in August 1957, Dr. Stone sent me a letter thanking me for my

many contributions to the University of Maryland and wishing me well in my return to my alma mater. A University of Maryland School of Medicine Bulletin states, "During his six years (actually 7) at our medical school Dr. Vanderlinde established a brilliant record as a teacher, lecturer, research worker, and participator in local scientific affairs." "Dr. Vanderlinde was very well liked by all the students and his colleagues who regret exceedingly his departure. We all wish him well in his new position (at the Upstate Medical Center)" (8). It was 20 years later before I rejoined academia on a full-time basis, providing both a challenge in Biochemistry and in Clinical Chemistry.

In 1957, after seven years of very extensive teaching involving over 60 hours of lectures each year and little research, I left to be closer to patient care as Clinical Chemist and Director of Laboratories at Syracuse Memorial Hospital (340 beds). In contrast, University Hospital, which became the SUNY Upstate Medical Center, had only 100 beds.

Shortly after I left the University of Maryland in the 1957, the old library and University Bookstore building, with Carl's Cafeteria and some student-living quarters in the basement, were razed to make room for a new Health Sciences Library further south on Greene Street. At that time, the Board of

Regents transferred the name Davidge Hall to the original Medical College Building, built in 1811–1813, in honor of the School's founder and first dean, Dr. John B. Davidge.

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Chapter 7

Chemistry and Medicine

Benjamin Franklin Bache (1792–1864), the great grandson of Benjamin Franklin, who, among his many accomplishments, invented bifocals, earned an MD degree from the University of Pennsylvania in 1814 and greatly influenced 19th century medical teaching. In Dr. Bache's long 43-year teaching career at Jefferson Medical College in Philadelphia, he emphasized to medical students the close relationship between medicine and chemistry and warned his students that they could not be "respectable physicians without being chemists" (1). However, a full century passed before the modern era of clinical chemistry began. For the reader who wishes to read more about the historical past, I recommend Louis Rosenfeld's *Four Centuries of Clinical Chemistry* (2) and for the recent past, *Biographies and Other Essays on the History of Clinical Chemistry*, a collection of 79 articles (3).

In 1989, Samuel Meites (1922–2003) wrote and had published a book on the life story of Otto Folin, PhD (1867–1934), which is titled *America's First Clinical Biochemist*. My copy, a gift from my friend Sam, a contemporary who recently passed away, was inscribed on the cover page, "You did much for clinical chemistry in your career for which I am able to thank you by giving you a copy of this book" (4).

Otto Folin was a young Swedish lad of 15 when he arrived in Stillwater, Minnesota, in 1882 to live on a farm with relatives (4). While needing to work to earn his living, he graduated from high school at age 21 with such a good showing, including some exposure to chemistry, that he was admitted to the fledgling University of Minnesota in 1888. There he worked his way through college, majored in chemistry, became managing editor of the college newspaper, and graduated in 1892. When Otto's college political science instructor, H. P. Judson, became chairman and professor of political science and dean at the newly opening University of Chicago, which had the financial backing of John D. Rockefeller, at least seven members of the University of Minnesota class of 1892, including Otto Folin, entered the new university (4, p. 29). He completed the requirements for the PhD degree in organic chemistry on November 2, 1896, and left immediately for Sweden where he received nine months of training in physiological chemistry, at his expense, with Professor Hammarsten at the University of Upsala, and visited his parents at Aseda. Dr. Folin then spent two months in Berlin, Germany, where an American physical chemist acquaintance told him "physiological chemistry is simply the 'wild and

wooly west' of science and there are vacant claims everywhere." As a project, Dr. Folin decided to continue his work on the Hopkins method for uric acid in urine and compare it with that of his new mentor, Professor Ernst Leopold Salkowski, MD, at the Institute of Pathology in Berlin, which was devoted to the science of urine, with the goal of publishing the results in German in Hoppe-Seyler's *Zeitschrift für Physiologische Chemie*. Within a two-month period, Dr. Folin had to set up and master the details of two analytical methods, perform a large number of analyses on pure solutions of uric acid and on urines from both normal and pathological conditions, complete evaluations, and write a manuscript in German (4, p. 79). Dr. Folin worked 12- to 14-hour days to complete the project and received little help from Dr. Salkowski, who in some ways hindered the project. This paper was very important to Dr. Folin's scientific future and his success in showing the superiority of the American Hopkins method over Salkowski's method was a terrific accomplishment and set the pattern for his approach to clinical chemistry (4, p. 79).

As of October 17, 1897, he borrowed more money and spent an additional year at the University of Marburg, where Albrecht Kossel, MD (1853–1927), who became a Nobel Laureate in 1910, was Director of the Institute and Professor of Physiology. Kossel's main interest was nucleoproteins and nucleotides (from genes) in yeast, and he became a friend who guided Dr. Folin. Although Folin's official mentor was Professor Kutscher, Folin worked on protein cleavage products under Kossel, and Kutscher helped him publish two manuscripts in German. Dr. Folin became secretive about his sideline evening project as he found he could isolate purer compounds than those available from a leading German chemical company, and he decided he would make it a major scientific endeavor in the future. His decision directly influenced my graduate training in which I was required to take Biochemical Preparations and isolate several biochemicals such as glycogen, urea, uric acid, creatinine, etc. Upon his return to the United States in 1898, after training with three eminent professors in Europe, Dr. Folin had difficulty in finding a starting position, especially one that would enable him to marry high school classmate and Vassar graduate Laura Churchill Grant, who had become a school teacher in St. Paul, Minnesota, and pay off a huge debt of \$1657 plus 7% interest owed to his relatives. He hoped to get a job in New York or at Johns Hopkins in Baltimore, but

nothing developed. He worked for a few months at the Columbus Laboratory in Chicago on making a substitute for milk for infants, lectured part-time to high school students on "Food and Dietetics," and married Laura in September 11, 1898 (4, p. 145). About the same time, he was offered a position at the new University of West Virginia in Morgantown, a modern village of 3,500 with sewerage, paved streets, modern hotels, and very inexpensive living, which doubled in size in two years. There he taught courses in quantitative analysis and physiological chemistry for one year, with the university providing a good salary, all the literature he needed, plus \$350 for chemicals and apparatus for research on foods and their relation to animal metabolism.

In spring 1899, Dr. Folin was invited to become the first research biochemist at McLean Hospital in Waverly, Massachusetts, a part of Boston, at an open date and salary. Among those who had recommended him were Russell H. Chittenden, PhD (1856–1943), the first physiological chemist in America and Professor at Yale from 1882–1922, and Henry Bowditch, Professor of Physiology at Harvard, who had introduced thoracentesis, the drawing off of chest fluid, in 1850. Among the brightest of the young students Dr. Folin had taught at Morgantown was 18-year-old Philip A. Shaffer (1881–1960), whom he encouraged to complete college at the end of the summer, go to Harvard for a PhD, and then join him as his assistant at McLean. In the late fall 1899, Otto Folin packed up and returned with his pregnant wife to Chicago, where his daughter, Johana was born the following August. His wife and 2-month-old daughter were left behind with friends in St. Paul when he left for Boston by train on September 27, 1900, to assume his new position at McLean Hospital at an annual salary of \$2,000 per year.

Dr. Folin spent seven of his most productive years at McLean Hospital, a private mental institution, which had its beginnings in the early part of the 19th century conjointly with the Massachusetts General Hospital, which had become the main clinical teaching unit of Harvard Medical School. The new McLean Hospital for the mentally insane was built in 1895, as a model of enlightened care for the mentally ill, on 176 acres of land under experienced visionary Superintendent Edward Cowles, MD. When Dr. Folin arrived in September 1900, McLean had a staff of seven physicians and a neuropathologist, August Hoch, MD, who soon became a good friend (4, p. 154).

As their first research biochemist, Dr. Folin was able to design, equip, and stock his new laboratory and an adjacent library with the best chemicals, apparatus, books, and journals available in America and Europe, with no expense spared. Meanwhile, for the first time in his life, 33-year-old Otto Folin had a 2- to 3-month opportunity to relax, play golf on the hospital golf course, go house hunting with Dr. Hoch, develop a research program, and plan for his family's arrival from St. Paul in early December 1900. After Dr. Folin was unsuccessful in finding toxic chemicals in the urines of mental patients at McLean Hospital, he began a study of protein metabolism in normal individuals and in mental patients by developing new quantitative methods for analytes in urine such

as ammonia, urea, uric acid, creatine (in muscle tissue), urinary creatinine (excretion product of creatine), nonprotein nitrogen (NPN), phosphate, and sulfur as sulfates (4, p. 119). Four basic techniques were available for quantification of body constituents: gravimetric (weighing), titrimetric (titration with acid or base), gasometric (measuring gas volume), and colorimetric (developing a colored solution). The latter involved either color matching, by eye, with standards, or using a DuBoscq colorimeter, which had been invented in Paris in 1854. By 1905, Dr. Folin achieved great success with these procedures and was very involved with the leaders in Physiology and the new field of Biochemistry; he became one of the founders of the American Society for Biological Chemistry.

In 1906, a new medical school consisting of five white marble buildings was built, not near Harvard University in Cambridge, but on Longwood Avenue in Boston. In May 1907, Dr. Otto Folin was invited by Harvard President Charles William Eliot, who had upgraded the inferior Medical School from a proprietary institution to a separate facility in Boston, to become the first PhD on the faculty and the first Professor of Biological Chemistry at Harvard Medical School at a salary of \$4,000 per year, with an assistant at \$700 per year. Under his agreement, \$1,000 of his salary was supplied by McLean Hospital, and he was allowed to keep his research laboratory there but gave his lectures at the Medical School. Dr. Folin recognized his new role as an educational leader in medical biochemistry and the fact that he was a non-New Englander who was unfamiliar with the other hospitals in Boston (the Massachusetts General and Boston City Hospitals were used for the clinical training of medical students); therefore, Dr. Folin spent much time organizing the new Department of Biological Chemistry, planning new course offerings, and preparing his lectures.

By 1912, Dr. Folin's improvements to urinary procedures, including reduced sample size requirements, permitted his group to develop similar methods for the same analytes in blood. The Folin-Wu technique for the acid precipitation of the proteins in whole blood samples in order to produce a clear filtrate became a routine procedure. Upon adding specific reagents and heat to aliquots of the clear diluted plasma, he was able to produce specific colored solutions for blood glucose and blood urea nitrogen (BUN) as well as for several other constituents (analytes). Of course, this approach required venipuncture of the arm for the collection of blood in a tube containing anticoagulant to keep the blood from clotting. Recognizing the need to follow blood sugar levels in diabetics and the unpleasantness of multiple arm sticks, Dr. Folin developed, in 1928 (after commercial insulin became available), a fingerstick procedure. Thus 0.1 mL of blood was collected in a microcapillary tube of fixed volume, which he persuaded Eimer and Amend to market, and he created the technology to measure glucose in this small sample (4, p. 316). I had extensive graduate training in such techniques at the Syracuse University College of Medicine under former Harvard faculty, and when I joined the University of Maryland faculty in 1950, I took over the supervision of teaching this technique to the medical students who performed glucose tolerance tests on

themselves. Upon my return to the SUNY Upstate Medical Center in Syracuse in 1957 as clinical chemist and Director of Clinical Laboratories of the main hospital unit (340 beds, 20 bassinets), glucose testing for diabetes and urea nitrogen (buns) for kidney disease by the Folin-Wu filtrate technique constituted 60% of the routine chemical test procedures we performed. Also, I introduced similar microtechniques for the routine measurement of 4–6 analytes in heel stick blood from newborns and infants.

After Dr. Folin was appointed Professor of Biological (Physiological) Chemistry at Harvard Medical School, the Folins bought a large home in Brookline, and he had a spectacular professional career until his death in 1934. His successor was A. Baird Hastings, PhD, who had been a postdoctoral trainee of Dr. Donald Van Slyke's at the Rockefeller Institute. Among the many graduate students Dr. Folin mentored was James B. Sumner (1887–1955), who became the first scientist to crystallize an enzyme, urease, in 1926, and who shared the Nobel Prize in 1946. Folin's only woman graduate student was Olive Watkins Smith who received her PhD in 1928 from Radcliffe College (the Women's Division of Harvard) and became a researcher at Brookline Free Hospital for Women, a part of Harvard Medical School. Dr. Watkins discovered that the synthetic estrogen, diethylstilbestrol, broke down in alkaline solution to give a substance that stimulated the ovaries of rats. As a young first-year graduate student at Syracuse, I isolated, in August 1946, after six weeks of effort, a product that Dr. Watkins found markedly stimulated the adrenals of rats, and later a second product that stimulated their pituitary glands, which we jointly published in 1950 (5).

Victor Caryl Myers, PhD (1883–1948), grew up in Hoosick Falls, New York, and attended Wesleyan University in Middletown, Connecticut, where he earned an AB and then an MA in Chemistry. In 1907, Myers was awarded a University Fellowship at Yale, where he studied under R. H. Chittenden, PhD, and Lafayette B. Mendel, PhD, and received a PhD in Physiological Chemistry in 1909 (6). Myers' first published paper was on normal body temperature, its daily fluctuations, and the effect of sleep pattern and muscular exercise on body temperature. After earning his PhD at Yale in 1909, he served as Professor of Physiological Chemistry and Director of Laboratories at the Albany Medical College from 1909 to 1911, the New York Postgraduate Medical School and Hospital from 1911 to 1924, the State University of Iowa from 1924 to 1927, and from 1927 to 1948 at Western Reserve School of Medicine in Cleveland, Ohio, where he died suddenly of a heart attack at age 65 on October 7, 1948. Dr. Myers became a member of every scientific and professional organization associated with chemistry, biochemistry, clinical biochemistry, biology, dentistry, gastroenterology, and medicine, including the American Medical Association (even though he was a PhD), and played a very active leadership role in all of them. In addition, he was a prolific researcher and published over 200 papers on body temperature fluctuation, the physiology and biochemistry of the kidneys and liver, the metabolism of aluminum compounds, acid–base balance, serum enzymes, and numerous analytic methods for constituents in blood, urine, spinal fluid, and gastric

juice (6). In 1913, Dr. Myers, with Yale classmate Morris S. Fine, PhD, published a book entitled *Essentials of Pathological Chemistry* in which each chapter provided a review of the topic, followed by the chemical method for that constituent (6, p. 10). It included gastric analysis, digestive changes and stool analysis, urinalysis, albuminuria (loss of serum albumin through the kidneys into the urine), glucosuria (glucose in urine), acidosis, pigmenturia (usually relates to liver function), microscopic examination of urine sediments, blood and other body fluids, and the chemistry and physiology of milk. Also in 1913, Dr. Myers described the operation of a hospital urinalysis laboratory for the collection, handling, and analysis of 100 specimens per day (6, p. 10). A urinalysis consisted of an examination of urine for color, reaction (pH with litmus paper), specific gravity, albumin, sugar, acetone, diacetic acid, and the microscopic examination of urine sediment for cells and crystals. Urinalysis provided clinicians with information on diabetes and kidney function and soon became a requirement for all newly admitted hospital patients for the rest of the 20th century, even though insulin was not isolated by Banting and Best until 1922 and available commercially for glucose control in diabetics until about 1926. As a matter of fact, Drs. Myers and Bailey's micromodification of the Lewis and Benedict method for blood sugar (glucose) permitted determinations on as little as 0.2 mL of blood and had enabled Banting and Best to study the blood levels of glucose in rabbits and facilitated their purification of insulin in the 1920's (6, p. 11).

Dr. Myers pioneered, for over 20 years (1910–1931), in the physiology of muscle creatine, its metabolism to blood creatinine, and its excretion by the kidneys as affected by dietary changes, and the pathological alterations taking place in various muscle and kidney diseases. In 1910, he gave a lecture, later published, to the Eastern New York Section of the American Chemical Society in Albany, New York, on nucleic acids, their cleavage products, the purines, pyrimidines, and phosphates, and identified uric acid in blood and urine as the main end product of purine metabolism. His studies of cell nucleoproteins and nucleotides over the next 25 years expanded to include the effect on uric acid metabolism of methylated xanthines as well as caffeine, theophylline, and theobromine found in beverages including tea, coffee, and cocoa.

Dr. Myers and his associates developed methodologies for serum creatine, creatinine, nitrogen, uric acid, potassium, chloride, and the acid–base status of blood and quantitative urine methods for total nitrogen, urea, ammonia, creatinine, creatine, phosphates, and uric acid. Readings were taken on a DuBoscq or a Hellige colorimeter. The latter was modified by Dr. Myers to an easier-to-use instrument, which he called a Biocolorimeter, and he used it to measure the pH of blood plasma, urine, gastric contents, and bacteriological culture media. In 1924, Myers published an updated edition of his methods book of 1921 entitled *Practical Chemical Analysis of Blood* (6, p. 38). One chapter includes the Folin-Wu system of blood analysis and each chapter is preceded by a discourse on the basic biochemistry, physiology, clinical alterations, and pathology of the constituents analyzed. Additionally, Dr. Myers published, over a period of 30 years, a number of review articles on the clinical applications of clinical biochemistry.

In 1939, Dr. Myers published on the hemoglobin content of blood, and in 1940 and 1942 on the human heart in health and disease and chemical changes in myocardium accompanying heart failure. Post World War II saw a need for change, and in 1946, Harland G. Wood, PhD, was appointed Professor and Director of the Department of Biochemistry at Case Western Reserve University in Cleveland, Ohio, and Victor C. Myers, PhD, at age 63, became Professor and Director of Clinical Biochemistry. Although in his later years, Dr. Myers took on more administrative duties and still lectured to medical students, but he succumbed to an acute heart attack at age 65 on October 7, 1948. Among his graduate students were Alfred H. "Al" Free, Donald "Don" G. Remp, and Leonard T. Skeggs, all professional clinical chemists I have known as contemporaries. Dr. Al Free and his wife Helen later developed a commercial dipstick method of testing known as Labstix, Bilistix, etc., sold by the Ames Company. Surprisingly, the many contributions of Victor C. Myers, PhD, do not seem to be nearly as well known as those of Otto Folin, PhD, who preceded him by about 15 years. We are very much indebted to Wendell T. Caraway, PhD, from Flint, Michigan, who authored *Victor C. Myers: Clinical Chemist*, published it at his expense in 1994, and was kind enough to send me a copy (6).

Donald D. Van Slyke, PhD (1883–1971), who grew up in Geneva, New York, earned his PhD at the University of Michigan in 1907 and, by chance coincidence, became a research chemist at the newly created Rockefeller Institute for Medical Research in New York City (3). John P. Peters, MD (1887–1955), graduated from Columbia University's College of Physicians and Surgeons in New York City in 1913 and, after a residency at Presbyterian Hospital, published in 1917 his first independent paper on "Carbon Dioxide Acidosis, Cause of Cardiac Dyspnea." In this paper, he showed that the carbon dioxide tension of the blood is increased by an inability of the lungs to take in oxygen and excrete carbon dioxide due to heart failure, resulting in the lungs attempt to overcome the retention of carbon dioxide by greater ventilation, which in turn produces dyspnea (shortness of breath). After serving two years in France with the Presbyterian Hospital Unit in World War I and one year at Cornell Medical College, Dr. Peters joined the medical staff at the Rockefeller Hospital, where he collaborated with Dr. Van Slyke on body acid–base problems. Even though Dr. Peters later became Professor and Chief of Medicine at his alma mater, Yale University, where he continued his avid interest in metabolic disease, he continued his collaboration with Dr. Van Slyke on body acid–base balance as affected by the lungs and kidneys.

Clinical chemistry has been stated by Louis Rosenfeld, PhD, to have had its real beginning as a scientific discipline distinct from biochemistry with publication of the two-volume classic *Clinical Interpretations in Quantitative Chemistry* in 1931 and *Quantitative Laboratory Techniques* in 1932, by John P. Peters and Donald D. Van Slyke (3, p. xix). Also, Dr. Peters and Dr. Van Slyke forged the earliest alliance between chemistry and clinical medicine. Only the *Clinical*

Interpretations volume was revised in 1945 due to the interference of World War II and both of their busy professional careers. Hence, only the volume on *Clinical Interpretations* became a mainstay in my graduate training in Biochemistry at the Syracuse University College of Medicine from 1946 to 1950.

Although Dr. Van Slyke mentored only his three technicians for PhD degrees, he helped train dozens of PhDs and MDs in biochemical research in his research laboratories at the Rockefeller Institute between 1907 and about 1948. They then went on to clinical chemical research positions, became heads of research organizations, or took faculty positions in universities with departmental names such as Physiological Chemistry or Biological Chemistry, now usually shortened to Biochemistry. One of his trainee graduates, A. Baird Hastings, PhD, succeeded Dr. Otto Folin as Professor of Biological Chemistry at Harvard Medical School. It is interesting to note that Dr. Van Slyke declined an offer to become Professor of Biochemistry and Dean of the Medical School of the University of Michigan where he had received his PhD in 1907 (3). Instead, the brilliant Dr. Van Slyke preferred to devote his time to research and studied the interrelationship between kidney physiology and kidney diseases, and the role of hemoglobin in red blood cells, which carries oxygen to all parts of the body and returns carbon dioxide to the lungs and kidneys. Dr. Peters' very prolific pioneering clinical studies on body water and electrolyte balance and on metabolic diseases including a classical explanation of diabetes and its role in body acid–base balance, permitted Dr. Van Slyke to clearly define body acid–base balance alterations in various disease entities through a complex diagram. Dr. Van Slyke became so knowledgeable clinically that he occasionally led the clinical staff on medical rounds at Rockefeller Hospital. After Dr. Van Slyke was required in 1948, at age 65, to retire from the Rockefeller Research Institute (renamed Rockefeller University), he did research for several years at the Brookhaven National Laboratory on Long Island, which had no such regulations.

Dr. Van Slyke's work led to the Henderson-Hasselbach equation, which defines the mathematical relationship of acid–base balance in the body in terms of three variables: blood pH, which is normally maintained at precisely 7.40, and the carbonic acid/sodium bicarbonate buffer system controlled by the lungs and kidneys. Amazingly, the body produces about 1,000,000 times the amount of acid daily than it contains in arterial blood at any one time, so the lungs and kidneys must maintain the proper balance or acid–base alterations can rapidly occur. About 1960, excellent laboratory instrumentation equipment became available for the simultaneous measurement of blood pH and carbon dioxide, and with two measured values of the Henderson-Hasselbach Equation known, the third was calculated by the instrument. However, arterial blood is required as the specimen of choice, limiting the routine use of the instrument. At our 610-bed Hahnemann University Hospital, we had a one-technician lab facility as part of the OR suite where blood pH and blood gases, electrolytes, glucose, urea nitrogen, and hemoglobin/hematocrit tests were available

to surgeons within 2–3 minutes. This facility was a part of the Clinical Chemistry Laboratories I organized and directed. It was especially important in cardiac surgery where we were the largest provider in the greater Philadelphia area. On the other hand, bedside venous specimens, collected under oil, arrived “stat” in the main hospital lab for routine clinical purposes. Undoubtedly, respiratory acidosis and alkalosis and metabolic acidosis and alkalosis with superimposition of one on top of the other, involves the most difficult concepts that exist for medical students to learn and clinicians to work with. However, my mentor for my PhD, W. W. “Weste” Westerfeld, PhD, had written a manual on the subject in 1948, and I was so thoroughly indoctrinated in the topic that I taught the fundamental principles to medical students and physicians most of my career.

John Reinhold, PhD (1900–1995), a pioneering hospital clinical chemist, grew up as a farm boy in Wisconsin where he became interested in chemistry at age 12. He entered the College of Agriculture at the University of Wisconsin in the early 1920’s and soon decided to make biochemistry his life’s work (7). After doing a thesis on calcium metabolism in goats, he got tired of goats and applied for a graduate fellowship in physiological chemistry at Yale with Professor LaFayette B. Mendel. There he never found a suitable problem for a dissertation which, combined with a pregnant wife and financial problems, led him to accept a generous offer of \$1800 per year (equal to a new PhD instructor at a medical school) as an assistant clinical chemist at the Philadelphia General Hospital (PGH), formerly the Blockley Alms House, which was founded in about 1750. There he worked in the Biochemical Laboratory under the tutelage of Bernard Karr, a PhD from Yale who had arrived three years before, another PhD, and one technician, serving 2,200–2,500 patients requiring about 1000 analyses a month. PGH provided facilities for teaching medical students from all five Philadelphia medical schools and attracted the most distinguished physicians in Philadelphia as volunteer staff because of its wealth of unique case material. Even the eminent Sir William Osler had served on the staff at PGH. John Reinhold was able to do some research, and Yale awarded him a master’s degree in 1926 for his published studies on the effect of various monosaccharides and disaccharides, for example sucrose (table sugar) and lactose (milk sugar), on blood sugar (glucose). PGH adjoined the Medical School and Hospital of the University of Pennsylvania (HUP), which also had a Graduate School of Medicine (GSM), the main function of which was to train physicians entering medical specialties. (Few if any certification boards existed in 1926; the American Board of Pathology was not founded until 1936.) The first-year course at GSM included a course in Clinical Chemistry for which the PGH Labs provided the faculty, and John Reinhold became an assistant instructor. His research work on bile secretions in dogs with infusions of acids and bases under Dr. D. Wright Wilson provided the necessary material for a dissertation and filled the requirements for a PhD degree, which led to his promotion to higher faculty rank.

In 1927, the PGH set up a special metabolism ward staffed with a physician, nurse, chemist, technician team, and a laboratory performing glucose, blood pH, and carbon dioxide content on a 24-hour basis for their dozens of comatose diabetic patients (commercial insulin had become available in 1926). The same year, Dr. Karr transferred to the GSM, and John Reinhold, PhD, became director of the PGH Chemical Laboratory. Procedures routinely carried out included blood sugar (glucose); blood urea nitrogen; serum carbon dioxide and chloride; uric acid (for gout); creatinine, icteric index, and bilirubin for liver disease; serum proteins, albumin/globulin ratio, cholesterol, and blood pH (Clark buffer method); and the measurement of basal metabolic rate (BMR) for thyroid disease (7, p. 65). I learned the chemical method for BMR in Medical School Physiology in 1947, and the test was being carried out by the clinical laboratory at the Upstate Medical Center where I became director in 1957. However, I was surprised to see an updated hand-held compact microversion of the BMR test being offered with on-the-spot testing at a large local grocery store about two years ago.

Sulfonamides became available in the early 1930’s, and clinical trials for their effectiveness in various diseases were carried out at Philadelphia General Hospital (PGH) after Dr. Reinhold studied their metabolism by the kidneys and developed methods for their determination in blood and urine. Shortly after Armand J. Quick developed a simplified procedure for prothrombin time (blood clotting time) in 1934, it became available to the PGH group. Dr. Reinhold was studying blood coagulation in liver disease patients and the effects of the ingestion of crude vitamin K, which is found in new mown hay and can be ingested as a smelly tea. On the other hand, if new mown hay is allowed to ferment and then fed to cattle, it leads to their bleeding to death. Farmers in Wisconsin complained to the agricultural biochemists at their University in Madison, Wisconsin, who soon identified the substance as dicoumarol (coumadin). It was patented by the University of Wisconsin Alumni Research Foundation (WARF) as Warfarin, an excellent rat poison. However, coumadin proved to be an extremely useful anticoagulant drug, clinically, for patients surviving a heart attack. Prothrombin measurements to monitor dicoumarol dosage soon became a routine clinical lab procedure (about 1934) and still are today.

Early on, PGH developed a toxicology laboratory to identify heavy metals such as arsenic and lead. Although lead poisoning is not an easy clinical diagnosis, it was very common in industrial workers in Philadelphia, leading them to make emergency visits to PGH (7, p. 59). Prohibition was in effect until 1933, and cheap “booze” was often tainted with methanol, which can result in blindness and/or death; therefore, gastric contents for methanol was an early emergency test. At PGH, the measurement of arsenic in urine by the Gutzeit method led to the uncovering of major insurance fraud in the Philadelphia area when several unsuspecting victims whose lives had been insured by the conspirators developed arsenic poisoning due to their being given free coffee with arsenic in it. Although the dastardly plot became recognized and the conspirators caught and convicted, it was not

until after a number of victims had died and others had become invalids (7, p. 59).

A major contribution from the PGH lab was made by P. A. Kingsley, MS, who developed the first practical procedure for the measurement of serum proteins by use of the biuret reaction. He salted out the globulins and measured the albumin remaining in solution, thereby determining the albumin/globulin ratio. Improvements were also made at PGH in the measurement of cholesterol and a method for glucose developed that was adaptable eventually to semi-automation. However, Dr. Rheinhold's most significant contribution was the use of sterile water for the preparation of parenteral (IV) solutions, permitting them to be produced in his laboratory for 5 to 10 cents per liter versus several dollars for commercial sources as WW II arrived.

During World War II, Dr. Rheinhold set up procedures for measuring liver function in body fluid specimens from patients in a human viral hepatitis study, which was being carried out at the Hospital of the University of Pennsylvania (HUP) under the auspices of the Army Epidemiological Board. Because no known experimental animal was susceptible to human viruses, it became necessary to set up the testing on human volunteers, and the challenge for PGH's lab was to evaluate, by means of liver function tests, the occurrence of the illness, its time of onset, its severity, and its clinical course. Specimens were supplied not only from the volunteers but from troops in the North African, Italian, and Middle Eastern theaters of War. However, their first success came from an outbreak of viral hepatitis in 150 campers in the Poconos, Pennsylvania, who showed up visiting their physicians in Philadelphia. The outbreak was demonstrated to have been caused by sewage contamination of one of the two wells used as a source of drinking water (7, p. 60). The tests ranking highest in sensitivity were bromsulfophthalein (BSP) retention, cephalin-cholesterol flocculation, and thymol turbidity, which became routine liver function procedures for ensuing decades. However, the transaminase enzymes were later found, by A. J. "Jack" Schneider, MD, PhD, an Army pediatrician, and later a colleague at the Upstate Medical Center, to be more useful in detecting hepatitis.

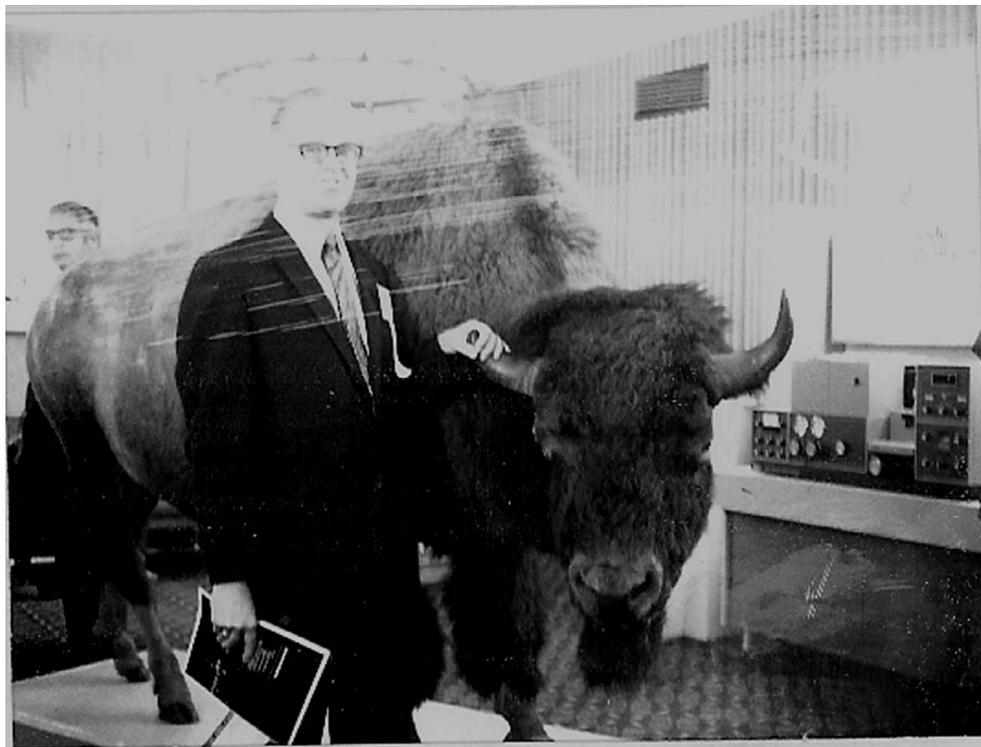
After F. William "Bill" Sunderman, MD, PhD, left in 1948 as Chief of Laboratories at HUP, an 800-bed teaching hospital, John Reinhold, PhD, became an associate in charge of the Chemistry Division of the William Pepper Laboratory at HUP, the first PhD to hold the position (7, p. 60). He had no assistant, but numerous experienced technicians performed the tests speedily and "kept errors and 'lab accidents' at a low level." David "Dave" Seligson, MD, at the Graduate Medical School Hospital (GSP) in Philadelphia, had earlier devised the "Seligson Pipette," a device that allowed the rapid delivery of a given volume of blood or of serum and diluent, which permitted greatly speeded up laboratory testing. My mentor in clinical chemistry, Marie Andersch, PhD, a former Associate Professor at Women's Medical College in Philadelphia where she probably learned about the Seligson pipette, had become clinical chemist and Associate Professor of Clinical Pathology at the Hospital of the University of Maryland and taught me these techniques in July/August

1957 as I embarked on my career as a clinical chemist. Dr. Reinhold found the adoption of Seligson's system so adequate that he never switched to newer automated systems before he had to retire, in 1964, as Professor of Clinical Pathology at the Hospital of the University of Pennsylvania (HUP) at age 65. Although one of my PhD clinical chemist colleagues from Upstate New York served there for about a year, the Pepper Laboratory at HUP then reverted to preferring MD clinical chemists for a number of years. Today, Donald Young, an MD, PhD British clinical chemist, is Director of Laboratories at HUP, and Leslie "Les" Shaw, PhD, who received his PhD under Dr. Westerfeld at the Upstate Medical Center in about 1970, is Professor and Director of Toxicology.

In 1950, Dr. John Reinhold had set up a laboratory in Jamaica to aid a study of protein-energy malnutrition in early childhood, and in 1962 he had been requested by the Agency for International Development (AID), on behalf of the Shah, to organize and nurture a university in Shiraz, Iran, in which English would be the primary language (7, p. 62). After Dr. Rheinhold's retirement from HUP, in fall 1964, he joined the faculty of American University of Beirut (AUB) in Lebanon, a 100-year-old institution, as chairman and professor of biochemistry. There, the Reinholds lived a delightful life among the cultured Armenians and Palestinians and he was able to continue his research on zinc deficiency in rats. At age 70, he became obliged to retire from the AUB faculty, but was invited to join an ongoing project in Iran directed by James Halstead, MD, who was treating an isolated village dwarf population successfully with zinc. The low plasma levels of zinc in the villagers turned out to be due to the village's bread, which included nearly all the fractions discarded as offal by Western milling technology (7, p. 63). As a result, the amount of phytate in the bread was greatly increased, which chelates (combines with) zinc and calcium, both needed for bone growth and normal development. In 1975, the Reinholds left Iran and moved to Mexico where, after earlier visits, they had purchased a home, and he continued his work at the University of Guadalajara and was living there in 1982 when his article on "Adventures of a Clinical Chemist" was published (7).

In the review of his career, Dr. Reinhold included a chart of "Noteworthy Advances in Instrumentation 1930-1950" (7, p. 65). His list includes the glass electrode by Stadie and O'Brien in 1932; photoelectric colorimeters by Evelyn and the much more useful Klett-Summerson, as it read in Klett units, providing a direct relationship between the standard solution and the unknown; the DU spectrophotometer and pH meter by Arnold O. Beckman, PhD; chromatography developed by Martin and Synge in 1940; moving boundary electrophoresis developed by Theodor Svedberg, PhD, in 1939; flame photometry for the measurement of sodium and potassium by Barnes et al. in 1945; and zone electrophoresis by Durrum et al. and Grassman et al. in 1950. At some point in my career, I have had personal experience with all of these instruments except moving boundary electrophoresis.

I never met Dr. John Reinhold, but on December 1, 1992, I had the honor of receiving the John G. Reinhold Award



Ray Vanderlinde (and buffalo) at AACC 1970 National Meeting sponsored by the Upstate New York Section.

(\$500 and a plaque) from the Philadelphia Section of the American Association for Clinical Chemistry (AACC) in recognition of my outstanding contributions to the profession of clinical chemistry.

A meeting of “hospital chemists” who “might be interested in forming an association that would raise the standards of the profession and of laboratories” was held at Mt. Sinai Hospital in New York City in December 1948 (7). The nine persons present became charter members and included Harry Sabotka, Max M. Friedman, Joseph Kahn, Miriam Reiner, Albert Sobel, Louis B. Dotti, Mary McKenna, Julius Carr, and Sam Natelson. The name, American Association of Clinical Chemists (AACC)—later revised to American Association for Clinical Chemistry—was adapted from the Peters/Van Slyke book, *Quantitative Laboratory Techniques*, “the Bible in all good laboratories at the time,” and the New York City group became the Metropolitan Section. Dr. John Reinhold of Philadelphia and Joseph Benotti of Boston attended some of the subsequent sessions at which the constitution and the aims and principles of the organization were developed and then founded, respectively, by the Philadelphia and Boston Sections of the AACC. The latter was soon followed by the Southern California Section, making the AACC, in 1950, a truly national organization, with 309 members. The Code of Ethics of the AACC was formally adopted in September 1953. I was one of the founders and charter members of the Upstate New York Section, in fall 1957, after accepting a new job challenge in clinical chemistry in Syracuse.

On September 1, 1957, I started my duties as Clinical Chemist and Laboratory Administrative Director of

Syracuse Memorial Hospital (SMH) (340 beds, 20 bassinets), a community hospital in an academic medical center where the Chairman of Pathology held the approval certification. Also, I became Assistant Professor of Biochemistry at the adjacent SUNY Upstate Medical College, where all faculty appointees were required to give a minimum of two lectures in each course the Department taught, including the medical students, the graduate students, and the nursing students. At this time, the nearby University Hospital, known as the Hospital of the Good Shepherd, had only 100 beds with available medical services limited to Medicine and Surgery. Construction of a new University Hospital was not completed until 1965. Memorial Hospital officially housed the Departments of Ob/Gyn, Radiology, Pediatrics, and Pediatric Endocrinology of the Medical School, and two floors each of Medicine and Surgery.

The SMH clinical laboratories occupied a second floor wing, which permitted rearrangement and expansion to meet the space requirements for a routine Chemistry Lab with lab glassware washing facilities, a Special Chemistry and Method Development Lab, a routine Hematology lab with facilities for coagulation tests, a Blood Bank with a small attached Rh Testing Lab, and an outpatient blood drawing unit. An additional small room was used to store the basal metabolic rate (BMR) apparatus used to measure thyroid activity and the EKG machine (only 5 leads). Alice Gwynn, the wife of obstetrician Dr. Charles “Chuck” Gwynn, was a medical technologist who had learned to type blood and perform Rh testing during World

War II and had set up the Blood Bank and the attached Rh Typing Lab. Alice worked part-time in the Rh Typing Lab, Mary Ford supervised the Blood Bank, and Jim Harris, a graduate student in chemistry at Syracuse University, handled the evening and on-call coverage. Mary Ford usually handled the required blood typing studies for Dr. William J. "Bill" Waters' paternity cases on which he had to observe the final matches. Offices for me, a secretary, and the chief medical technologist, Rita Robinson, MT (ASCP), were available. However, it was necessary to add a commercial dishwasher for the large glassware and a new larger still to make sufficient "pure water" available for lab usage and for rinsing glassware. Pipettes were cleaned by placing them in a stainless steel basket in acid and rinsing them in several changes of water, with distilled water used as the final rinse.

A small room off the central lab hallway housed the equipment to measure basal metabolic rate (BMR) for thyroid activity and stored the portable rolling cart EKG unit. Later, this room was lined with copper and converted to a facility for the measurement of EEG's (brain wave measurements) at the request of the new neurosurgeon who came aboard. Tessie, the dishwasher, and Jim Harris were black, medical technologist Jean Chaldecott was from Nova Scotia, my secretary Hazel Thomas was from England, chemical technologist Natalie Turtschin was from Russia, my grant funded research assistant, Harjant Dosanjh, MS, was from India, etc., so when Ruth and I held a party or a picnic for the lab staff at our home it was like a small United Nations. Also the seasoned Chief Medical Technologist, Rita Robinson, was exceedingly capable and knowledgeable, as was Marylu McIntyre, the lead technologist in Chemistry among others. The staff was congenial and there were no problems in recruiting additional technical staff. Thus, my inheritance of an excellent well-qualified staff, who only needed direction, assured my success, and the Hospital Personnel Department was very supportive in finding replacements and/or additional staff, an ideal situation.

At the time of my arrival, International Business Machines (IBM) employees were working to set up computerization of pharmacy inventory, the patient delivery of drugs and charges. However, given the pioneer opportunity to achieve this goal and possibly move on to become the leading experts in laboratory data computerization, IBM staff never accomplished even the former goal by the time I left SMH five years later in early 1962. On the other hand, it was about 1970 before the earliest computerization of a clinical chemistry laboratory was achieved.

Miss Miriam Curtis, an older nurse with a Master of Hospital Administration degree from the University of Minnesota, was the administrator of the hospital. As a practical matter, I reported to William "Bill" Waite, the assistant administrator, who was a wonderful chap about my age (33), was very progressive and a delight to work with. Bill also had a Masters Degree in Hospital Administration from Minnesota, and John Ruhe an intern from the same program served as an assistant.

In my teaching position at Maryland, I always followed a detailed daily schedule. I tried this at Syracuse, but after the first week I discovered that I hadn't been able to follow it at all as I had no control over who walked into my office. Although I

could have my secretary ask a chemical supply salesman to wait, she couldn't have busy clinicians sitting around waiting to see me. I communicated with the medical staff through William J. "Bill" Waters, MD, and I wrote innovative monthly newsletters describing lab test improvements and providing a description of each new test procedure, stating its availability, its clinical use, a brief description of the test, the specimen required, and the cost. This creative means of communication resulted in greatly increased physician ordering of both inpatient and outpatient tests and directly benefited the lab's net income. At this point in history, the clinical laboratory and X-ray departments were the big money makers in all medium and large hospitals and medical centers. Of course, the net income from laboratory operations more than doubled during the first year I was there, which greatly pleased the Hospital Administration.

Rita Robinson, MT (ASCP), the chief technologist, welcomed my coming aboard to take over the responsibility for the Clinical Laboratories. This was especially true considering the two unfortunate major lab errors that had occurred and that the Chief and Professor of Medicine, Richard "Dick" Lyons, MD, had removed his residents from training at SMH because of the laboratory situation. Natalie Turtchin became my lead technologist in developing microtechniques for collecting and measuring electrolytes, glucose, buns, and bilirubin in newborns and in developing new test procedures. Blood specimens were collected in microcapillary tubes from a heel stick of the newborns or older infants, including outpatient requests. These were far less traumatic than a jugular or femoral vein syringe stick. The laboratory was already using Dade's commercially available Labtrol (normal range) and Pathotrol (abnormal range), modified serum controls with assigned values to verify lab results. I had Rita handle all the personnel schedules and implement Bill Waters' recommendations for Hematology and Blood Banking, but keep me fully informed since most of Hematology, except for the differential (microscopic counts of the white and red cells) of a complete blood count (CBC), involved chemical techniques. Rita and I worked together on prothrombin tests and specialized coagulation tests as most of these used chemical enzymatic techniques. Within a couple of months, the Chief of Medicine, Dr. Lyons, had reestablished the residency program in Medicine at SMH.

After semiautomating the glucose and BUN tests with a Seligson pipetting system, which constituted half of all chemical testing, we standardized the liver function tests, one of which was thymol turbidity with a normal range of 0-4 units. When a staff surgeon received a grossly abnormal value of 40 units on a patient, instead of requesting a free repeat test, he said to his OR team "Undoubtedly the lab is wrong as usual" and proceeded with the surgery. Unfortunately, the lab result was correct and the patient died. As a consequence, I was invited to review "The Clinical Significance of Liver Function Tests" at Grand Surgical Rounds of the medical school the following month.

It came as a surprise to me to learn that an internist friend, who had trained at the well-known Leahy Clinic in Boston, thought a phosphorus value of 48 mg/L (normal range, 25-48 mg/L) was an exact number. He had no concept of the fact that with up to a 5% error in the analysis, which is ± 2.4 mg/dL, the

reported value could range from 45.8–50.4 mg/L. Thus, an upper borderline result did not clearly classify the patient's status. Several other factors further complicate the interpretation of lab data, as we use ± 2 standard deviation limits of the mean as being the normal range for a given serum analyte (constituent), which by definition means 2.5% of normal individuals fall below the normal range and 2.5% fall above normal range. The point is, a lot of science goes into establishing methodologies and normal values and, by inference, a pure standard (reference material) and a reference method (known to give accurate results), although not necessarily practical for daily usage, is essential to bringing laboratories into agreement for a given analyte. The best national effort, using reference materials and reference methods, was for cholesterol in the 1980's, and was organized by NIH under their Laboratory Standardization Panel (LSP) of the National Cholesterol Education Program (NCEP)—in which I played a significant role as a panel member and Chairman of the Council of the National Reference System for the Clinical Laboratory (8).

The chemistry lab at SMH had one of the first commercially available flame photometers for the measurement of sodium, potassium, and lithium, a Baird DB unit, which had been purchased by the Hospital Auxiliary. The propane gas cylinder, needed as a source of fuel, was kept out on the adjacent roof to meet fire regulations, and was connected by copper tubing to the instrument. Sodium ion (atom with a plus charge as it exists in solution) is the main cation in the vascular compartment and potassium ion (K plus) is the main cation within all body cells. Therefore, serum K ion level is controlled within a very narrow range because a serum level that is too high results in tachycardia (heart beats too fast) and a low serum level results in bradycardia (heart beats too slowly), and the measurement of serum electrolytes [Na plus, K plus, chloride ion (Cl minus) and bicarbonate (HCO_3 minus)] is very important clinically. Lithium, as measured by serum level using a flame photometer, has been important in the treatment of schizophrenia (bipolar disease) for over 50 years, but newer drugs have been marketed in recent years.

A priority project was to develop microcapillary heel stick blood collection techniques such that the four electrolytes (sodium, potassium, chloride, and bicarbonate as carbon dioxide), glucose, bun, and bilirubin could be determined on newborns and infants. We developed microcapillary techniques to provide 4–6 of these tests routinely, with bilirubin only on weekends. However, in order to keep the electrolyte demand under control, I required a call on weekends as we didn't always have staff on duty who had the capability or time on Saturday afternoons or on Sundays. Also, the instrument was tricky to work with and often gave problems, which were eliminated usually by taking the instrument apart, cleaning it, and then reassembling it. Although I never questioned a request for electrolytes, the simple act of needing to make a telephone call kept the situation under control. I never knew until many years later that I was a pioneer in pediatric clinical chemistry, as a number of large well-known children's hospitals in the United States did not institute microtesting until the 1970's.

It was not long before the entire staff of the Pediatrics Department of the Medical School were my friends, both professionally and socially. Jules "Juli" Richmond, MD, Chairman and Professor of Pediatrics, was a pioneer child psychiatrist who had two research fellows working on measuring the learning patterns of newborns. Dr. Richmond later became Dean of the Medical School and subsequently Surgeon General in charge of the U.S. Public Health Service. Unfortunately, his son, who had just graduated from the University of Chicago, was murdered in a robbery for \$60 in 1960. Bill Waters, MD, had a half-time office in the clinical lab area and was the area bilirubin-exchange specialist. When serum bilirubin reaches a level of 20 mg/dL in a newborn due to immaturity of development or to Rh incompatibility with the mother (hemolytic disease of the newborn), exchange transfusion of the newborn is required, which was Bill's subspecialty. In 1968, the Ortho Pharmaceutical Company published a report, RhoGam—One Year Later: Complete Proceedings of a Symposium, in which it was estimated that there were potentially 300,000 Rh-sensitized Rh-negative mothers in the United States (9). At that time, they estimated that with RhoGam available, hemolytic disease of the newborn would be wiped out in one generation. It is extremely rare today but does occur according to my physician daughter, who is Director of Blood Banks and Tissue Banks for the New York State Department of Health.

Tyree C. "Ty" Wyatt, MD, was an elderly pediatrician at Syracuse who had two patients with galactosemia. Lactose is a double sugar containing a molecule of glucose and a molecule of galactose. People with lactose intolerance lack lactase (as do adult Siamese cats), the enzyme necessary to hydrolyze the molecule. Individuals with the inherited disease, galactosemia, lack the ability to metabolize galactose due to the lack of the enzyme: galactose-1-phosphate uridyl transferase (10). Kalckar and his colleagues developed a spectrophotometric technique for its measurement using the change in NAD to NADH, which Dan Broida of Sigma Chemical Company made available as a kit in 1958. One case involved a family, from near Watertown, New York, with about 10 children. One of the children had died and another, an eight-year-old boy, had galactosemia. The other patient of Dr. Wyatt's was a two-year-old child whose parents were stationed at Rome Air Force Base. I carried out the Sigma uridyl transferase reaction on both patients, the eight surviving siblings of the eight-year-old boy, and both sets of parents. The deceased sibling had apparently died of galactosemia before it was clinically recognized, which is how Dr. Wyatt came to have the family as patients. In addition to my studies, Alice Gwynn of our Rh Typing Lab at SMH carried out the major blood groups and Rh subgroups of all of the children and their parents. We found no correlation between the blood types of the two patients with galactosemia and their relatives (the negative findings were never published). Galactosemia is transmitted by an autosomal recessive gene and occurs in about one of every 20,000 births (10). The principle symptoms are cataract formation, mental retardation, and hepatosplenomegaly (enlarged liver and spleen). The only known treatment is to simply remove milk from the diet at an early age and place the infant on glucose (dextrose). After I joined the Division of Laboratories

and Research of the State Health Department in Albany in 1965, we immediately added galactosemia screening to the phenylketoneuria (PKU) screening of all newborns.

Another pediatric-inherited metabolic disease test I instituted at Syracuse Memorial Hospital was the sweat chloride test for cystic fibrosis (mucoviscidosis). Dr. Bernard Schwachman, a pediatrician in Boston, Massachusetts, discovered cystic fibrosis, an inherited defect, which is characterized clinically by the production of thick, sticky mucous plugs blocking the bronchi of the lungs and leading to the progressive loss of lung function as the usual cause of death. Abnormally salty sweat is the basis for the diagnosis of cystic fibrosis as the disease interferes with the sweat glands in the skin. Dr. Schwachman made this discovery in about 1950 and, by 1957, a manufacturer sold plastic jackets that could be placed on the infant to collect sweat on a preweighted piece of gauze for two hours. One of our laboratory technologists, in conjunction with a nurse in Pediatrics, carried out the sweat collection procedure. In the laboratory, I then weighed, on an analytical balance, the collected volume of sweat and gauze, subtracted to get the weight of sweat, diluted it with a fixed volume of distilled water, and measured the sodium content by flame photometry. Because normal sweat has a low content of sodium in mEq/L and the sodium content is very high in cystic fibrosis, it was not difficult to determine whether or not the child was normal.

I used to drink coffee and eat lunch in the staff dining room because it gave me an opportunity to communicate with the staff physicians, and I often ate lunch with Bill Waters, MD, and Lawrence "Larry" Pickett, MD, a pediatric surgeon who specialized in surgery on newborn infants, including rare patients with biliary atresia, that is, no bile drainage tube into the gut. I always marveled at Larry, who had gigantic hands but was an exceedingly skilled pediatric surgeon who later returned to Harvard Medical School. I remarked once at lunch about my younger two children with diaper rash, and Larry said, "That's nothing, Ray, we have acne and diaper rash both at our home." Other pediatricians who were my good friends were William "Bill" Bergstrom, MD, PhD, and A. J. "Jack" Schneider, MD, PhD, both of whom had research labs in the Biochemistry Department of the Medical School. Jack had been in the service when he had been the first to recognize the importance of the transaminases in hepatitis.

Continuing education is a very important adjunct for any professional career. While still at the University of Maryland, I participated in a course in Medical Electronics and taught two evenings per week for one semester. The American Board for Clinical Chemistry, a certification body for doctoral level clinical chemists, was founded in about 1954. Almost 250 individuals were qualified to be certified on the basis of submission of their credentials or "grandfathered in." I applied in 1958 with the proper fee and documentation, and after several months of delay I was required to take a five-hour written examination. In fall 1959, I studied evenings and weekends for six weeks, and in December 1959 took the examination at the Rockefeller Institute in New York City. In May 1960, I received shingle #252, certifying me in Clinical Chemistry and allowing me to add Diplomate ABCC after my name and degree. The diploma

also increased my membership rank from Member to Fellow in the membership directory of the American Association for Clinical Chemistry. Originally, the examination included the measurement of aspirin, alcohol, and barbiturates, and therefore one was additionally qualified in Toxicology. However, several years later, a new American Board for Toxicology was created to cover full-time toxicologists in medical examiner offices, police laboratories, and crime labs, etc. In February 1961, I completed a one-week course in Management Development in Chicago given under the auspices of the American Hospital Association.

Mornings, particularly on Mondays, got to be very hectic in the Blood Bank as we tried to meet the morning surgical demands, and often we had to crossmatch the same pint on two different surgical patients with the hope they didn't both need it. Bill Waters and I surveyed our surgeons and each major type of operation they performed and put together average amounts used for each type of operation. Because pre-op patients came in ahead of time for the drawing of their CBC and a urine sample, we were able to type them and plan our blood needs a couple of days ahead of time. Thus, we developed a chart specifying minimum amounts of blood, which were automatically set up for each OR procedure but gave individual surgeons the opportunity to specify more, if they felt they might need it. This innovative approach did away with the extreme pressure on the Blood Bank staff on Monday mornings and made it a very efficient operation. Although we never published our master chart, the clinical pathologist at the new University Hospital, which opened in 1965, inherited a copy and published the concept. However, by this time, Dr. Bill Waters had deceased acutely from a brain aneurysm of the circle of Willis and I was with the State Health Department in Albany.

Syracuse Memorial Hospital (SMH) had a large emergency room, which gave me the opportunity to develop expertise in toxicology. Adult poisoning due to an overdose of barbiturates was very common, and I set up a spectrophotometric absorption spectrum technique for their quantitation. SMH also received most of the area emergency childhood poisonings. Some years before I returned to Syracuse, the son of a pediatrician with whom I had taken biochemistry, physiology, and pharmacology had gotten into his father's medical bag and had died from aspirin poisoning. Aspirin (acetylsalicylic acid) poisoning in children had become so common a household occurrence in Syracuse that I set it up as a routine test procedure available 24 hours per day. It was several years later, and perhaps as a result of papers published by the Pediatrics staff at Syracuse, that the FDA required childproof caps be placed on all aspirin bottles. Also during this time, laborers commonly used oil of wintergreen, a methyl ether of salicylic acid and unmetabolizable, to relieve their aching muscles. When it was swallowed by a child, it usually resulted in a fatality. Young toddlers eat or put in their mouths whatever they can find in the house or the garage, and we had poisonings ranging from kerosene, naphtha, and turpentine, often stored in Coke or other soft drink bottles in garages, to Draino (lye) found under kitchen sinks. Unfortunately, stomach pumping did not always take care of the situation because after petroleum-based products are absorbed they seriously

interfere with respiration and lye destroys mouth and throat tissues irreparably. I gained a lot of experience in emergency room toxicology, which I built on some years later leading to my chairing a professional committee, resulting in a booklet of recommendations on emergency room toxicology (11).

One of the most interesting poisoning cases that I encountered was that of a Syracuse University coed who attempted to commit suicide with aspirin on Thanksgiving Day 1957. Since pediatricians were the experts in aspirin poisoning, Paul Wherle, MD, a pediatrician, and I were in the lab following the blood pH levels on the patient. The initial effect of aspirin is to induce a respiratory alkalosis, which is followed by a metabolic acidosis as the free salicylic acid is released; therefore, it was necessary to alter the patient's intravenous fluid therapy as needed, thereby enabling the patient to survive. Paul's prime subspecialty was infectious disease and he subsequently accepted a position as head of a 60-bed pediatric infectious disease unit at Los Angeles General Hospital, which is a part of the University of Southern California. Some years later, Paul became the Chairman and Professor of Pediatrics at Southern California and President of the American Academy of Pediatrics. In the 1970's, I briefly encountered Paul at the Communicable Disease Center (CDC) in Atlanta, and after we talked as old friends, one of his professional colleagues said to me, "How do you know him so well?" I replied "We shared a lab experience together many years ago."

I joined the AACC in spring 1957, and after becoming Clinical Chemist at Syracuse Memorial Hospital in the fall, I was invited to attend an organizational meeting of the Upstate Section. In attendance were several clinical chemists who, like me, were laboratory directors of hospitals, including Michael "Mike" Vanko, PhD, from the Albany Medical Center, Max Chilcote, PhD, from Erie County Hospital in Buffalo (over 1000 beds), and William "Bill" Mason, MD, PhD, from the University of Rochester, as well as Martin Murray, MS, from Genesee Hospital in Rochester, Roy Rand, PhD, from St. Mary's Hospital in Rochester, Nathan "Nate" Radin, PhD, from Rochester General Hospital, Theodore "Ted" Peters, PhD, from the Mary Imogene Bassett Hospital in Cooperstown, and a couple of others. The latter hospital is unique as it is staffed by full-time clinical faculty from Columbia University College of Physicians and Surgeons through funding by the Clarke Foundation (Clarke sewing thread fortune). In 1960–1961, I was the third chairman of the Upstate New York Section, and I served again as chairman in 1966–1967 after joining the State Health Department in Albany in 1965.

Clinical chemistry was still in its infancy in 1957 and we met three or four times a year in an organized format on a Friday/Saturday at some member's laboratory between Albany and Buffalo, the distance between the two being about 300 miles by the New York State Thruway. Early sessions were devoted primarily to the presentation of various methodologies for a given analyte (serum constituent) and we then shared what difficulties or problems we had encountered. I kept a scrap book of the correspondence related to the founding of the Upstate Section and its meetings from 1957 to 1962, which was one item in the six cartons of professional materials that I gave

to the Chemical Heritage Foundation in Philadelphia in August 2002. They were pleased to receive them as they had little material in their library on clinical chemistry.

One of the methodologies that our Upstate Section shared in was the color development procedure for the determination of blood urea nitrogen (buns), which involved diacetylmonoxime added to sulfuric acid. Not all commercially available sources of diacetylmonoxime were the same, and we collectively found that aging of the reagent for 30 days improved the results. Although our standard curve checked out with the values assigned to Labtrol and Pathotrol (Warner-Chillcott Inc.), which are modified serum controls, it came as quite a shock to receive a call from Weste stating that we had reported a normal bun on a patient whose creatinine was abnormal and known to have kidney disease. As I always said, "There is a little alchemy in the best of chemistry," that is, chemical aspects that we don't understand and can't explain; this was one of them. The diacetylmonoxime reagent we were using defied all the laws of chemistry and when very large amounts of urea nitrogen were present (way above the mildly elevated value of Pathotrol), the curve doubled back down to give normal range values. I had the dubious honor of presenting my findings to Dr. Richard "Dick" Lyons, the Chief of Medicine, at his office. Weste's comment was, "It's not the first or last time you will be wrong." I learned the hard way that new and modified methods must be thoroughly verified with actual abnormal patient specimens. This important lesson helped me greatly in eventually becoming an expert in quality control, standard methods, and in developing reference methods and materials for the Council of the National Reference System for Clinical Chemistry (12).

Ironically, about a year later, Dr. Dick Lyons referred a patient of his to me, whose laboratory had reported his bun value as abnormal, but had been found not to have kidney disease. The patient turned out to be a surgeon from Oneida, who was on the Board of the Oneida County Laboratory where the error occurred, and he requested me to solve the problem. I received permission from my hospital administration to look into it, which turned out not to be a problem with the method but in the cross contamination of the blood collection tubes prepared by the laboratory. The laboratory was drying tubes containing liquid sodium ammonium oxalate for Hematology in the oven along with tubes containing liquid potassium oxalate for Chemistry, thereby adding variable amounts of ammonia to the tubes for Chemistry that the bun test measured. Our SMH Lab was already using commercial Becton Dickinson Vacutainers when I took over in 1957, so I never faced this potential problem. Thus, I became a consultant one afternoon a week to the Oneida County Laboratory, which my hospital administration approved since I was professional staff, worked many more hours a week than required, and took call on weekends.

On an early visit to the Oneida County Lab, I asked the technician to demonstrate a prothrombin time. She proceeded to pull out a bread tin, ran in water from the lab faucet, adjusted the temperature to roughly 37 degrees, and carried out the wire loop clotting step using a stop watch. Of course, good technique would have required an electrically controlled water bath. The tech then wrote down the patient result and proceeded to

write down the control result as well. My question to her was, "Where is the control?" She replied, "Oh I did that a month ago when I standardized the thromboplastin reagent." With this reply I suddenly realized the technical staff was inadequately trained and didn't have proper equipment, and that many pathologists were inadequately trained in Clinical Pathology (Clinical Chemistry, Hematology, and Microbiology). As a matter of fact, they were granted certification in Clinical Pathology after spending five years of directing a clinical laboratory, without any examination regardless of the quality of their lab operation. The problem was further aggravated by the fact that pathologists had departmental administrative duties, performed tissue pathology (specimens removed at surgery and autopsy), read the Pap smears, performed autopsies, and frequently had poorly trained laboratory technicians. Usually, they relied on a well-trained technologist, if they could obtain one, to handle all affairs associated with the clinical laboratory.

Among the most unusual happenings during my sojourn at SMH was the admission of the Gypsy Queen, whose tribe camped out in the hospital front lobby. I surely would have hated to be her physician after one of the tribesmen came up, stuck a knife under his chin and said, "Gypsy Queen die, you die." Fortunately, she recovered. Gypsies are a Romanian nomadic tribal people, long associated with traveling circuses who sometimes would try to flimflam people or would go door-to-door looking for a handout like tramps or hoboes did up until the 1970's. Many still live in Romania today.

In the 1960's, neurosurgical outcomes were about 10% successful, whereas today the odds have reversed and outcomes are possibly 90% or more favorable. Although this is a rough approximation, it illustrates the point I wish to make. Robert "Bob" King, MD, a brilliant young neurosurgeon, joined the staff of the Upstate Medical Center in 1961 and one of his first requests was for the latest Astrup pH/blood gas equipment manufactured by Radiometer, a Danish company. This very sophisticated instrument, which cost about \$5,000, was essential to his success in neurosurgery. Ironically, I left Upstate for a position in Cumberland, Maryland, as of December 31, 1961, and never did work with the new sophisticated blood gas equipment. Subsequently, at Hahnemann (1977–1991), we had three such units, one in the Emergency Room, one in Routine Chemistry, and one I had installed in the small laboratory that became part of the OR suite. The latter was essential for open heart surgery, of which Hahnemann was the largest provider in Philadelphia and the Delaware Valley.

In fall 1961, Lester "Les" Kiefer, MD, whom we had known from our Baltimore days, called and asked me and my wife to visit him in Cumberland, Maryland, where he had recently become chief of pathology at Memorial Hospital. Les held a Bachelor's degree in Microbiology from the University of Maryland at College Park, and in the post World War II era became an Army Major in charge of Bacteriology in the European theater of operations. He graduated from the University of Pennsylvania School of Medicine in about 1953 and completed a residency in Pathology at Maryland, where both of our Departments were located in the Pathology Building. After completion of his residency, he joined the

Pathology faculty for a couple of years before deciding to accept a full-time position as the pathologist at Memorial Hospital in Cumberland as of September 1, 1961. The previous pathologist had cut as many corners as possible in the services of the clinical laboratory in order to make as much money as possible; therefore, the medical staff had requested that the Hospital Board fire him.

Les soon found he had a competent technical staff who lacked direction and adequate space and equipment. Although Les could handle hematology and blood bank, and Paul Williams, a master's degree microbiologist was covering microbiology and clinical chemistry, neither of them was competent in the latter. As a matter of fact, blood urea nitrogens were being reported both as urea nitrogen and as urea, a paper conversion making the monthly total of tests performed for this analyte twice what the count should have been. The Cumberland area economy was roaring in 1961 as it was the home of Springfield Tire Company, the Celanese Corporation, and Allegany Ballistics Laboratory (ABL), and was close to the Pittsburgh Plate Glass Company plant, and a Westvaco (West Virginia Pulp and Paper) Plant was in nearby Luke, Maryland. I was offered the position of Clinical Chemist and Associate Director of Laboratories at a salary greater than my previous combined income, with contract guarantees for the future and excellent vacation and fringe benefits. In addition, I had taught, as medical students, several of the younger staff physicians, and was assured of immediate acceptance. On October 21, 1961, I accepted the position and gave three months termination notice at Syracuse Memorial Hospital.

We built a brick split-level home with four bedrooms and two bathrooms on an acre of land in the new Sunset View Development on historic Haystack Mountain off Braddock Road in LaVale, Maryland, a suburb west of Cumberland. During the French and Indian War in 1755, British General Edward Braddock, accompanied by young 23-year-old Major George Washington and Daniel Boone, had hacked out and created Braddock's Road in order to attack the French at Fort Duquesne in Western Pennsylvania. The Narrows, on the other side of Haystack Mountain, is a mile-long gorge through which passes the Potomac River, the B & O Railroad, and Route 40 to the West.

In the 1950s, Leonard T. Skeggs, Jr., PhD, Clinical Chemist at the VA Hospital in Cleveland, Ohio, found himself with only 3.5 technicians to do all the chemical testing for an 800-bed teaching hospital. Dr. Skeggs developed the concept of a flow-through system for the determination of glucose and BUN using a dialysis membrane to obtain a protein-free filtrate that could be split for color development (13). Working in his garage, he developed his concept into a successful working model, which he had a great deal of difficulty selling to a manufacturer. However, the Technicon Company of Chauncey, New York, finally bought the concept because it had been manufacturing, for many years, a circular tissue bath processing system by which tissue samples removed at surgery or post-mortem could be imbedded in wax blocks for thin slicing by a microtome and mounted on glass slides, the main tool for pathologists the world over. The first commercial model of the

AutoAnalyzer appeared on the market in 1957 and came to dominate the world for fully automated equipment for clinical chemistry analyses for over a generation (14).

Because the hospital administrator's goal was to make Memorial Hospital in rural far western Maryland (about 150 miles from either Baltimore or Washington, DC) the equivalent of a modern university hospital, I attended AutoAnalyzer (AA) School in Chauncey, New York, for four weeks with 24 other laboratory personnel, graduating on February 6, 1962. The basic clinical model of the AA consisted of six components: a sampler for picking up the specimen to be analyzed from a circular tray of specimen cups, a "proportioning" pump that maintains the flow of liquids in the system, a dialyzer that produces the equivalent of a protein-free filtrate, a heating bath corresponding to the heating vessel in which a technician would normally develop a color reaction, a colorimeter for measuring the amount of developed color in the samples, and a recorder. The heart of the system is the "proportioning" pump. It can continuously pump up to eight separate fluids while varying their individual output in any ratio up to eight to one. Across the pump platen lays the manifold, made up of a set of flexible plastic tubes with different diameters determining the flow rate through each, thereby permitting the addition of the proper volumes of each reagent at the appropriate time. Delivery is accurate and reproducible from test to test.

Initially, the AutoAnalyzer was limited to a single determination at a time, but many laboratories wished to simultaneously perform glucose and urea nitrogen, which constituted about half of chemical testing. To meet this basic need, production models were equipped with two dialysis units, a second heating bath, a second colorimeter, and a second recorder. My training was on the actual two-channel unit that was to be shipped to our Memorial Hospital Clinical Laboratory. Other trainees from larger laboratories trained on four-channel units, which measured the electrolytes sodium, potassium, carbon dioxide content, and chloride, and soon six-channel units combined the measurement of all six analytes. The concept of more tests on a single specimen was further expanded to include the determination of total protein and albumin so that from one serum sample, eight results were produced. Thus the eight-channel AutoAnalyzer was born.

Although initially there were eight recorders and eight sets of data to be calculated, the installation of time-delay coils allowed all of the colorimeters to be connected to a single recorder, and the results of all determinations on a single serum specimen could be recorded individually on a single piece of paper. A single colorimeter was made adequate by arranging a cell block holding six colorimetric cells with two switch positions so as to record the flame photometer for sodium and potassium. The cell block is motor positioned so that each colorimeter cell is observed in sequence. Because a method for calibrating and calculating the data was necessary, special electrical circuits were devised whereby the recorder could be supplied with precalibrated chart paper. This allowed the reading of results directly from the chart.

Field experience with the eight-channel analyzer encouraged the construction of a 12-channel machine by May 1966,

which determined the basic eight analytes plus calcium (for bone-related diseases), alkaline phosphatase (related to bile flow and bone diseases), bilirubin (liver function), and transaminase (hepatitis and liver disease). The 12-channel AutoAnalyzer or Sequential Multiple Analyzer 12 or SMA 12 chart results became the 12-channel chemical profile (14). I have a collection of profiles, taken over the years, which I used in my teaching in Laboratory Medicine at Hahnemann to illustrate the constancy of values in a given person.

The very stable clinical laboratory staff at Memorial Hospital were well trained, flexible, and adequate to carry out the challenge at hand. One of the chemistry technicians was the mother of medical student, Joe Darr, whom I had taught while several of the medical technicians and medical technologists alternated between Hematology and Blood Bank. However, we narrowly avoided a major disaster one Friday evening when the entire Blood Banking staff, except the one on duty, went partying together and wound up in a major auto accident. Additionally, a bottle of liquor was found on the back seat floor of the car; as I recall the accident occurred in nearby Pennsylvania. Fortunately for us, their injuries turned out to be relatively minor.

In September 1962, my sister, Marge, and her husband from Rochester, New York, visited our new home and I took them to visit the clinical laboratory at Memorial Hospital. While there, we passed Les in the hall. Les had an altered gait, pin point pupils, and slurred speech, and Marge said, "What's wrong with him?" I simply said he was having a bad day and proceeded to show her my office and the labs. Les had kidney stones and during a siege it became a matter of a vicious cycle between medical need and drug abuse. Walt Himmler, MD (class of '54), his urologist whom I had taught as a medical student, was the only one who could counsel him. However, after he started obtaining Demerol illegally, the hospital administration put him on notice to "shape up or ship out." Belatedly, I learned that Les did not have a physician's narcotics license because he had had the same problem previously. At this period in our history, drug abuse by physicians was not uncommon.

Another incident happened early one morning when Les, looking very distressed, called me into his office where he opened his desk drawer, pulled out an envelope and said, "These are the products of conception which I am expected to report out as a normal D&C (dilation and curettage)." I calmly turned to him and said, "What choice do you have other than to report it for what it is?" Subsequently, it never happened again during routine operating room hours. About a year later, we attended a dinner party for several staff members at Les and Ginny's home, which was a very large old brick house on Washington Street, and later in the evening he confided to me how much he admired "my quiet, calm demeanor in handling difficult situations." Les was a very large man, about 6-and-1/2-feet tall who weighed at least 250 pounds and gave an outward appearance of great confidence. However, in reality, his father had walked out on his mother when he was 12 years old and he was very insecure, relying on prestige such as joining the country club and buying the best of everything to impress people. This was a revelation, which I felt explained his narcotic drug abuse and, several years later, an alcohol problem.

Memorial Hospital had a nursing program in conjunction with the Allegany County Community College for which I gave some lectures. Also, I organized in-service training programs for our laboratory staff, a majority of which I taught. In the summers of 1963 and 1964, we provided about two months of laboratory training to six college students from the area who were either premed students or interested in paramedical areas. Les was a good teacher and, while I declined his offer to attend an autopsy, I often took time to watch him carve up organs, such as a lobe of liver or a kidney to look for gross abnormalities, and cut specimens for histological examination. The tissues were processed by a Technicon Tissue Processor (Chauncey, New York) and then the wax blocks thin-sectioned on a new microtone. I spent a lot of time drinking coffee in the staff dining room and took long lunch hours in order to informally consult with the medical staff and make suggestions about lab tests. Les once said to me, "I don't know why they ask you instead of me" and I passed it off as my being more available, but they did seem to prefer to talk to me.

When I was on the faculty of the University of Maryland from 1950 to 1957, a concern I had was the fact that newly graduated medical students who passed the National Boards were licensed to practice medicine and surgery in the State of Maryland without doing an internship. Although most graduates went on to internships and many took residencies in specialties only rarely would a new graduate open an office practice without taking an internship. The Maryland State Medical Board permitted experienced local physicians with special training to be certified for special procedures and many hospitals utilized nurse anesthetists. About 1960, Memorial Hospital in Cumberland had begun requiring board certification as a requirement for a medical staff appointment, but there were no ear, nose, and throat (ENT) surgeons on the staff between 1962 and 1965 when I was Director of Clinical Chemistry and Associate Director of Laboratories. There were no board-certified ENT surgeons on the staff because a general practitioner had been certified to perform tonsillectomies and adenoidectomies (T&As), and performed up to 500 per year. However, there was an older board-certified ENT surgeon in his sixties who lived in Frostburg, Maryland, about 12–15 miles westerly, who performed occasional T&As at Memorial Hospital. Unfortunately, after he performed a T&A on a 12-year-old boy at Memorial, the boy was bleeding in the middle of the night and badly needed medical attention, but he refused to come in and the boy died. As a result, he was removed from the medical staff.

Another sad case I remember was a cute little girl about four years old with acute myelogenous leukemia who came in every week for several months for blood counts, but passed away a couple of days before Christmas. As the father of children ages 12, 4, and 3, I felt these deaths personally and came to realize I would not have made a good clinician as I had too much sympathy for patients, be they young or old. However, Les had carte blanche permission to order additional lab tests on hospitalized patients, and the last year I was there every day we reviewed all of the laboratory reports (chemistry, hematology, microbiology, and urinalysis) and often went jointly to see

patients to decide what additional laboratory or other tests should be done. Hence, I practiced a lot of medicine, but Les's signature on patient records made it legal. The Allegany-Garrett Medical Society actually altered their constitution and made me an Associate Member. Early on, Les and I became consultants at Meyersdale Hospital, about 35 miles north in Meyersdale, Pennsylvania. I made the majority of the clinical presentations at the monthly medical staff meetings of this small 12-bed hospital, which was a first-class operation that he or I visited every other week.

As a pathologist, Les alternated weekend and vacation coverage with Nicholas "Nick" Giaritta, MD, the pathologist at Sacred Heart Hospital, also located in Cumberland. They had a radioisotope laboratory and performed our radioisotopic thyroid testing, and as a clinical chemist I performed their PBI (protein bound iodine) thyroid test requests. After we left Cumberland in 1965, a new Sacred Heart Hospital was built several blocks away from our home on Haystack Mountain. A merger was discussed several years ago, but the two competing hospitals were only recently combined into the Western Maryland Health System (WMHS). On October 9, 2005, Barry Ronan, the president and chief executive officer of the System, announced officials had received the design-development plan for a new 275-bed hospital to be built on Willowbrook Road, with ground breaking projected for May 2006 (15). However, before ground breaking occurred, negotiations were concluded between the WMHS and the Allegany County Health Department (ACDH), which resulted in the WMHS acquiring the site on June 9, 2006, of the former ACDH on Willowbrook Road, appraised at \$3.8 million dollars. In spring 2005, the WMHS purchased the old Kelly Springfield Tire Company building and annex across the street from the Maryland Economic Development Corporation.

During the 1950's, the Pediatrics Department of Johns Hopkins University published several papers on inherited metabolic diseases, a number of which were discovered in the rural and provincial areas of Western Maryland and nearby Pennsylvania where there were huge families of people, all of whom were interrelated and distant cousins. Although I did not have an opportunity to do research in genetic diseases, I did become involved with two unique patient situations. Joe Marx was the cystic fibrotic son of a very devoted mother who had spent many hours a day, from infancy on, having him undergo postural drainage of the mucous from his lungs. Joe did a research project with me the summer before his senior year at Johns Hopkins University, where he was a premed student. However, he was rejected for medical school on the basis that he should not spend his life in close association with sick patients. Accordingly, I talked with Weste, my old chief at the Upstate Medical Center in Syracuse, who accepted him as a graduate student for a PhD in Biochemistry. After receiving his doctoral degree, Joe was employed by a New Jersey pharmaceutical company. Although cystic fibrotic individuals usually died in their twenties, Joe lived into his early 40's because of the excellent postural drainage care his devoted mother had provided for many years. Today, most cystic fibrotic children live longer due to early detection through public and private newborn screening programs and greatly improved treatment.

The second case was a rare malignancy that I helped identify in a woman in her late 40's who had developed an unusual type of hypertension in which there was a sharp line of demarcation between her white chest and the redness of her body below her waist. The condition is caused by a carcinoid tumor of the gut, which puts out large amounts of serotonin that can be measured as vanillyl mandelic acid (VMA) in the urine. I used a Hycel Company VMA reagent kit system to quantify the large amounts of VMA in her urine. The patient was referred to the NIH Clinical Center where she later passed away due to a metastasis of the liver. At the time, I sent several urine specimens to the NIH Clinical Laboratory and requested confirmation of my quantitative results, but no response was ever received.

The last year I was at Memorial Hospital, I was able to arrange with Rex Conn, MD, a clinical pathologist at West Virginia University some 80 miles away, to give two lectures to the medical technologists every other week at Morgantown, West Virginia, and served as an Adjunct Assistant Professor of Pathology. Rex's main specialty interest was clinical chemistry, and I knew him through the Pittsburgh Section of the AACC to which we both belonged. We both attended most of the monthly dinner meetings of the AACC Pittsburgh Section even though they were 90–125 miles distant, and I served as Secretary of the Section during 1964–1965. Another member of the Pittsburgh Section was Mel Gindler, a PhD clinical chemist at St. Francis Hospital in Pittsburgh, with whom I worked on a titration method for the measurement of serum calcium, which we published (16).

Les had kept a relationship with his former colleagues in Pathology at Maryland and I flew down and back with him a couple of times in a chartered twin engined Piper Aztec. However, I didn't choose to fly with any of the physicians who were pilots after hearing about two who flew to a medical meeting in Boston and, after finding themselves low on gas in a cloudy rain storm over Massachusetts, descended and were directly over a small airport. Les also flew once to Philadelphia with Roy Hodges, MD, an obstetrician, who was taking his son back to medical school. Upon landing in Philadelphia, Roy forgot to lower the wing flaps and severely damaged the wheel brakes; thus upon their return to Cumberland Airport, they barely stopped before the end of the runway went off a cliff. Early on in Cumberland I did try out a two-seat glider that accommodated an instructor plus a passenger, but decided it wasn't a very practical hobby.

In September 1964, I attended a New York State Department of Health Symposium in Albany, New York, relative to a newly enacted law regulating the hospital and clinical laboratories in the state as of July 1, 1965. It was a Friday and I drove on to the Adirondacks Mountains to stay overnight with my parents at their camp in Eagle Bay. The weekend turned out to be the last time I saw my father alive, as he underwent a fatal massive dissecting heart attack as he stepped off the curb walking the dog two days before Thanksgiving in November 1964. The following spring, I was in contact with Donald "Don" Dean, DVM, the Associate Director of the Division of Laboratories and Research of the New York State Department of Health, and Theodore "Ted" Beecher, MD,

formerly Chief Pathologist for the VA Hospital System and now State Laboratory Pathologist. They negotiated the best civil service level position they could for the new State Laboratory Clinical Chemist position which required one to hold certification by the American Board of Clinical Chemistry (I held certificate # 252). On June 25, 1965, I accepted a final offer at a cut of 30% in salary for the opportunity and challenge to organize and direct a new innovative statewide program. At that time our oldest daughter was an entering high school freshman and our younger two children were entering first and second grade. Since my contract with Memorial Hospital required a three-month notice of termination, I took my vacation in August and left as of late September 1965. For the only time in my career, the family moved before I did.

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Chapter 8

Public Health

Although the New York City Department of Health was founded in 1873, the New York State Department of Health in Albany, the state capital, began as the Board of Health and Bureau of Vital Statistics in 1880. Unlike the New England states in which towns and churches kept records of births, marriages, and deaths from their earliest origins, vital statistics in New York State are available infrequently before 1881. The Health Department in Albany was also made responsible for a new Act to Prevent the Adulteration of Food and Drugs, passed in 1881, and established a Sanitary Committee to carry out this law (*1, p. 5*). Subsequent bacteriological studies involved Dr. Theobald Smith of Washington, DC, who used his new fermentation-tube technique for the detection of *Bacillus coli* and showed the Mohawk and Hudson Rivers to be polluted with bacteria, causing diseases including typhoid fever. In 1895, the Bender Hygienic Laboratory, a private corporation, was constructed on City of Albany-owned land by funds given by Matthew W. Bender. In 1896, a contract was made with the State for the bacteriologic examination of water and the examination of specimens for disease by the Bender Laboratory in association with the Albany Medical College and its teaching programs in bacteriology and pathology. The contract also provided for the instruction of county health officers in the techniques for bacteriological and pathological examinations. However, on January 1, 1910, the State Board of Health took over and established a State Hygienic Laboratory.

In 1906, Eugene H. Porter, MD, the new Commissioner of Health, established the first Sanitary Institute in the United States as a school for health officers and others interested in sanitation. It held sessions in Albany, Binghamton, and Rochester so that most city and county health officers could participate. Also in 1906, Leonard M. Wachter was appointed as Sanitary Chemist to the State Hygienic Laboratory to work on sewage purification at a small laboratory established by the Board of Sewer Commissioners of Saratoga Springs (*1, p. 33*). In 1914, the Division of Laboratories and Research and a Public Health Council were simultaneously established. The Public Health Council, with Leonard M. Wachter (1874–1933) in charge, had the authority to establish a State Sanitary Code and a Sanitary and Analytical Chemical Laboratory to handle water contamination and sewerage pollution problems. It was a source of interest and pride to the New York City Department of Health that the Legislature had extended to the state at large the principles

and methods of sanitary administration and research, which had been developed in the New York City program. (*1, p. 49*). In 1934, F. Wellington Gilcreas succeeded Mr. Wachter as the Director and served until August 1, 1955, when he resigned to become Professor of Sanitary Science in the College of Engineering at the University of Florida (*1, p. 189*). He was succeeded by Wallace “Wally” W. Sanderson, a staff member since 1940, who was in charge when I joined the state lab in 1965. Shortly thereafter, the Sanitary Laboratories became a part of the new Environmental Health Laboratories.

Herman M. Biggs, MD, and Augustus B. Wadsworth, MD (1872–1954), the first laboratory director, were instrumental in founding, in 1914, the Division of Laboratories and Research of the New York State Department of Health. Both had been associated with the Department of Bacteriology and Pathology of the College of Physicians and Surgeons of Columbia University. Dr. Biggs became chairman of the Commission that reorganized the New York State Department of Health, established a Public Health Council, which could make legally binding rules and regulations, and founded the Division of Laboratories and Research, the capstone of his career. The internal organization of the Division was made independent of the Commissioner of Health, a remarkable foresight, which kept its policies and actions independent of political interference until 1979 when Governor Hugh L. Carey appointed David Axelrod, MD, the Director of the Division of Laboratories and Research, to be the Commissioner of Health.

Dr. Augustus B. Wadsworth decided not to establish branch laboratories but to cooperate with hospital laboratories and directly with physicians and surgeons. He perfected a system of approvals under which private and hospital laboratories were authorized to perform tests of public health importance as early as 1915 on condition that they had demonstrated proficiency in procedures endorsed by the State Laboratory. Diagnostic methods and materials were supplied by the State and working relationships, ideas, and new developments were communicated through the meetings of the New York State Association of Public Health Laboratories founded in 1919. Dr. Wadsworth’s second operational principle was a goal of excellence and thoroughness for the Division of Labs and Research. One of Dr. Wadsworth’s most effective administrative procedures was a “scientific secretariat” whereby the several secretaries in the operating sections were women with an interest and training in science who served as a

group to coordinate the activities of the Scientific Staff, Media and Glassware, the Serum and Vaccine Laboratories, the Diagnostic Laboratories, and the Sanitary Chemical Laboratories. Decisions related to equipment, purchase, budgets, reporting, and the publishing of scientific findings were also handled by the "scientific secretariat." A Director's Scientific Staff at the doctoral level (PhD or MD) was established who were individual pioneers in medical research and assisted operating groups as the need arose. Members of the Scientific Staff were available as a resource to the technical staff of the operating sections, most of whom were women college graduates who had majored in science with a reading knowledge of French or German. Thus, after two years of schooling in research techniques at the Division, these women had the equivalent of master's degrees and worked as independent scientists who published their own findings.

Dr. Wadsworth opened the new Division of Laboratories and Research in 1914, in the old Hygiene Labs Building, with a staff of 36. By 1916, the staff had been increased to 70, with four times as much typhoid vaccine sent out as in 1914 and the most antitoxin ever. Also, the supply of testing materials to supply stations for local laboratories throughout the state had been increased. A State Farm and a Veterinary Laboratory for the production of rabies vaccine was established in 1914 near Voorheesville, southwest of Albany, and renamed the Griffin Laboratory in 1959 after its first veterinarian bacteriologist director, Charles A. Griffin, DVM (1889–1955) (1, p. 86). A nine-acre site for the new laboratories and animal facilities on New Scotland Avenue, opposite the Albany Medical College, was authorized for purchase in 1916 by the legislature at a cost of \$40,000. However, because the State Laboratories were involved in supplying antisera for pneumococcus, meningococcus, dysentery, and typhoid as well as being the sole source for antitoxins for the Army in World War I, construction was delayed until after 1920. The eight large brick buildings for the new, well-equipped labs on New Scotland Avenue included a power house for steam heating of the complex, facilities for media and glassware, tissue culture, bottling, and the manufacture of therapeutic and prophylactic preparations. In addition, research laboratories were provided for up to 1,500 staff. Owing to the immensity of the construction project, it took until 1929 to complete the largest public health laboratory complex in the world.

A 6,000-sq-ft branch laboratory was built in 1921 as a seven-story wing adjacent to New York University College of Medicine and Bellevue Hospital in New York City; 33 years later it was no longer needed and it was closed in 1954. In 1922, an International Conference of the Health Committee of the League of Nations met at the Pasteur Institute in France with representatives from 12 countries. Attendees included Dr. August B. Wadsworth as delegate for the Rockefeller Institute and for the United States; the Standardization of Serums and Serological Tests at the international level was implemented.

In 1923, new legislation provided for cities and counties to set up public health laboratories and, if they met the Division's approved standards, to be subsidized limited amounts for their construction and receive a 50% state reimbursement annually for their operation. However, participating laboratories were

required to demonstrate their proficiency (capability of doing the tests correctly) on test specimens. Belk and Sunderman first showed the need for proficiency testing of the clinical laboratories in the United States in 1947 (2), and Sunderman and Sunderman are given credit for setting up, nationally, the first monthly test specimen program. However, the submission of bacteriological specimens for proficiency testing by the State Laboratory in 1923 preceded by over 25 years the Sunderman and Sunderman Monthly Test Specimen Program of two analytes (components being tested) in chemistry or hematology started in 1950. I coauthored and updated the Program from 1977 to April 1981 when F. William "Bill" Sunderman, Sr., MD, PhD, turned it over to the American Society of Clinical Pathology. Bill Sunderman, Jr., MD, who became Chairman and Professor of Laboratory Medicine at the University of Connecticut School of Medicine in Farmington, Connecticut, was my second daughter's research mentor as an undergraduate medical student (1984) and directed her residency in clinical pathology and blood banking.

By 1928, 20 cities or counties maintained 26 main or branch laboratories. In 1929, the legislature enacted and Governor Franklin Delano Roosevelt signed a bill giving the Public Health Council the authority to establish qualifications for Directors and Bacteriologists in charge of laboratories (1, p. 98). Governor Roosevelt, on May 1, 1930, appointed a blue ribbon Commission of five distinguished medical leaders to survey the current and future health needs of the State, which is considered to be the outstanding event in public health since the founding of the Division in 1914 (1, p. 113). In 1931, an epidemic of poliomyelitis in New York City expanded to the Upstate area, and Governor Roosevelt, himself a victim of polio since 1922, persuaded the legislature to meet the emergency in spite of the Depression by providing \$115,000 to the Health Department, half of which went to the Division of Laboratories and Research.

It was 1927 before the first edition of *Standard Methods of the Division of Laboratories and Research of the New York State Department of Health* was published by Augustus B. Wadsworth, MD, and it soon became the "Bible" for public health laboratories the world over. An organizational chart is included in the third edition, published in 1947, which lists the then-current staff with references following each chapter, crediting the individual contributors (3). In 1929, research at the Division was devoted to communicable diseases and epidemics, such as "meningitis," that had been identified by county public health officers and observed by physicians at hospitals.

Thomas Parran, Jr., MD, became the new Commissioner of Health on March 10, 1930, the year that introduced the second half century of the New York State Department of Health, and spoke in Buffalo, on June 2, during the meeting of the New York State Public Health Laboratory Association. He reviewed the major role that the State Laboratory and its approval system had played in public health and blunted criticism of the predominant role it had played in public health by urging other phases of public health teaching and administration to push ahead and catch up. He further stated that he would see that future public health developments in the control of communicable diseases, as a

means of providing more scientific medical care, would not be made at the expense of the public health laboratory as a state activity. Subsequently, Dr. Parran served as Surgeon General of the U.S. Public Health Service (1936–1948) and was largely responsible for the founding of the National Institutes of Health (NIH) in 1943 as four bureaus, each dealing with a specified area of public health. Today, it is made up of 27 institutes and controls 25 billion dollars in funding (TV statement by Dr. Elias A. Zerhouni, Director, on September 20, 2005).

The resources of the Division of Laboratories and Research (DL&R) were open to many types of students for practical training in public health technology. In the 10 years from 1919 to 1929, nearly 200 students were admitted to the two-year volunteer course, with many assigned by the Federal Vocation Training Board and the War Department, and others assigned from other laboratories. In addition, numerous graduate students in public health, including those at the Johns Hopkins School of Public Health, founded in 1916 by the distinguished pathologist, Dr. William Welch, as well as many from abroad were trained in public health laboratory techniques and principles at the DL&R in Albany. In 1929, the State Laboratory was “duly approved by the Secretary of Labor as an institution of learning for immigrant students in accordance with the Immigration Act of 1924” (1, p. 103). At its peak, there were almost 1,500 staff and visiting scientists who came from all over the world to study public health laboratory methods, as well physicians from many academic institutions and countries to be trained in public health by the world’s leading authorities. Cooperative research with many other institutions was also carried out with Division staff.

Following recommendations from the Laboratory Committee and the Committee on Cancer, in 1931 the Public Health Council established qualifications for surgical pathologists, which became mandatory in 1932. Also, the approval system was extended to require the examination of tissue for neoplastic (cancerous) tissue. The American Board of Pathology, requiring similar qualifications, was established in 1936, four years later. In 1937, the Public Health Council adopted a resolution, which stated that diagnostic laboratory service is intimately concerned with the practice of medicine; therefore, a licensed physician or person eligible for a medical license must be in charge of the diagnostic service.

In 1931, Drs. Frank and Elizabeth Maltaner, members of the Director’s Scientific Staff, published a classical report on the serological complement-fixation test. In 1941, Mary C. Pangborn, PhD, isolated and purified a phospholipid from alcoholic extracts of beef heart, the antigen of the Wasserman test for syphilis used since 1922, which she identified as cardiolipin. This discovery by a member of the Director’s Scientific Staff was soon taken up by the National Institute of Serology for its worldwide application as a practical test for syphilis. Dr. Pangborn was the senior author of the World Health Organization Report on Cardiolipin Antigens in 1951, which was revised in 1955, the third of only three papers she ever published, but all classics, for which she won many national and international awards. In 1950, two antifungal agents were isolated from soil by mycologists Rachel Brown, PhD, and Elizabeth L. Hazen, PhD, one of which became Nystatin [NY

(for New York) plus statin; trade name Mycostatin]. Nystatin was the first broadly effective antifungal agent available to the medical profession and is still in use. The royalties have been used to support the Brown-Hazen Fund Lectures in medical sciences, which were established in 1958, and to help Division staff, such as Kent Miller, PhD, and Sally Kelley, PhD, attend medical school and earn MD degrees at the Albany Medical College, and my young protégé, Bob Rej, to earn a PhD in Biochemistry from the College in 1976.

In 1948, Gilbert Daldorf, MD, Director of the Division, and Grace M. Sickles isolated from stool the Coxsackie virus, which is related to the polio virus and produces muscle paralysis in children. It is “polio’s little brother” and not polio itself. Of some nearly half million polio victims in the United States by 1950, the best known was President Franklin Delano Roosevelt, former Governor of New York State, who died in 1945.

The military was very familiar with the influenza virus epidemic associated with World War I and decided in the first year of World War II that it wanted no health crisis heaped on top of a military crisis. Therefore, the celebrated Thomas Francis, Jr., MD, Professor of Microbiology at the University of Michigan, was ordered to work on influenza (4). In 1942, he recruited young Jonas Salk, MD, just coming off his residency, whom he had met at New York University (a private institution) when he was still a student. By 1944, Francis and Salk gave the military the world’s first influenza preventative in the form of the dead, not just weakened, virus. Dr. Salk was convinced that this approach would work for the polio virus, known for its century of devastation, and he and his colleagues, now at the University of Pittsburgh, first demonstrated between 1947 and 1952 that there were three different polio viruses (4). Next, Salk and his associates came up with ways to grow the viruses and then worked on a vaccine that could protect against all of them. In December 1951, the National Foundation for Infantile Paralysis (NFIP) gave Dr. Salk permission to move on to children with his new vaccine. Clinical trials on 40 childhood volunteers with polio, carried out in June 1952 at the D. T. Watson Home for Crippled Children in Leetsdale, Pennsylvania, near Pittsburgh, showed the vaccine to have variable degrees of effectiveness with the three strains of polio, but to be practical and worthwhile (4). After three more years of development, the success of the Salk vaccine, which was administered by needle, was announced to the world on April 12, 1955, 10 years to the day after the death of President Roosevelt, a polio victim. Later, Dr. Jonas Salk (1915–1995) founded the Salk Institute for Biological Studies in La Jolla, California.

In 1961, Albert Sabin of the University of Cincinnati perfected a polio vaccine made from a live weakened virus, which had the additional advantage of being administered orally on a sugar cube or by eye dropper to small infants. Our oldest daughter received the Salk vaccine and our two youngest children received the Sabin vaccine. By using the two vaccines, Salk and Sabin, polio has been almost totally eliminated worldwide (only 1,200 cases in Afganistan, Egypt, India, Pakistan, Niger, and Nigeria in 2004) (4). Rotary International, the only service club I have ever belonged to (1966–1998), contributed over \$200,000,000 toward its worldwide eradication. In addition, Rotary International has given over \$1.5 billion for various

humanitarian programs to promote literacy, alleviate hunger, provide safe drinking water, and protect the environment worldwide.

Blood transfusion techniques were developed during World War II and a Reference Blood Group and Rh Typing Laboratory was started at the State Laboratory in Albany in 1947 by Gretchen R. Sickles, a sister to Grace Sickles, who later directed the unit.

An Annual Conference in Surgical Pathology, for approved laboratories, was started in 1940 and in 1962 was renamed "The Joseph Schleifstein Pathology Conference" after the conference's organizer, from 1954–1962, passed away. At that time, Doris Collins, MD, a Jamaican graduate of McGill University who was the State Laboratory Pathologist, took over and sponsored the most distinguished pathologists in North America as guest lecturers. She was in charge of the several loan collections of "case type" tissue slides, collected mostly by the Pathology Department at Memorial Hospital Sloan Kettering Institute for Cancer in New York City between 1948 and 1952. Doris has a greenhouse at her home where she raises orchids and only recently retired at age 85. She is the most competent tissue pathologist I have ever known.

Maurice Hilleman, PhD (1920–2005), was a Philadelphia microbiologist who helped save millions of young lives by developing vaccines for mumps, measles, German measles, chickenpox, pneumonia, bacterial meningitis, and hepatitis A and B. He began work on a vaccine for mumps in 1963 after his five-year-old daughter, Jeryl Lynn, developed mumps. He was a co-discoverer of the adenoviruses, and discovered changes in the flu virus known as "drift." By monitoring these changes, public health departments can now track new flu viruses. Dr. Hilleman retired in 1984 as Sr. Vice President of Merck Labs in West Point, Pennsylvania, and undoubtedly was the most famous vaccinologist in history (5).

In 1963, Robert "Bob" Guthrie, MD, a research pediatrician in Buffalo, New York, published a simple filter paper blood spot method for the detection of inherited phenylketonuria (PKU) in newborns, enabling mass screening of large populations (6). Blood can be obtained from a newborn by a heel stick with a lancet. A couple of blood drops are placed on filter paper, with the filter paper then mailed to a central laboratory. The brain damage from PKU, which occurs in one out of every 10,000 newborns due to their lack of the enzyme tyrosinase that converts the amino acid phenylalanine to tyrosine, can be avoided by placing the child on a phenylalanine-free diet containing tyrosine. The state provided the special phenylalanine diet to parents, at no charge, for humanitarian reasons and because it avoided the child's later institutionalization in a mental health facility. At Bob's instigation, the New York State Legislature passed legislation in 1963 requiring that all newborns be tested for PKU as of July 1, 1964. Screening laboratories were set up at four sites in the state, including the State Laboratory in Albany, which I directed from 1965 to 1977.

We expanded the testing program to galactosemia, a condition in which infants are intolerant to lactose or milk sugar, which is made up of a molecule of glucose and a molecule of galactose. It too occurs once in about every 10,000 births and is well worth testing for, as it is easily treated by placing the

infant on a glucose (dextrose) formula. On the other hand, many adults develop lactose intolerance, including about 75% of African Americans, Jews, Native Americans, and Mexican Americans, and about 90% of Asian Americans. Later, congenital hypothyroidism in infants was recognized, which results in stunted growth in infants, and was added to the screening program. About 1975, we added the sickle cell factor, an abnormal type of hemoglobin that occurs in the heterozygous state in approximately 8% of American blacks and 30% of Central African blacks. In the heterozygous sickle cell trait, sickling does not occur until the oxygen tension falls to 40%, but in the homozygous sickle cell state (double S factor), sickling follows a fall of oxygenation to 85%. Thus, a mild chest cold or other breathing problems can put a patient in crisis. Several different sickle syndromes exist as the sickle cell gene can occur in combination with other hemoglobins such as Hb F (foetal), Hb C (a variant), and the thalassemias (inherited variations of hemoglobin-producing disease states) (7, p. 626). Owing to our diverse hospital patient population in Center City Philadelphia, hemoglobin electrophoresis was a routine laboratory test at the Hahnemann University Hospital Clinical Laboratories I directed from 1977 to 1990.

A news brief from August 2006 is titled *States Expand Newborn Screening* and states that almost 67% of the babies born in the United States in 2006 will be screened for more than 20 disorders, nearly twice the number as in 2005 (8). By June 1, 2006, eight more states, covering more than 64% of newborns, had initiated screening for more than 20 disorders.

Although the Public Health Council had declared in 1937 that a physician had to sign out all laboratory test findings, meaning bacteriological and public health specimens, there were no requirements as to their training or competency. This situation led to many hospital and independent clinical laboratories having inadequate direction by the early 1960's, and because the Division had little expertise in other areas of clinical pathology, such as clinical chemistry and hematology, there were no standards or requirements for independent laboratory directors.

William "Bill" Mason, MD, PhD, Director of Laboratories at the University of Rochester Medical Center and later a president of the AACC, became an advisor to Senator Metcalf of Auburn, New York, who sponsored pioneering legislation in the form of the Clinical Laboratory Act (CLA) of 1964, which took effect beginning July 1, 1965. It provided for an Advisory Committee representing all interests in clinical laboratory testing and performance standards for all clinical laboratories in New York State. CLA of 1964 also specifically recognized, as qualified laboratory directors, PhDs certified by the American Board of Clinical Chemistry and by the American Board of Microbiology, plus PhDs in biological sciences, who had five years of experience. After I became State Laboratory Clinical Chemist, I recall Bill telling me that he had asked Senator Metcalf if he needed any more help, and the Senator replied "If you were any more helpful, I couldn't stand it." Fortunately, Morris Schaeffer, MD, Director of Laboratories for the New York City Health Department, had detected problems in the operation of clinical laboratories in New York City as early as

1958, and they already had laws in effect regulating laboratories in the five boroughs of New York City. However, this still resulted in about 500 laboratories in the state program, including about 125 laboratories in Nassau and Suffolk Counties on Long Island, which were a part of Upstate New York from a regulation point of view. Through state regulation, economic factors, and normal attrition, the total number decreased to 460 by 1968. The new Clinical Laboratory Act of 1964 was one more instance where New York State provided national leadership in the public health field.

In 1965, major legislation at the Federal level resulted in the adoption of Medicare by Congress. Eventually, Medicare reimbursements for laboratory testing made unnecessary the 50% reimbursement to city and county laboratories by the State of New York. This cost shifting to the federal government, along with the new New York State Clinical Laboratory Act, had a major financial impact on the city and county, as well as independent laboratories and the large and small hospital laboratories in New York State.

The Division of Laboratories operated under three types of law: the first being the intent of the legislation; the second, the Sanitary Code as defined by the Public Health Council; and the third, the Rules and Regulations as promulgated and filed by the Division. Because the latter were the easiest to change with the passage of time, laboratory director requirements, quality control and quality assurance requirements, and performance standards fell into this category. Violators had the opportunity to state their case before an independent administrative judge who made a decision, which if not accepted, could be taken to the Supreme Court, the Court of Appeals, and then the Appellate Division (highest court in New York State). We took a soft-glove persuasive educational approach to bringing laboratories and directors into compliance with the Rules and Regulations, and I only participated in administrative hearings twice in my over 12-year career with the Health Department. The power, authority, fairness, and reputation of the Health Department were sufficient to bring any laggards into the fold without any need for a contentious legalistic approach.

Recognizing that I was in a legal interface with science, I kept notes on every telephone call I received or made and tried to be very discrete in my comments on new instrumentation. Early on, I had a neighbor who was the sales representative for a very excellent Swedish serum electrophoresis instrument, and he wanted to demonstrate the instrument to my group. However, before he could do so, I heard that he was telling people that we were evaluating his instrument, and so I called up and cancelled the appointment. Warner-Chillcott had a quick and simple test tube strip method for semiquantitating urea nitrogen, which increases in kidney disease, but we took the position that it did not meet the standard of a quantitative blood urea nitrogen (BUN), and my decision was never challenged.

In 1965, laboratories operated by bioanalysts, technicians, and persons with little educational training and very variable credentials provided routine laboratory services in clinical chemistry and hematology. Because one cannot, by law, *ex post facto* take away a person's right to make a living, the new law grandfathered-in existing laboratory directors. The Clinical

Laboratory Act provided for an Advisory Committee to the Division, which was in operation before I joined the Department and had adopted a reference laboratory system. Five University Hospital clinical chemistry laboratories set the target values for the unknowns to be circulated to participating laboratories; a brilliant approach that has withstood the test of time. Laboratories were permitted to use any chemical test method they desired to determine the two-test specimen results. Commercial controls with assigned values were used for early evaluation purposes.

Testing was soon expanded to samples mailed four times a year. Because the Division had bottling facilities for small vials, we collected waste serum from the Albany Medical Center Clinical Chemistry Laboratories and outdated blood from their Blood Bank and manufactured our own normal and abnormal samples with unique values. Although we used a normal and an abnormal specimen in both the hand-carried and mailed specimen programs with multiple coding, the participating laboratories had no clue as to the identity of the pair of specimens they were to analyze. In addition, our program soon had eight clinical laboratory investigators (medical technologists who were knowledgeable in state requirements), with state cars, who were assigned to various regions of the state and who hand-carried specimens, which were required to be done on-site at the time of the inspection. We trained the lab investigators in Albany, reviewed their evaluation reports as needed, and provided in-service training opportunities for them.

The pathologists of the state took the position that they were already licensed to practice not only Anatomic Pathology, but Clinical Pathology (Clinical Chemistry, Hematology, Microbiology, Blood Banking, etc.), which today is known as Laboratory Medicine since the boundary lines between the disciplines have diffused. Unfortunately, the College of American Pathologists (CAP), after five years, grandfathered Anatomic Pathologists as being qualified laboratory directors in Clinical Pathology, even though they had had no formal training. Their challenge to the New York State Public Health Law went all the way to the Supreme Court of the United States and, in a consent degree in 1969, the CAP accepted that Clinical Pathology (now Laboratory Medicine) was not the practice of medicine and the State of New York had the right, under Public Health Law, to protect the health of its citizens by requiring all hospital and independent clinical laboratories operating in New York State to meet the requirements of the Clinical Laboratory Act of 1964.

The American Chemical Society (ACS), the largest scientific society in the world with 110,000 members in 1969 and chartered by Congress in 1937, and the American Association for Clinical Chemistry (AACC) had strongly supported the Supreme Court challenge as *amici curiae*. Today, the AACC has 9,500 members, and over 15,000 laboratory scientists and technologists attended its annual meeting and clinical laboratory exposition in Orlando, Florida, in August 2005, the largest such show in the world. The field of chemistry (not just clinical chemistry) has expanded to include molecular diagnostics and immunology and has become a multidiscipline, with the ACS now having 159,000 members from around the world—ranging from corporate executives to unemployed chemists—for which it provides meetings,

programs, publications, and services, and holding a billion dollars in assets (9). I joined the ACS in 1947 and served as a member of the ACS Committee on Clinical Chemistry from 1976 to 1990. From 1971 to 1989, I was a delegate from the ACS to the National Committee on Clinical Laboratory Standards (NCCLS), which became the Clinical and Laboratory Standards Institute (CLSI) as of January 1, 2005. I served on the Council of the National Reference System for Clinical Laboratories, a part of NCCLS, from 1978 to 1991, and as Chairman in 1988–1990 and Vice Chairman in 1991. During my 13-year tenure on the Council, we approved about 20 standards and guidelines, which I coauthored, a number of these as the first author. Earlier, I had founded the Subcommittee on Enzymes of the AACC Standards Committee (1971–1974), was a member of the Standards Committee from 1971 to 1976, and became the third Chairman to hold the office in 1974–1976. From 1980 to 1993, I served on the Commission on Accreditation in Clinical Chemistry (ComACC), which inspected, on-site, postdoctorate and master's degree training programs, and served as its Treasurer from 1982 to 1984 and its President from 1985 to 1988.

Although pathologists today are required to pass an examination in Clinical Pathology (Laboratory Medicine), there are still problems, as revealed by a major clinical laboratory failure at Maryland General Hospital in Baltimore in May 2004 that

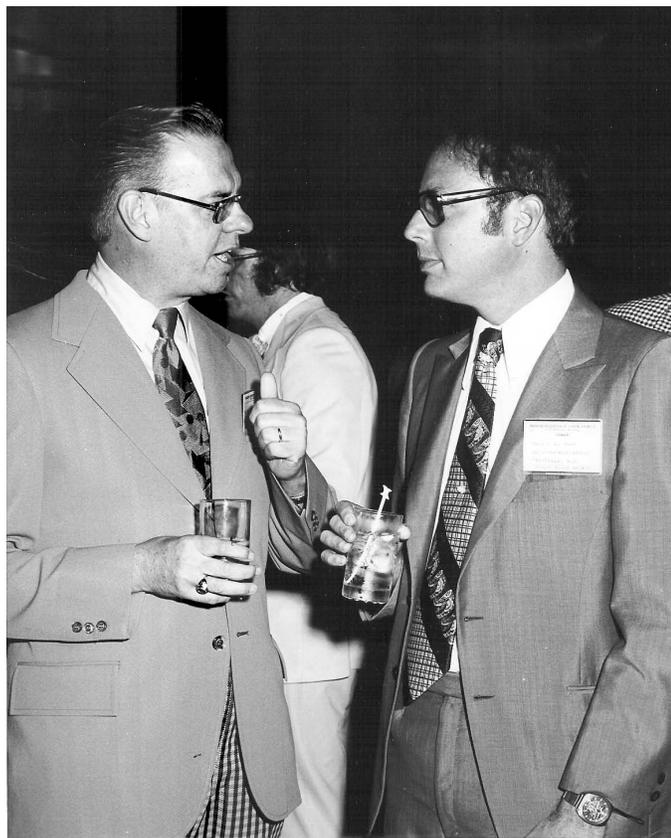
led to a Congressional investigation. As an emeritus Professor of Pathology and Laboratory Medicine and a university hospital clinical laboratory director, it is my view that pathologists become well-trained in tissue pathology, their main interest, but are inadequately trained in Laboratory Medicine and in the review of quality control and quality assurance as it applies to clinical laboratory data. Although the College of American Pathologists improved its inspection program to include more thorough and unannounced inspections beginning on January 1, 2006, it has not addressed the issue of better training in Laboratory Medicine and quality control and quality assurance.

As of July 1, 1965, almost 500 laboratories in the state of New York were required to be certified and meet performance standards. Because the New York State Society of Pathologists opposed the law, volunteers in the clinical laboratory specialties (Blood Banking, Hematology, Clinical Chemistry, and Microbiology, and subspecialties such as Mycology, etc.) performed many of the original inspections, and I performed some on Long Island in August 1957 as a consultant to the Department during a vacation from my position at Memorial Hospital in Cumberland, Maryland. I had earned certification (#252) by the American Board of Clinical Chemistry (and Toxicology) in 1960 and had 11 years of clinical laboratory experience, which led to my selection as the first State Laboratory Clinical Chemist, serving from September 15, 1965, to January 15, 1977.

Victor "Vic" Thompkins, MD, was the Assistant Commissioner and Director of the Division of Laboratories and Research (DL&R or State Lab). However, Donald "Don" Dean, DVM, was Director of Operations and the decision maker for the Clinical Laboratory Center (CLC), the Sanitary Chemistry Center, and the Scientific Laboratories for Research, with Clark LeBoeuf in charge of Administration (Finance, Human Resources, meeting Civil Service requirements, etc.). Don also accompanied Hollis Ingraham, MD, the Commissioner of Health, on all of his out-of-town trips.

After one year, Theodore "Ted" Beecher, MD, the first State Laboratory Pathologist, left to become Director of Pathology at St. Peter's Hospital in Albany, and was replaced as head of the CLC by William "Bill" Kaufmann, MD, recently retired Chief of Pathology at Springfield Hospital in Springfield, Massachusetts. Bill, who wore a leg brace as a result of polio, was born in Belgium and attended medical school in Switzerland. Bill foresaw Hitler's persecution of Jews coming, arrived in the United States in 1936, and took his training in Pathology at the Albany Medical College. His parents had lived in Belgium for a long time and he considered himself to be Belgian and supported numerous Christian charities in the United States. Although he was a member of the College of American Pathologists, he was an independent thinker and maverick pathologist who did not accept the party line of the College; in his words "You don't put the FAA (Federal Aviation Authority) in charge of the airlines."

The culture of the Division was for Division-trained college graduates to work independently. The PKU screening unit was promptly made a part of Clinical Chemistry, and Miss Krumwied, who was the old-time Division-trained associate in charge, quickly resigned. On the other hand, Miss Grace



Ray Vanderlinde, left, and Dr. Robert Bush, right, at AACC meeting, 1973.

Photo by Bela, CSEH, East 83rd St., New York, NY. Sent by Chris Monahan of General Diagnostics.



AACC Professional Affairs Committee meeting on January 27, 1985, at the Hotel Coronado in San Diego, California. Ray Vanderlinde, Chairman, in center. Pamela Nash, current AACC Vice President of Policy & Programming is seated to the right of Dr. Vanderlinde. Sam Meites, PhD Childrens Hospital, Columbus, Ohio, is seated to the left of Dr. Vanderlinde.



ComACC (Commission on Accreditation in Clinical Chemistry) Board meeting in July 1991. All present were PhD Clinical Chemists. Left to right, beginning from bottom left: Roger Thibert, Bob McComb, Alan Wu, Ed Bermes, Owen Ash, Bob Roberts, Larry Silverstein, and Ray Vanderlinde. Presumptively Ed Bermes was President and Chairman. Dr Vanderlinde was the first President and later the treasurer of ComACC.

Photo by Oscar and Associates Inc., Chicago, Illinois.

Sickels, the Division-trained associate in charge of Blood Typing, could not have been any kinder and taught me how to inspect Blood Banks. I quickly found an excellent replacement for Miss Krumweid from Civil Service eligibility lists where one had the choice of any of the three top qualifying candidates.

A French physician, Jacques "Jack" Bourdillon, MD, who was on the Director's Scientific Staff and had been nonproductive, was assigned to Clinical Chemistry, where he automated the PKU blood screening method on a new one-channel Technicon Autoanalyzer, and documented in a paper published in 1966 (10). A few months later, Jack retired to his native France. His vacated position was later filled by Hiromichi "Hiro" Narahara, MD, a board-certified internist turned biochemist, who established his own NIH-funded biochemical research program involving, over the years, several postdoctoral (MD/PhD) students from Japan.

In 1965, Medicare was approved by Congress, and, in 1967, I became a member of a committee establishing many of our New York State requirements as part of the Federal Code of Regulations for Medicare (11) and the Committee for Defining Satisfactory Achievement for Laboratories Engaged in Interstate Commerce, also in 1967 (12). The Communicable Disease Center (CDC) in suburban Atlanta became the organization in charge of the Interstate Program and they sent their newly hired clinical laboratory investigators to Albany for training. However, most significant was the fact that Medicare reimbursements for outpatient laboratory testing on Medicare patients effectively did away with New York State's need to provide 50% of the funds needed by city and county laboratories.

We were soon able to demonstrate, over a 21-month period and using specimens of known content, the incompetence of several hospital and independent laboratories in satisfactorily quantitating glucose and urea nitrogen, the most common tests, with our findings published in the prestigious *New England Journal of Medicine* (13). Our paper called national attention to the fact that there was a serious problem with the clinical laboratories in the United States and, particularly, in small hospital laboratories. These two test procedures were the major tests for diabetes and kidney disease, and constituted about half of all routine laboratory testing in Clinical Chemistry. Dr. Dean said, "The Department cannot condone poor performance," and as of July 1, 1967, we did not renew the permits of about two dozen small independent laboratories and about two dozen small hospital laboratories in New York State. This placed these laboratories in the awkward position of either having to refer their specimens to a laboratory under permit, or to operate illegally and be subject to lawsuits. The prestige and authority of the New York State Health Department were so great that we had no need to act like a police agency to bring about compliance. As the first full-time director to come aboard in the Clinical Pathology subspecialties of Clinical Chemistry, Hematology, Microbiology, and Blood Banking, I led the way with an educational approach to laboratory improvement, which was welcomed with open arms.

Dr. Dean felt that clinical laboratories operated by other state units, such as the departments of Mental Hygiene, Civil Service, Social Services, and Corrections, etc., should meet

the same standards. Because nine assistant or deputy commissioners and one commissioner were my fellow church members in Delmar, it became an easy matter to learn what facilities each had and the proper agency contact for the Commissioner of Health. Our CLC secretaries were astonished at what I accomplished in a couple of hours one morning. Maybe this is what later made me the Commissioner's resource for unique problems (through John Browe, MD, a physician who had been on the Bataan Death March in the Philippines and was head of our Bureau of Nutrition). I answered the phone one morning and John said, "Ray, what do you know about tit stretchers?" My reply, when I knew he had a secretary close by, was to admonish him for such crude speech. His reply was "That's all right, I have a male secretary." Apparently, in New York City they were selling devices to "enlarge women's breasts," and the State Attorney General's Office had asked our Commissioner to provide an expert medical witness. As it happened, about a month earlier, a Cornell Medical School research endocrinologist spoke at a Radioisotope Symposium in New York City that I had organized, and he fulfilled the role as our expert witness. Another time, John asked me for an expert on setting up a human breast milk bank (like a blood bank). It didn't take me long to recall, from my training in nutrition, that human breast milk and cow milk are very similar and that Cornell Agricultural College in Ithaca, New York, had a number of dairy experts. Although the human breast milk bank was never set up, in 2006 The International Breast Milk Project in Rochester, Minnesota, became "the first organization in the world to provide donor breast milk from the United States to babies orphaned by disease and poverty" (14).

The most sensitive problem in 1966 was at Roswell Park, the world-renowned New York State cancer research institution and hospital in Buffalo, a part of our State Health Department, whose clinical laboratories were in shambles. In fall 1966, Dr. Bill Kauffman, director and chief pathologist for the Division, and I were assigned to inspect the facilities of this "publish or perish" institution where the clinical laboratories were in charge of an MD research scientist with about 250 publications, who knew little about directing a clinical laboratory. Also, one of their prominent surgeons served as Deputy Commissioner of Research of our Health Department. We were greeted at Roswell Park by James "Jim" Grace, MD, an internationally known surgeon, who was our gracious host for much of the day and let us thoroughly inspect the laboratories, which were even more abominable than we had anticipated. Thus, we were in a very delicate and sensitive situation. While flying back to Albany, we discussed the problem and what was needed. After further discussion, the next day Bill said to me, "Write it up, Ray, and we'll go over it." I wrote a four-page draft summarizing the problems, with recommendations for their correction, and sat down with Bill to discuss it. He edited it, added a couple of comments, and after being retyped on Department stationery, we both signed it and sent it off to the Commissioner of Health. We decided it was worth putting our jobs on the line because we both had good credentials and, in the worst scenario, we could get better positions in the private

sector. However, the Civil Service and Budget Departments acted promptly on the crisis, and within a few weeks Roswell Park was authorized to hire a qualified clinical pathologist as director and several new staff members, and to purchase much new equipment. Unfortunately, about two years later, a tragedy occurred when Dr. Jim Grace and his wife were killed in a head-on automobile accident.

Early on, I learned that many technical personnel and small laboratory directors did not know the difference between the pure material used to set the measuring stick, that is the standard, and the serum material, a control, used to make sure the analytical procedure is giving the correct result. My response was to organize traveling training programs at various central locations over the state, where we taught proper standardization and quality control techniques and recommended analytical procedures we knew had accuracy and reliability. I was assisted at the early sessions by Pat Kowalski, a bachelor's degree biochemist on my staff and my associate, Charles Fasce, PhD, who had been trained in Clinical Chemistry by Mike Vanko, PhD, Director of Clinical Chemistry at the Albany Medical Center. As a state unit, we could not accept money *per se*, so we set up an account in Health Research, Inc., a separate organization, which enabled us to charge \$3 for registration at our teaching and symposia programs. The small registration fee enabled us to provide coffee and doughnuts during coffee breaks and let us know in advance the number of attendees.

Later, after James "Jim" Kelly, MRCP (Member of Royal College of Physicians), an Australian, came on board, he and his technologist participated in providing training in basic Hematology. Serum uric acid, which increases in gout, the disease of the well-born and well-fed, and serum creatinine, an alternate test for kidney disease, were the next two analytes we investigated before including them in our routine proficiency test specimens. Bill Copeland, MS, participated in some of the later road shows involving creatinine/uric acid (15) and the measurement of the transaminase enzymes (SGOT and SGPT) for liver disease and the lactate dehydrogenase enzymes (LDH) for myocardial infarction.

Even though the New York State Society of Pathologists did not support the Clinical Laboratory Act of 1964, their members worked with the Upstate New York Section of the AACC. In 1967, Ted Beecher, MD, and I co-chaired the planning meeting for a very successful symposium on liver function and disease, held on October 20–21, 1967, at the Thruway Motor Inn, in Albany, New York. Participants included both local and national figures in medicine, including J. Lowell Orbison, MD, Professor of Pathology and Dean of the University of Rochester School of Medicine and Dentistry, Frank N. Allen, MD, of the FDA, Hyman J. Zimmerman, MD, of the Veterans Administration and George Washington University in Washington, DC, Kamal Ishak, MD, PhD, of the Armed Forces Institute of Pathology, and Stanley Robbins, MD, of the



Bill Copeland, MS (left), NY State Department of Health, Albany, NY, Royden Rand, Ph.D. (middle), St. Mary's Hospital, Rochester, NY, and Ray Vanderlinde, Ph.D. (right). Photo taken at an enzymology session, Marriott Hotel, Arlington, VA, in 1981.

Mallory Institute of Pathology in Boston. Later, Dr. Robbins became Visiting Professor of Pathology at Harvard and coauthored *Robbins' Pathologic Basis of Disease*, the pathology textbook we used at Hahnemann. This was the first of several joint sessions that the Upstate New York Section of AACC held with the pathologists. I was a charter member of the Upstate New York Section in fall 1957, served as the third chairman in 1959–1960, and, after returning to New York State in 1965 as part of the State regulatory program, was elected as chairman for 1966–1967. In summer 1967, I spent a week at the Nutrition School at the University of Texas at Galveston, after which my staff at the Division performed 27,000 analyses for the New York State Nutrition Survey, which was sponsored by the Womens, Infant, and Children's Division (WIC) of Health and Human Services.

In 1972, Bob Rej, a young bachelor's degree chemist at the State Lab under my supervision, isolated and purified the main enzyme used to test for liver damage, which is known by most clinicians as serum glutamic oxalacetic transaminase (S-GOT) or, technically, by the name L-aspartate: 2-oxoglutarate aminotransferase (AST) (16). Subsequently, we took it through the proper official bodies for its recognition as the first and only enzyme to be standardized at the national and international levels except for its sister enzyme, serum glutamic pyruvic transaminase (S-GPT) (17).

Of the over 40 papers we published on various serum enzymes, the most outstanding are "An L-Aspartate: 2-Oxoglutarate Aminotransferase Reference Material from Human Erythrocytes: Preparation and Characterization," important in the detection of liver damage (14); "A Discussion of Enzyme Reference Materials: Application and Specifications" (18); and our pioneering work on the pure isoenzymes, lactate dehydrogenase (LDH) 1, observed in heart damage, and LDH 5, observed in liver damage (19–21). Also, our New York State surveys included "A Study of Ultraviolet and Visible Wavelength Spectrophotometers" (22), probably the finest evaluation of instruments ever carried out and, in 1973, "Proficiency Testing in Acid-Base Analyses: An Interlaboratory Evaluation" (23), the first ever evaluation in the area of blood gases, which are so clinically important in the regulation of body acid–base balance by the lungs and kidneys. In 1985, I attended a three-day symposium sponsored by the NCCLS on "A Reference System for Enzymology," where it was my pleasure to present major papers entitled "Enzyme Assay Standardization: Early Activities" and "Enzyme Reference Materials: Early Activities" (24).

Dr. Bernard "Bernie" Brody, an internist with a masters degree in chemistry, Medical Director of the Genesee Hospital in Rochester, one of the best hospitals in the state of New York, and Director of Laboratories, and Martin Murray, MS, Director of Clinical Chemistry at the Genesee Hospital in Rochester, were very generous in having us as their guests and providing up to week-long educational training sessions for our clinical investigators and our staffs in Clinical Chemistry and Hematology, at no cost to the State. Because our State Laboratory was not a service laboratory in Clinical Chemistry and Hematology, their generosity as hosts enabled us to stay

up-to-date on newer and specialized tests in the field. At that time, laboratory testing was growing at a rate of 10–15% per year and doubling in volume every five years. Martin was a very forward-looking individual and saw, in 1970, the need for the computerization of laboratory data. Flooded with volumes of patient data from a variety of instruments, Martin had four bachelors degree clinical chemists trained in computer technology, and his laboratory became the first clinical laboratory, that I know of, to successfully interface multiple instruments to a computer and produce directly reportable patient charts. As I recall, he used a large free-standing IBM 1070 computer. Previous attempts by others had been unsuccessful because of the inability of computer programmers to understand laboratory tests and needs.

After the Technicon automated SMA 12/60 (Sequential Multiple Analyser; providing a 12 chemistry test panel at a rate of 60 specimens/hour) instrument became available in early 1966, it soon became the routine workhorse in most of the large hospital and large independent laboratories throughout America (25). Even some small institutions began using the SMA 12/60 because of its availability and a shortage of adequately trained technologists and technicians to keep up with the expanding workload of test demand. When I was a visiting scientist in South Korea in 1974, there was only one SMA 12/60 in the whole country, which was at the Yonsei School of Medicine where I gave a lecture and received a plaque.

However, by 1975, almost every patient receiving an annual physical examination expected an SMA 12-chemistry panel to be performed as part of it, and this was called by one author "The Great American Fiasco." Although chemical profiles were very useful in diagnosing clinical disease entities (26), most clinicians did not realize that as many as 46% of normal individuals will have one or more tests out of limits when a battery of 12 tests is run using limits of ± 2 SDs. Because clinicians looked at only individual patient charts, they probably ignored occasionally slightly abnormal results.

About 1966, the Federal Highway Safety Commission started requiring states to have breath and blood alcohol programs in effect at the 0.15 level if they were to obtain matching Federal Highway funds. Because no traffic safety commission existed in New York State, the Division of Labs & Research of the Health Department became the responsible agency. After reading up on the subject, which had been covered in my American Board of Clinical Chemistry examination, and consulting with the leading American expert on blood alcohol, Kurt Dubowski, PhD, a state of Oklaholma toxicologist who attended our AACC national meetings, it was my privilege to write our new departmental regulations with Ambrose P. Donovan, Jr., Esq, associate attorney for the Health Department, and an advisor from the State Police Laboratory, Captain Stark Ferris, who became a good friend. Bill Kauffman, MD, became the agent who signed the permits, and I became Technical Director of the program.

At the time, New York State Law expressed blood alcohol content as volumes percent rather than in gm/dL, so the first

agenda item was to write Departmental Rules and Regulations stating that volumes % shall be interpreted to mean gm/dL for both blood and breath alcohol. Secondly, in measuring blood alcohol with a Breathalyzer or by a chemical procedure, we required that a control be run with each test specimen. The state crime labs dealt with whole blood specimens and analyzed them by a chemical method, but police officers primarily used Breathalyzers. Under our Rules and Regulations (equivalent of law), if the control in the method being used came out within acceptable limits, the results were *prima facie* evidence of driving under the influence, without the police officer having to be present to testify in court. Our certification program was very important because so much police time was spent waiting for hearings, which were often postponed or rescheduled. I had the opportunity, as a civilian, to attend a meeting of the five State Police Majors, each head of a division barracks, to explain how the new program would function. Also, Bill Kauffman and I visited the New York City Police Department for a tour of their Manhattan headquarters.

In 1966, a law was passed making it illegal in New York State to drive under the influence of a stimulant, depressant, narcotic, or hallucinogen. There was no possible way to enforce this piece of legislation because no one knew how to measure the blood levels of the analytes, but the analytes or their metabolites were detectable qualitatively (presence or absence), in urine, by at least two well-known chromatographic systems (27). Heroin on the East Coast was primarily cut (diluted) with quinine, which leaves telltale markers in the urine. Although a Drug Abuse Addiction Commission had been created by the legislature in about 1968, its function was to identify and treat drug addicts at methadone clinics. Because Buffalo was a jungle of "drug abuse," much like New York State, but on a smaller scale, in 1971, we initiated the first proficiency testing for identification of drugs of abuse in urine, as a joint program with New York City Department of Health Toxicologist, Bernard "Bernie" Davidow, PhD.

Because my staff handled the preparation and bottling of all the test urine specimens, I drank gallons of tonic water over the next several years because urine specimens had to be drug-free except for quinine spots. Some specimens with known drugs present were furnished by my clinical chemist colleagues, John Meola, BS, and Mike Vanko, PhD, at the Albany Medical College. Early on, I called my friend Irving "Irv" Sunshine, PhD, Cuyahoga County (Cleveland) Toxicologist, and he said, "Ray, if a lab finds present a drug metabolite that isn't there, i.e., a false positive, they should be failed." I knew that with ten urine specimens for testing, we could not fail labs with one false positive, so I set up an evaluation system in which a false positive cost the lab twice as many points as missing a drug. We used the State Police Lab and the four medical examiner labs in New York State as our reference laboratories. I held the Federal Narcotics License for the Department of Health and obtained several of our pure reference drugs from Captain Stark Ferris of the State Police Laboratory, as well as purchasing several others. During a visit to the State Police Laboratory, their walk-in refrigerator

was primarily full of marijuana plants that were to be used as evidence in court.

The drug of abuse program included both mailed and hand-carried specimens, but we did not send our lab inspector for an on-site inspection with hand-carried specimens until the laboratory had performed satisfactorily on one set of mailed specimens (28). On November 9, 1973, I presented our two years of experience in drug of abuse testing at a meeting of President Nixon's Special Action Office for Drug Abuse, which was attended by military brass who promptly implemented our techniques, as did the Communicable Disease Center for the Interstate Laboratory Program. About 1975, four vice presidents of a large New Jersey pharmaceutical company that analyzed urine specimens from New York State wanted instantaneous approval (maybe they had lost their license) and went to see Dr. Kaufmann. However, a few minutes later, they appeared, slightly embarrassed, in my small office because Bill had told them, "Dr. Vanderlinde is in charge of that program; you'll have to see him." No wonder Bill was such a wonderful chief and that we stayed lifetime friends from 1976, when he retired, until his death about 4 years ago at age 94! My reply to them was "Sorry, gentlemen, but you'll have to abide by the same rules as any within-state laboratory." In a court case much earlier, it had been decreed that, similar to milk inspections across state lines, we had to offer out-of-state laboratories that analyzed patient samples from New York State equal opportunity to participate in our programs.

In 1974, we expanded into a quantitative toxicology evaluation program in which serum samples containing a barbiturate and phenytoin, together with either glutethimide, procainamide, or theophylline were sent to participating laboratories (29). Within the first two years of the program, the percentage of laboratories able to quantitate 75% of test samples within 25% of the true value increased from 25% in 1974–1975 to 40% in 1975–1976. The prime obstacles to obtaining uniform accuracy were the lack of adequate calibration or the availability of a matrix (serum)-based drug standard (30).

In 1972, I was one of 13 laboratory physicians and scientists, including two clinical chemists, appointed to the FDA Advisory Committee for new federal regulations requiring proper labeling of clinical laboratory reagents and medical devices. I became chairman of the Subcommittee on Clinical Chemistry and Toxicology. This was a very difficult task and I soon learned it was impossible to try to reach a consensus until everyone "had their say." The committee operated as a "sunshine" committee, with all of the manufacturers having high-level officials, primarily their directors of quality control or vice presidents of marketing, present around the fringes of the meeting room. Recognizing early on the importance of calibration materials as the basic source of variation of results between laboratories, Alfred "Al" Bracy, MS, of the FDA, Ronald "Ron" Laessig, PhD, clinical chemist from the Wisconsin State Laboratory (the other clinical chemist serving on the Committee) and I wrote an excellent document on calibrators. In 1974, the Advisory Committee recommended unanimously that this document,

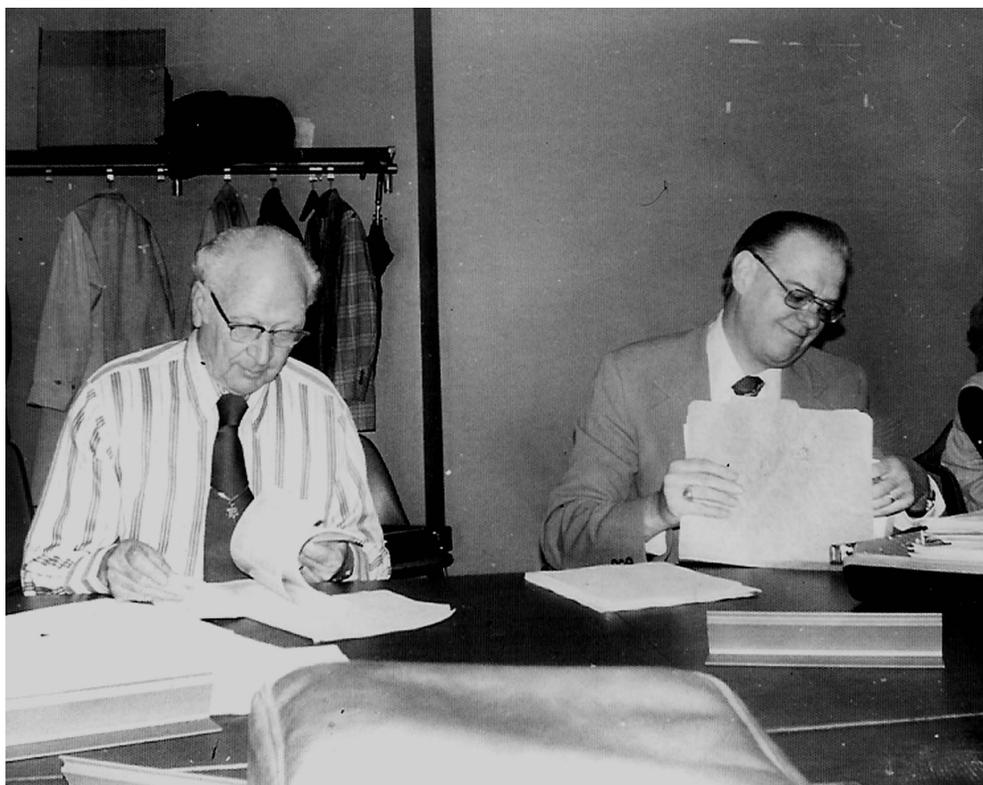
applicable to all areas of Laboratory Medicine, be adopted by the FDA. Instead, it languished on the desks of FDA officials. Thus, a golden opportunity to solve this very serious problem was lost for all time because high officials of the FDA failed to act and implement it. As a matter of fact, I wrote a letter of resignation to the FDA in late 1976 citing this fact. I was very pleased to recently read about FDA Safety Officer Dr. David Graham “blowing the whistle” on the inability of FDA officials to carry out their responsibilities in regard to drug safety. As an Advisory Committee, we had to look at all of the tests in clinical chemistry and clinical toxicology and classify the tests into categories. Secondly, when the response to every test procedure became “Yes, someone could die in the case of an extremely abnormal value,” my creative mind got bored with the whole process and I resigned, politely telling the FDA where they could go.

A letter from George Bowers, Jr., MD, Director of Clinical Chemistry at the Hartford Hospital in Hartford, Connecticut, and Professor of Biochemistry at the University of Connecticut School of Medicine, best summarizes my 1965–1977 career with the Division of Labs & Research: “The New York State Health Laboratories will never be the same without you, Ray. I consider the work you sponsored while at Albany the outstanding example of what a scientific approach towards regulations can produce. My hat’s off to you.”

THE NEW YORK STATE ASSOCIATION OF PUBLIC HEALTH LABORATORIES

The directors of local public health laboratories in the cities and counties of New York met in Albany in 1916 for intensive training in pneumococcus typing, which resulted in the formation of The New York State Association of Public Health Laboratories. Dr. Warren B. Stone, Director of the Laboratory of Ellis Hospital in Schenectady, was elected the first president. Shortly thereafter, Dr. Stone brought about the expansion of their hospital laboratory to meet the needs of both the city and county. In 1919, an assistant director of the Division of Labs and Research for local laboratories was appointed, and the New York State Association for Public Health Laboratories (NYSAPHL) held its first mid-year meeting on November 12, 1919, in the initial building of a complex of eight buildings and a powerhouse the Division was to occupy on New Scotland Avenue in Albany. Over the next 45 years, the NYSAPHL, aside from routine business and committees, devoted its meetings to a lecture of general interest, training in the latest approved techniques, and the updating of pathologists, cytologists, bacteriologists, mycologists (fungi), and blood bankers from approved laboratories.

This distinguished organization held most of its annual two-day workshop meetings at the State Laboratory facilities in Albany, including in 1965 through 1976, but the emphasis had



Grant Wernimart, PhD (left), retired statistician/QC expert from Eastman Kodak, and Ray Vanderlinde, PhD (right), Chairman of the Subcommittee on Clinical Chemistry and Toxicology, during an FDA Advisory Committee meeting in 1972.

changed to Clinical Pathology (now Laboratory Medicine). I was heavily involved in making the arrangements and organizing the sessions as several centered on clinical chemistry, toxicology, coagulation, and hematology, as well as microbiology and serology. In 1975–1976, I had the honor of serving as the third PhD president of this illustrious group of pathologists, blood bankers, hematologists, microbiologists, and clinical chemists.

In 1964, Governor Nelson Rockefeller, a very progressive leader, had legislation passed for the development of a new Department of Environmental Conservation. However, environmental testing involving health issues became a part of the Health Department, and the Division of Labs & Research was assigned heavy trace metals detrimental to health. These pollutants consisted primarily of mercury, which was present in edible fish, and lead in interior house paints, which affected young children.

One of my early assignments with the Health Department was to review the literature on lead poisoning, and over a nine-month period, I collected almost a file drawer full of information on its determination and its effects on health. The literature made me recall our Baltimore days where a lead-in-homes program had been introduced in Baltimore City in about 1950. Dr. Julian Chisholm at Johns Hopkins, a local authority on lead's effects on health, led the drive for instituting a program of abatement. Toddlers who chew into the multiple layers of lead paint on the window sills of old row houses suffer permanent brain damage. Abatement, which has continued intermittently over the years, was carried out by covering the walls and window casings with sheet rock. Older rural homes have been found to have the same problem. The technology for detecting lead in the red blood cells (RBCs) in whole blood, as well as mercury and other trace metals in food or other matrixed material such as urine, is complex and involves atomic absorption spectrometry (AAS), which is based on absorption at a specific wave length, or a mass spectrophotometry (MS), which depends on the ratio of the mass or weight of the lead atom to its charge, both costly sophisticated technologies. In the human body, lead interferes in the synthesis of hemoglobin and results in basophilic stippling (bands) on RBCs because of increased free erythrocyte protoporphyrin (FEP). Some usage has been made of the FEP analysis for lead in infants as it requires only capillary blood and not a venous blood puncture. Unfortunately, lead-paint problems still exist in older housing in the Baltimore area and in many other areas where the law did not ban the use of leaded paints, although titanium-based paints have been available for many years. A very recent special report by Sumanthi Reddy, published in the August 31, 2006, issue of the *Baltimore Sun*, summarizes the current status (31). Although the number of children with elevated lead blood levels decreased in 2005 to 1.3% from 1.7% in 2004, this still means 1,289 children were at risk for brain damage in 2005.

The addition of tetraethyl lead to gasoline, starting in 1929, has resulted in millions of tons of lead being spread over the United States. The greatest accumulations have occurred in our large, densely packed cities like New York City, where streets are often old and narrow and packed with tenements and apartment buildings. Hence, many, many young children have been

exposed to lead since infancy. In State Laboratory studies, carried out by Brian Mitchell, PhD, and his associates in the Environmental Health Division, gasoline station workers and toll booth collectors were found to have the highest levels of exposure. In about the middle 1970's, unleaded gasoline was phased in, and, subsequently, catalytic converters have been required on all new cars.

About 1970, The New York State Department of Health was able to eliminate its three state-operated TB hospital centers because this communicable disease was under control due to the newer drug agents that had been developed that could pierce the thick outer lipid (fatty) wall of the organism. However, TB has recently returned, quietly, in the United States, and with a vengeance globally. TB has become the leading cause of death worldwide, and, in July 2004, The Bill and Melinda Gates Foundation awarded \$44.7 million to a consortium, led by Johns Hopkins scientists, to find the best way to combat TB. According to an article published recently, iminosugars may provide leads for a new class of TB drugs (32). Scientists in England have designed and synthesized the first inhibitors of an enzyme that is essential for the survival of the TB bacterium. The compounds synthesized may lead to better treatments for TB, which annually affects 8–10 million people and kills 2–3 million.

Before going to the Orient for two months in 1974, I was vaccinated against cholera, malaria, and yellow fever. However, as global travel has increased, not only have these diseases become more common, but we have had the emergence of Legionnaires' disease in Philadelphia in 1976, toxic shock syndrome, Venezuelan hemorrhagic fever, new kinds of diarrhea, and nastier antibiotic-resistant forms of staph infections, some of which have invaded hospitals and nursing homes. Epidemiologists at CDC have recently found that one such infection in five is picked up by inmates or children and athletes who are out in the community, with children under two at greatest risk.

According to an article published in the *Archives of Surgery* in February 2005, of the 30,000,000 operations performed each year in the United States, about 2% or 600,000 patients, have their recovery complicated by an on-site infection. One physician believes the best protection for the patient is to insist that every person within a hospital, including physicians and nurses, wash their hands with plenty of soap and water and put on clean gloves (33). It is ironic that the greatest source of in-hospital contamination is a physician's tie. As of July 1, 2006, Maryland law requires all hospitals in the state to collect and report data on hospital-acquired infections to the Maryland Health Care Commission, which will post the information on its Web site (34).

Recently, the threat has occurred on an almost annual basis of new strains of influenza (flu) in the young and the elderly, who are the most vulnerable subpopulation. The West Nile virus, first detected in New York State in 1999, is potentially a dangerous culprit. Our physician daughter made a presentation on New York State's experience with the West Nile virus at the American Association of Blood Banks National Meeting in Baltimore in October 2004. According to CDC, the mosquito-borne West Nile virus resulted in 4,156 cases and 284 deaths in

2002, and in 2003 it sickened 9,858 people with 262 deaths involved, but was milder in the 2004 flu season. UNICEF, in their United Nations children's report in December 2004, stated that 640 million children of the world's 2.2 billion children lack adequate shelter; 500 million have no access to sanitation; 400 million lack safe water; 270 million receive no healthcare; and 140 million children, mostly girls, receive no education, with 90 million children severely deprived of nutrition.

It is unfortunate that science has been unable to find a cure for the common cold, but the viral culprits are much craftier than one might think—with 101 strains of rhinoviruses (35). Although a person becomes immune to each cold strain that has given the person a cold, even with two colds per year, it would take over 50 years to become immune to colds. In addition, two other types of viruses behave like colds, the coxsackie virus and an adenovirus.

A very important national event in public health took place in June 1981 when the Centers for Disease Control reported that five homosexuals in Los Angeles had come down with a rare type of pneumonia; they were the first recognized cases of what later became known as AIDS (acquired immunodeficiency syndrome). Our immune systems have two types of cells, the B cells and the T cells, which protect our bodies from foreign materials and infections. Although the circulating T cells, also called CD4 cells, stand ready to pounce on any invaders, they are no match for the human immunodeficiency virus (HIV) (36). Next, the virus penetrates the T cell, hijacks it, and then makes copies of itself. The new virus-loaded T cell then attacks other normal T-cells until most of the normal T cells are converted and the body's immunodefense mechanism is shut down, resulting in full-blown AIDS. Individuals in this state, which takes 8–10 years to develop, then succumb to opportunistic infections such as pneumonia or to cancer. Drugs used to treat the condition include those acting against the virus after it has infected the T-cells, which were developed first, and fusion inhibitors, which block the HIV virus from entering the cells. There are 900,000 people in the United States infected with HIV, of whom 280,000 don't know it; it is believed that more screening and counseling would be cost effective and would provide an additional year of life for each of these patients for \$40,000 a year. It is most prevalent in Africa where 499,000 of South Africa's roughly 44 million people died in 2002, with 77 male deaths for every 100 female deaths. A recent estimate (November 2005) by the United Nations estimates the world population of AIDS at nearly 40,000,000, with a very high incidence in sub-Saharan and North African countries, the Caribbean, Thailand, and Vietnam. However, it is increasing in South Africa, Eastern Europe, China, and Papua New Guinea. Areas with a significant decrease include Barbados, the Bahamas, and Bermuda. There has also been a decrease in AIDS among women in urban Kenya.

The World Health Organization (WHO), in conjunction with epidemiologists from Johns Hopkins University, reported in 2004 that malnutrition leads to more than half of all the deaths of children around the world, including deaths from diarrhea, pneumonia, malaria, and measles (37). Their investigations show that poor nourishment leaves children underweight

and weakened and thus vulnerable to infections that do not have to be fatal. They estimated that feeding all children worldwide an adequate diet would prevent about 1 million deaths a year from pneumonia, 800,000 from diarrhea, 500,000 from malaria, and 250,000 from measles.

Are outbreaks of disease that occur in specific locations just happenstance clusters or are they coincidental and therefore cannot be called epidemics? Good examples are: more than 100 Long Island women living close to high-voltage power lines developed breast cancer, in Nevada 16 children from one county developed leukemia, and 15 employees of a large Philadelphia chemical company were diagnosed with brain tumors (38). Michael J. Thun, MD, the head of epidemiological research of the American Cancer Society, said "These situations are typically very challenging and unsatisfying to everyone involved" as they involve disease, but "the level of scientific certainty that one can achieve in these situations is much less than the level most people expect" (38).

David "Dave" Axelrod, MD, who joined the Department in 1968 as Director of the Infectious Disease Center of the Division of Laboratories and Research, became Assistant Commissioner and Director of the Laboratories of the State Health Department in 1977 after Dr. Bill Kauffman retired as Chief Pathologist in 1975 and I had left early in 1977. Even while I was still there, Dave was in the process of reviewing dozens of boxes of environmental data on the Love Canal, a major industrial chemical pollution site located in the Niagara Falls area of Western New York State. He succeeded in reducing the voluminous quantity of data into a report on environmental pollution, which was so significant that it propelled him into being appointed Commissioner of Health by Governor Hugh L. Carey in 1979. A consequence was that the Division was no longer free of political interference and pressure, as had previously existed under the law dating from 1914.

In 1980, Dr. Axelrod, as Commissioner of Health, became new Governor Mario M. Cuomo's most influential cabinet member, with authority far beyond health issues, where he gained national attention for his stringent regulation of hospitals and doctors (39). As Health Commissioner for 12 years, he undertook innovative policies such as limiting interns to an 80-hour work week and curtailing round-the-clock work shifts that were blamed for a number of deaths in New York City hospitals, set up mechanisms to protect the confidentiality of AIDS patients, supported anti-smoking legislation, and endorsed the concept of universal healthcare. Further, he waged a vigorous campaign to make healthcare more affordable across the state, especially to the poor and in neighborhoods and communities not adequately provided with medical services. Also, he imposed strict controls to cut costs and improve the quality of medical care and opposed increases in insurance rates for hospitals in order to redirect primary care to community clinics.

Although not successful in his fight for universal healthcare for all New York State residents, Dr. Axelrod began several subsidy programs, including Child Health Plus, a state insurance subsidy that in 1994 covered 67,000 children in families who were earning too much money to qualify for Medicaid, and a prenatal care program covering uninsured pregnant women.

Unfortunately, Dr. Axelrod never recovered from an incapacitating stroke suffered in February 1991 and he died at age 59 in early July 1994. He probably suffered the stroke working 12- to 14-hour days, with his output requiring two secretaries. On June 24, 1992, it was my privilege to attend the dedication of the new David Axelrod, MD, Viral Institute of the Health Department and renew acquaintance with many of my former colleagues.

In August 2002, the Charitable Leadership Foundation started construction of a \$60,000,000 Center for Medical Research on the site of the original Division of Labs complex on New Scotland Ave to house researchers from the Ordway Research Institute, Wadsworth Center Laboratories, Health Research Inc., Albany Medical Center, and the Albany College of Pharmacy.

After I joined the State Laboratory in 1965, one of my earliest tasks was to plan for new laboratories for the Clinical Chemistry Section at the gigantic Empire State Plaza, the largest seat of state government in the world, which covers several dozen city blocks. The State Laboratory was located in the first basement level under the State Health Department Tower. We moved into the new laboratories in August 1976, which were all inside rooms with no windows. Every laboratory was identical except that each laboratory had a different color entrance door. I found the dull, gray environment to be like working in a mausoleum and was delighted to leave for my new academic position at Hahnemann University in Philadelphia as of January 16, 1977. When I left the Division, it had a staff of close to 2,000, which today has expanded to a staff of 5,000.

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Chapter 9

Changing Medical Education

The education that I received at the Syracuse University College of Medicine from 1946 to 1950 was of the traditional classical type with a heavy emphasis on laboratory experimentation. Today, however, medical schools introduce students to case presentations their first year and students are no longer trained in the classical basic sciences with hands-on laboratory experience.

I grew up in the village of Newark, New York, 30 miles east of Rochester, New York, as the youngest of four children and the only one to go to college. I earned a scholarship to Syracuse University and graduated in seven semesters in May 1944. The attack on Pearl Harbor was during my freshman year, and after serving two years in ROTC, I failed the physical for further service. After graduating Phi Beta Kappa magna cum laude, I earned a master's degree in science education and taught five different science and math courses at Gorham Central School, near Geneva, New York, in 1945–1946. By spring 1946, I was disillusioned about teaching high school because there were only 20–25 graduates each year and, at most, one or two students went on to college from this rural farming community.

At Easter break in 1946, I went to the Medical School at Syracuse to talk, informally, to a member of the admissions staff for advice. I was directed to see Dr. W. W. Westerfeld, the new head of the Biochemistry Department. After a review of my academic credentials, Dr. Westerfeld said they were planning a new doctorate program in the medical sciences, which would take at least 4–5 years to complete and would require a minimum B grade in each medical school course taken, with no possible transfer of credit toward an MD degree. He explained that he had arrived from Boston only the previous fall and the program was a year away. However, he suggested that in the meantime I could work toward a master's degree in Organic Chemistry at the University and do my research with him, and he thought he could obtain a full-tuition scholarship for me. I replied that I had saved about half of my \$2,100 teaching salary and his proposal sounded very good to me. Dr. Westerfeld then went on, "If you can accomplish the Master's program successfully, I'll guarantee you full funding for a doctoral degree."

What I did not learn until later was that Wilfred Wiedy ("Weste") Westerfeld (1915–1998) had received his PhD at age 23 under Nobel Prize winner Edward A. Doisy, Sr., PhD, at St. Louis University School of Medicine, and had spent

two years as a Rhodes Scholar at Oxford University where he met and married Nora Fleming, the niece of Sir Alexander Fleming, who had discovered penicillin. After serving as a Teaching Fellow in Biological Chemistry at Harvard Medical School in Boston for two years, Weste had become a 27-year-old Assistant Professor at Harvard. At age 30, he had been selected as Professor and Chairman of Biochemistry at the Syracuse University College of Medicine after the death of Dr. Brewer, the former head, in fall 1945. He brought with him as Associate Professor, John "Jack" McKibbin, PhD, a nutritional and lipid biochemist from the Harvard School of Public Health, and as an Assistant Professor, Daniel "Dan" Richert, PhD (1915–1971), a protein biochemist, who had worked in E. J. Cohn's Blood Fractionation Program, an important World War II project carried out at Harvard. Although Weste was my thesis director and prime mentor, Jack and Dan taught graduate courses in their specialties and became informal advisors and colleagues.

On July 1, 1946, I began the synthesis of two compounds related to diethylstilbestrol, a synthetic estrogen or female sex hormone, completed the University undergraduate course in Biochemistry, and took University courses in Histology (microscopic cell structure) and Mammalian Anatomy, which was the dissection of a cat correlated with human anatomy. Only graduate students majoring in Pharmacology were required to take the fall medical student program in Gross Anatomy, which included the dissection of a cadaver. The Graduate Division of Medical Sciences began officially as of July 1, 1947, and as of that date Chuck Remy joined me in Biochemistry. I completed the requirements for an MS degree in Organic Chemistry in June 1947 and officially received the degree on September 7, 1947.

In 1945, Syracuse University College of Medicine added many outstanding scientists to their basic science faculty. Medical students completed their Gross and Microscopic Anatomy courses in the fall of their first year and took Biochemistry (10 credits) and Physiology (10 credits) during the spring semester, each requiring two full afternoons of laboratory per week. Students worked individually in Biochemistry, but in groups of four, one of which I joined, for the extensive laboratory sessions in Physiology (included Neurophysiology; 10 credits) and Pharmacology. Medical students took a full semester of Pathology in the fall of the second year and Pharmacology (9 credits) and Microbiology (9 credits) in the spring. These were

the days when one worked with live animals, most often rabbits, and revolving, smoked paper drums recorded the tracings of animal responses. I still have one from medical school physiology in 1948, which was sprayed to preserve it, that demonstrates the "Effect of Vagus Stimulation on Heart Block." We performed many experiments as a group of four, including EKG's, five experiments each in relation to eyesight and the ear and balance, basal metabolic rate (BMR) for thyroid activity, and learned to take blood pressures and pulse rate among others. The experiment I remember most vividly was swallowing a gastric tube for measuring gastric juice under various conditions and the sterilized but plugged needle syringe my classmates were given to draw the first of a series of venous blood samples.

I recall two valuable principles I learned from Pharmacology: (1) "No drug is given without some attendant hazard"; and, (2) when we gave a diuretic to a rabbit, it went into complete anuria, and the reverse happened when we gave the antidote. Thus, experimental animals and even humans do not always respond in a predictable manner to a given drug. My 91-point grade average in Physiology was only adequate, earning me a B in the course, but my experimental laboratory training in Physiology was so extensive that I became qualified to teach either Biochemistry or Physiology at the medical school level. Robert Pitts, MD, PhD, a shy bachelor, who had a PhD in both Renal Physiology and Neurology as well as an MD, and headed the staff of five in Physiology, later returned to Cornell Medical College in New York City as the Chairman of Physiology. Allan Bass, MD, who was Chairman and Professor of Pharmacology, later became Dean of the School of Medicine at Vanderbilt University. I talked to him over the phone in 1973 as my oldest daughter entered the Graduate School at Vanderbilt University. Other outstanding faculty at Syracuse were Jay and Helen Tepperman, both MD pharmacologists, William "Bill" Lotspeich, MD, who later became Chairman of Physiology at the University of Rochester. and "Bud" Sartorius, MD, a teaching fellow in Physiology. My three mentors in the Biochemistry Department were outstanding teachers. and several years later John "Jack" McKibbin became Chairman of Biochemistry Department at the University of Alabama School of Medicine.

Among the Syracuse University courses that I took as part of my graduate studies were Advanced Endocrinology and Steroids, the Chemistry of Carbohydrates, and Organic Heterocyclic Compounds (heterocyclic compounds all have a nitrogen or sulphur atom in their carbon ring structure and include many drugs and antibiotics). My mentors in Biochemistry taught graduate courses in Nutrition and Blood Fractionation, and a Biochemical Seminar every semester in which we had to present a topic at least twice. Also, I completed 10 hours of Biochemical Preparations, several of which were those Dr. Otto Folin had introduced as the first Professor of Biochemistry at Harvard Medical School. I recall going to a kosher slaughterhouse to obtain bled-out cow's liver from which I had to isolate purified liver glycogen, the storage form of glucose. As part of the Graduate School requirements for a PhD, I had to pass written reading exams in scientific French

and German. At the end of three years of graduate education, I took a five-hour examination covering all of my training.

As a teaching fellow in my final year, I gave two lectures to the medical students and taught full-time in the medical student Biochemistry Laboratory. This experience was very beneficial to my future career in teaching and research. I lectured from outlines my entire career and practiced every lecture the night before for timing and to ensure that it flowed well. I kept a file on each lecture topic and added notes on new developments as they occurred throughout the year.

The research for my PhD thesis involved three projects, the first being the effect of a low protein diet on liver xanthine oxidase (an enzyme) and on the ability of rats to inactivate the female sex hormone, estrone (1). The experimental study required surgery, at which I became quite proficient, in order to implant pellets of estrone in the gut area of the white rats and later, the taking of vaginal smears seven days a week. At the end of the testing period, the rats were sacrificed in order to measure their liver levels of xanthine oxidase by a gasometric method. In July 1948, a crisis struck early in my marriage when I arrived home for dinner on a day that I had sacrificed a group of 60 white rats and calves liver was being served for dinner!

In early fall 1948, I attended a symposium on steroid chemistry (the sex and adrenal cortical hormones made from cholesterol) at the University of Wisconsin in Madison. One of the prime speakers at the symposium was Edward C. Kendall, PhD, of the University of Minnesota, who had isolated and characterized many of the adrenal cortical steroids. However, not all good researchers are good speakers and Dr. Kendall turned out to mumble and be one of the worst speakers I had ever heard. This was a big disappointment to me at the time because, as a young graduate student, I had looked up to him as being someone I would like to emulate. Dr. Kendall and Thaddeus Reichstein, PhD, of Switzerland shared the Nobel Prize in 1955 for their work in isolating and characterizing the adrenal cortical hormones.

Olive Watkins Smith obtained her PhD under Otto Folin, PhD, the first Professor of Biological Chemistry at Harvard Medical School, but received her degree from the Women's Division of Harvard and became a researcher at Brookline Free Hospital for Women, a part of Harvard University Medical School. In the early 1940's, Dr. Smith established that, in rats, the release of tropic hormones by the ovary after the administration of diethylstilbestrol ("stilbestrol," a synthetic estrogen) was not inhibited by the presence of testes or the administration of progesterone. She found further that the release of pituitary hormones by stilbestrol was not due to its estrogenic effect but to a breakdown product of stilbestrol. My challenge for my main thesis project was to isolate and identify the active breakdown product(s).

The project involved the extraction of the product(s), into ether, from 5-gallon bottles of dilute alkaline stilbestrol solution, which had been allowed to stand several days before the extraction procedure, evaporate down the ether, acetylate the oily material, and isolate and purify sufficient crystalline product to chemically characterize and identify it. I achieved my first success in six weeks. Four months later, Dr. Smith

informed me, by telegram, on December 20, 1948, that the compound markedly stimulated the adrenal glands of rats, not the ovaries as we had hoped. Dr. Smith invited me to come to Boston as their house guest to discuss the results. (Her husband was George Van S. Smith, Distinguished Professor of Obstetrics and Gynecology at Harvard Medical School.) By spring 1949, I had identified the compound as para-acetoxy benzoic acid, an isomer of aspirin (same chemical formula but a different spatial configuration or shape). I presented a paper at the Federation meetings (2), but was scooped by the publication of a manuscript in the April 1949 issue of the *Proceedings for Experimental Biology and Medicine* showing the effect of aspirin and its related isomers, including the one I had isolated, on the adrenals of rats.

An animal care center occupied the top floor of the Syracuse University Medical College basic science building where I carried out a large number of bioassays on six compounds closely related to stilbestrol, some of which were inactive estrogenically. I also investigated their possible competitive inhibition of estrogenic activity in rats. The estrus cycle was determined by vaginal assays and cytological readings similar to a Pap (Papanicolau) Smear Test. Dienestrol (an active estrogen) and its inactive stereoisomer, isodienestrol, which I had isolated from inactivated stilbestrol (1 mg/cc), were also studied after long-term injection, and their effects on the endocrine system of immature rats observed. If I had been successful in the competitive inhibition study, I might have established the basis for the first birth control pill.

The extraction and purification of 200 gallons of oxygenated, very dilute alkaline diethylstilbestrol (only 0.3% as concentrated as the former preparations) yielded a further breakdown product of isodienestrol, isolated in milligram amounts, which melted at 242–243 and in its stabilized acetylated form at 157° C. It was partially characterized by a professional microanalysis laboratory as to its molecular weight and carbon, hydrogen, and oxygen content, and I performed the spectrophotometric absorption pattern. Although its unique structure could not be defined further, I proposed rearrangement mechanisms for its possible structure based on its chemical characteristics. The biological effects of this nonestrogenic oxidation product of diethylstilbestrol were published jointly with Olive Watkins Smith in fall 1951 (3).

As a graduate student, I took part in a third project involving Antabuse, a drug first marketed in 1948, that helps reforming alcoholics kick their habit by making them nauseated if they drink. I maintained rats on a diet containing Antabuse and found that it inhibited the liver enzyme, xanthine oxidase (4). Alcohol is involved in about half of all car accidents today including 17,000 fatal accidents in which alcohol played a major role, and up to 1 in every 10 Americans are said to be alcoholics. Just recently, Antabuse has come back into usage to treat alcoholics who have not had success while attending Alcoholics Anonymous.

The defense of my thesis went well and I officially received the first and only PhD degree in Biochemistry and Physiology from the Graduate School and Division of Medical Sciences of Syracuse University College of Medicine at the end

of August 1950. The Medical College had been sold to the State for one dollar as of July 1, 1949, and during the 1949–1950 academic year, I was a Teaching Fellow in Biochemistry at the SUNY Upstate Medical Center at Syracuse at \$2,700 per year. During the Spring semester, I gave two lectures in Biochemistry to the medical students and taught in the Biochemistry Laboratory for the experience. Although I completed the program in four calendar years, all subsequent graduates took at least five years and received their degrees from the SUNY Medical Center.

I was offered research positions at Upjohn Laboratories in Kalamazoo, Michigan, at Smith, Kline and French Laboratories in Philadelphia, Pennsylvania, and as an Assistant Professor of Biochemistry at the University of Maryland School of Medicine in Baltimore, Maryland. In late June, I decided to accept the three-year contract with Maryland, where I served on the faculty from 1950–1957 (see Chapter 6).

Because I was only peripherally involved in medical education between 1962 and 1977, I cannot describe the evolution of changing medical education that took place during this period. However, in 1972 John Fenton, PhD, and I (an Adjunct Associate Professor of Biochemistry at the Albany Medical College) wrote a manuscript on medical education suggesting that medical students and graduate students in the biological sciences take a two-year in-common program with the granting of a Master's degree in Biological Sciences, which would qualify them to enter medical school at the upper division level or complete a PhD research degree in Biological Sciences (5). I did not return to full-time academic involvement until I was recruited by Hahnemann University in Philadelphia as Professor of Pathology and Laboratory Medicine and Director of Clinical Chemistry Laboratories and Professor of Biochemistry and Director of the Postdoctorate and Master of Clinical Chemistry Programs in January 1977. However, since my primary appointment was in Pathology, I spent the first month writing a research grant application, which was funded by NIH as of July 1, 1977.

HAHNEMANN UNIVERSITY

Homeopathic medicine was founded on the theory of similia similibus curantor, or “likes are cured by likes,” which was developed in 1796 by Samuel Hahnemann, MD (1755–1843), in Germany (6, pp. 4–6). Dr. Hahnemann, a well-respected physician, became dissatisfied with the German government's policy of administering drugs in an unscientific manner according to vague formulas. Having been well-educated in medicine at Erlangen University and having taught briefly at the University of Leipzig, he believed impure drugs and the way they were combined, accompanied by much bloodletting and the use of poisonous calomel (mercury bichloride), a practice also common in America, might actually harm patients. By studying 18th-century medical writings and by trying medications on himself, Dr. Hahnemann developed a new system of defined therapeutics he called “homeopathy.” He placed great emphasis on the past history of the patient and the analysis of his clinical

symptoms, followed by therapy with a defined homeopathic drug that had been shown to relate to the condition. Struck by the similarity of the clinical symptoms of quinine and those of the disorders it cured, Dr. Hahnemann theorized that “likes are cured by likes” and proposed that substances used in this manner are most effective in small doses. Basically, a substance given in large crude doses will produce specific symptoms, but when this material is diluted and administered in minute doses, it helps the body to improve these same symptoms. Accordingly, several different types of homeopathic medications were developed for treating patients. Today, it is thought that homeopathic drugs may act by stimulating the body’s immunological system and some are being tested as alternative medicines. Dr. Hahnemann’s chief work, published in 1810, was *Organon of Rational*, which expounds his system, and in 1811 he published *Pure Pharmacology* in six volumes. One of the earliest homeopathic physicians was American-born Hans Burch Gram, MD (1788–1840), the son of Danish immigrants, who had taken homeopathy while studying at the Royal Medical and Surgical Institute in Copenhagen (6, p. 4). In spite of bitter opposition, Dr. Gram introduced the practice of homeopathy to America in New York City in 1825, and in 1835 began publication of the *American Journal of Homeopathy*.

By the late 1840’s, a popular health movement had occurred in America, and the number of medical schools in the United States had doubled, with no standards for medical education. In the 1840’s, there were three young homeopathic practitioners in Philadelphia: Quaker Jacob Jeanes, MD, an outstanding practicing physician; Quaker Walter Williamson, MD, an obstetrician; and Constantine Hering, MD, a homeopathic surgeon educated in Germany, who had in common being medical graduates of the University of Pennsylvania, the oldest and most prestigious medical school in America (6, pp. 15–16). In 1848, they rented rooms in the rear of a pharmacy at 200 Arch Street and began a medical school with 15 students and 8 instructors. On April 8, 1848, the state legislature in Harrisburg granted incorporation, with a Board of Trustees, to the Homeopathic Medical College of Philadelphia, soon renamed Hahnemann Medical College after Samuel Hahnemann of Germany, the founder of homeopathy who had died in 1843. At the time of its opening, six of its faculty were graduates of the University of Pennsylvania and the seventh was a graduate of Jefferson Medical College. Homeopathic pharmacies stocked literally hundreds of specific remedies, and the College prospered and grew. In 1865, the faculty voted to “allow ladies to sit in the anteroom to listen to lectures,” but it was 1941 before women were admitted to Hahnemann Medical College and Hospital. However, Hahnemann graduated its first African American, Thomas Creigh Imes, in 1884 (6, p. 78). Pennsylvania’s reorganization of their licensing laws in the 1890’s reinforced Hahnemann as the leading homeopathic medical school in America and as a prestigious rival to the other medical schools in the Philadelphia area.

Although the American Medical Association had been founded in 1847, it was a voluntary organization, did not set requirements or standards for medical education, and thus almost anyone could set up a proprietary medical school, gain a

charter, and issue medical degrees. A major turning point in 20th-century medical education took place when the 1910 Flexner Report on Medical Education in the United States and Canada was brought to the attention of the public by its sponsor, the Carnegie Foundation (6, pp. 87–92). Abraham Flexner, PhD, was not a physician but an educator and reformer from Johns Hopkins University who under funding from the Carnegie Foundation personally visited all of the 146 medical schools existing in the United States in 1909. The 1910 Flexner report was a scathing indictment of many of the medical schools in the United States and recommended that over half of them be closed. The public outcry that ensued forced the closing of a number of weak and proprietary medical schools, raised admission and graduation standards, and resulted in the introduction of intensive laboratory science courses and the clinical teaching of medicine integrated with basic science. Thus, over the next 30 years, the various approaches to conventional medicine and homeopathy evolved into a common curriculum such that Hahnemann taught its last course in homeopathy in 1941, the year it admitted its first women students.

Hahnemann’s most famous graduate, Charles Philamore Bailey, MD (class of 1932), was a surgeon who, before the days of heart–lung machines and open heart surgery, operated on a patient with heart disease from rheumatic fever by using ice packs to lower the patient’s body temperature (hypothermia) (6, pp. 185–188). In 1948, Dr. Bailey performed the world’s first successful closed-heart surgical operation, which he called a mitral commissurotomy, the now classical procedure used to correct mitral valve damage from rheumatic fever. He then became head of Hahnemann’s new Department of Thoracic Surgery, one of the founders of the American Board of Thoracic Surgery, and published, in 1955, a textbook called *Surgery of the Heart*, which summarized the status of cardiac surgery. Dr. Bailey’s work on “deep freeze” surgery was described in *Life* magazine and in *Modern Medicine*, and in March 1957, he made the front cover of *Time* magazine (6, p. 186). I was on the faculty of Hahnemann from January 1977 to 1991, and in 1980 had the rare pleasure of hearing Dr. Bailey review the procedure, using a women’s corset and the attached garters as props.

Fortunately, the Hahnemann Hospital Clinical Laboratories, operated and staffed since 1973 by Upjohn Laboratory Medicine Inc., were excellent and I only needed to review our quality control data and present it at a joint monthly meeting of Upjohn Procedures Laboratories, which William “Bill” Kashatus, MD, the Clinical Pathologist Director of Laboratories, presided over. I learned a lot at the sessions about specialized tests, which we didn’t perform at Hahnemann, kept abreast on both their and our quality control (QC), and could devote my time primarily to teaching responsibilities the spring semester of 1977. In 1981, SmithKline bought out Upjohn Procedures Laboratories, so ironically I had an association with the laboratory corporations owned by the two pharmaceutical houses I had been offered research positions with after obtaining my PhD in August 1950.

Simultaneous with my arrival at Hahnemann, Emanuel “Manny” Rubin, MD, arrived as the new Chairman of Pathology and brought with him the distinguished British pathologist, George Lumb, MD, whose main interest was clinical toxicology

(lung damage due to asbestosis, etc.), and Ronald “Ron” Maenza, MD, who was in charge of departmental teaching, all of whom became close personal friends as well as colleagues. Because I was a full-time member of the Pathology Department, Ron immediately assigned me to organize the course in Laboratory Medicine (formerly Clinical Pathology) for the second-year medical students. Hematology and Microbiology were in separate departments but cooperated in teaching their subspecialties. The first year I organized and gave about a dozen lectures on major topics in clinical chemistry. My first lecture to the medical students was in a large auditorium and I was very surprised to have the students wander in nonchalantly, eating food and drink, with only about half the class of about 180 in attendance since they could review a videocassette tape of the lecture at their convenience. Also, one student took notes, which he sold to his classmates for cost. What an astounding change had taken place in medical students’ attitudes between the years 1962–1965 when I gave two lectures in biochemistry to the first-year students at Albany Medical College and the spring of 1977 when I gave my first lecture to Hahnemann students who were paying \$25,000 a year in tuition.

As a part of the course in Laboratory Medicine, we required attendance at two laboratory exercises, one on urinalysis and one on venipuncture. Because we were unable to find a satisfactory commercial film on venipuncture, we made our own videocassette tape using Bonnie, the head venipuncture technician of our blood-drawing team. However, providing the experience of these two laboratory exercises for 175 second-year medical students required a lot of manpower as each of our available 5 lab rooms handled 15–20 students. As the organizer, I simply split the class in half so we could accommodate about 90 students including graduate students in two sessions for each exercise. I recruited our available Pathology Residents, in training on-site at the time, and staff colleagues as needed to cover as instructors, most of whom loved to teach.

We took the collected clotted bloods, spun the clots down, and performed SMA 12/60 profiles on the approximately 175–180 specimens. At a subsequent class lecture session, the accumulated results were presented and each student received his or her profile. Since we use plus or minus two standard deviations (95%) as the limits for the routine interpretation of lab tests, 46% of normal individuals will have one or more tests beyond normal limits. By their own profile data, we were able to demonstrate to the class that these statistics held true, a most dramatic way to demonstrate the importance of knowing this for interpreting profile data. I also used a slide of my own data to show the consistency in pattern maintained by a person in a state of health. To me, this was excellence in teaching. My associate, Fred Kayne, PhD, continued it until he retired in 2004 and has served as a consultant in Clinical Chemistry to the clinical pathologist in charge of the clinical laboratories through November 2006. In a recent email, Fred states that the severing of his relationship with Hahnemann marks the end of Clinical Chemistry at Hahnemann.

Teaching became easier after my first semester at Hahnemann because I was able to hire Frederick “Fred” Kayne, PhD, as my associate. Fred, Associate Professor of Biochemistry

at the University of Pennsylvania, had been in charge of postdoctoral training at the Johnson Foundation, which closed down as of June 30, 1977, upon the retirement of its distinguished director scientist, Britton Chance, who held two PhDs and was a sailboat designer. Fred recognized the need to move into a related area like Clinical Chemistry, joined me as Associate Director, and five years later passed the examination for certification by the American Board of Clinical Chemistry. Fred and his wife Marlene had received their PhDs together in Biochemistry at Michigan State University, and then Fred completed a postdoctorate in Physics at the Max Planck Institute in Germany. Marlene found a position at Trenton State University as of July 1, 1976, and they moved from Bryn Mawr to Yardley, Pennsylvania, where each could commute conveniently to their new positions. Fred turned out to be a gem of an associate, both in teaching and research. Between 1977 and 1989, in addition to our clinical lab responsibilities and teaching and research activities in the Pathology Department, Fred and I taught the courses and provided technologist training for about 30 students working toward their Master of Clinical Chemistry degrees in the Biochemistry Department.

Hahnemann was the largest hospital in Philadelphia and in the Delaware Valley in heart surgery and the treatment of heart disease. To meet the need of the cardiac surgeons, I organized a one-technician laboratory unit, as part of the OR Suite, that provided results for blood gases, the four electrolytes, blood glucose, and blood urea nitrogen within two or three minutes. Both our teaching and clinical laboratory services were cutting edge. However, I knew sooner or later a problem would arise because I was teaching the senior medical students the accuracy of the calculated bicarbonate value from the blood gases, and three full professors of medicine were teaching its inaccuracy and that serum bicarbonate was a more reliable measure. As a result, in May 1988 I was invited to explain my position at Grand Medical Rounds. I satisfactorily compared the derivation of each on the blackboard and tactfully proved my point. About this time, I became interested in the new Faculty Senate and subsequently became one of three founding members of the Hahnemann University Chapter of the American Association of University Professors (AAUP), and in 1990–1991 I became its first president.

In about my second year at Hahnemann, the Admissions Committee asked me, as a faculty contribution, to assist with the interviews of prospective medical students; henceforth I interviewed about 20 prospective medical students each year. Because of my experience in dealing with the New York State Civil Service, I wrote a list of 20 questions pointed toward establishing the candidates’ intentions and goals in medicine, asked every candidate the same questions, and sent their replies to the Admission Committee. I attended one of their meetings and I obtained no insight into who they admitted or why, but they assured me that my evaluations were the most valuable and useful they received from any interviewer. Once I even interviewed a Thai woman candidate from Bangkok and she was very surprised that I had been there.

In spring 1989, I presented Laboratory Medicine lectures titled “Laboratory Evaluation of Fluid Balance and Electrolytes,”

“Laboratory Evaluation of Blood Gases,” “Laboratory Evaluation of Renal Function,” “Laboratory Evaluation of Cell Damage I” [myocardial infarction (MI) and heart diseases with a case history of an MI], “The Laboratory Evaluation of Cell Damage II (liver diseases),” and the “Laboratory Evaluation of Porphyria.” I also participated, with Dr. Lumb, in Pathology lectures on “GI Tract Disturbances,” as I had become an expert in the gut hormones, and on the “Clinical Aspects of Liver Diseases,” for which I had given seminars and had published on the clinical interpretation of the transaminases (SGOT and SGPT) (7). Over a period of years, Fred took over my lectures on “Statistical Concepts Useful in Problem Solving,” “The Serum Proteins and Immunoglobulins,” “The Laboratory Evaluation of Lipid Metabolism,” and “Therapeutic Drug Monitoring.”

Thyroid function and hypoadrenal and hyperadrenal function were presented by Leslie “Les” Rose, an MD endocrinologist, who when he presented a session at Grand Rounds would dress in spats and formal clothes, which delighted the students. Pathology Department colleague George Lumb, MD, presented the “Laboratory Diagnosis of Gastrointestinal (GI) Function” and colleague Michael “Mike” Zimmerman, MD, PhD, presented the “Laboratory Evaluation of Body Fluids” (spinal fluid, saliva, etc.). Mike was also Director of Clinical Pathology but let me make all decisions involving Clinical Chemistry; we and our wives remain close friends and get together once a year to share our mutual interest in old car collecting. Mike retired a couple of years ago but, as a PhD in anthropology (who has performed autopsies on Egyptian mummies and the Aleuts from Alaska who have been buried alive in their igloos in early spring thaws), teaches a course in the fall as a part-time Professor of Anthropology at the University of Pennsylvania; he and Bobbie (MS in Engineering and Computer Technology) intersperse overseas travel with their teaching at Villanova University during the spring semester.

On September 15, 1986, we made a successful transition from the operation of our laboratories by SmithKline Bioscience Laboratories to Hahnemann University staff, saving approximately \$3,000,000 a year (8). Through excellent cooperation between the Hahnemann and SmithKline administrative staffs, the contract was dismantled with the salaried rights and vested and unvested interests of the technical laboratory staff fully protected. Prior to the transfer, a strategic plan was developed to handle changes in personnel, purchasing, the facilities, and the consolidation and relocation of services. A reference laboratory agreement was established between SmithKline Bioscience and our Hahnemann Laboratories under which our low-volume technically complex tests went to them and we provided highly specialized tests to them. In Clinical Chemistry, we analyzed their specimens for choline esterase, a test used to detect insecticide poisoning in toddlers, one of whose parents often worked in the manufacture, distribution, or application of pesticides, and in individuals who had been exposed. We received numerous specimens because the agricultural section of DuPont was in nearby Wilmington, Delaware, and I often consulted with the submitting physician on the interpretation of the test. We also performed all of SmithKline’s radioisotopic allergy (RAST) testing and their

estrogen and progesterone receptor assays, technically very complex tests. I held the radioisotope license for the Hahnemann University Clinical Laboratories from 1977 to 1990, when I retired.

The brightest resident I ever worked with was Arnold Berkowitz, MD, who was so Orthodox Jewish that he would not take Anatomic Pathology and do autopsies, but did 15 months of residency in Clinical Pathology. Arnold was an exceptional resident in that he was excellent in reading *x*-rays because he had spent nine months in Radiology before joining Pathology. In 1983, Arnold set up a bar code system for rapid data entry of laboratory test data into a computer with a telephone attached such that it would read off the test results to a physician. Although it electronically read the cation for potassium as the letter, K, the unit worked like a gem. In a letter sent to me, dated July 10, 1984, from the University of California at Irvine where he was taking a residency in Radiation Therapy, Arnold stated that he had been invited to be a consultant to the Clinical Laboratory and to write articles on medical applications of computers for *Medical Tribune*, a newsletter, which had a circulation of 60,000. Arnold visited Hahnemann about a year later, and most astounding to Fred and me was that Arnold had adopted full California style with no yarmulke, a short-sleeved bright-colored sport shirt, shorts, and sandals. After completion of his training, Arnold became a radiation therapist in Phoenix, Arizona.

Each year we had one or two students with Doctorates in Dental Surgery (DDS) transfer in as junior medical students, planning to specialize in broken jaw surgery or plastic surgery, who took our course in Laboratory Medicine as an elective because they had not had any previous exposure to laboratory tests. We also offered a one-month elective in Laboratory Medicine to the senior medical students in which they spent a week each in Clinical Chemistry, Hematology, Blood Banking, and Microbiology, which enriched their backgrounds in clinical applications and gave them an opportunity to see if they wanted to become pathologists. About 35–40 senior medical students participated. Each day, I had a set of handouts describing the interpretative tests that we signed out each day, such as the cardiac isoenzymes, serum protein electrophoretic patterns for identifying major alterations in serum proteins and the spike peak paraprotein of multiple myeloma, hemoglobin (Hb) electrophoretic patterns for sickle cell anemia and trait and other Hb abnormalities, and cryoglobulins, which precipitate out from serum in the cold, etc. I always emphasized my strong belief that laboratory test results that were modestly out of range should be watched only, and asymptomatic patients should not be treated.

Fred assumed my position after my retirement on June 30, 1990, although I stayed active during the 1990–1991 academic year. While I was still there, he took a one-year sabbatical leave in Germany, which included a return to the Max Planck Institute. Fred continued at Hahnemann through its mismanagement, bankruptcy, and the many resulting changes that took place in the 1990’s. In 2002, Hahnemann was taken over by Drexel University of Philadelphia as Drexel University School of Medicine. It provided clinical facilities to support their

extensive program in Biomedical Engineering. Fred and his wife retired permanently to their new home on Marco Island, Florida, as of June 30, 2004.

Our heavy emphasis on laboratory medicine, which Fred continued, was an important aspect of medical education in light of a very recent study. Recently, Steven "Steve" Kahn, PhD, Director of Clinical Laboratories at Loyola University in Chicago, Illinois, has shown that the mislabeling of patient specimens, including Blood Bank specimens, is a major and serious source of hospital error. Although the error results in an average cost of \$800 per specimen, in one case it resulted in an \$8,000 error when two patients were interchanged because of incorrect labeling of very expensive radiological procedures. Steve spoke at a meeting of the AACC Capital Section in December 2004, and it was very intriguing to hear about this current major source of medical error, which is characteristic of both inpatient and outpatient blood specimens. At a Capital Section meeting in December 2005, Steven "Steve" Soldin, PhD, Professor of Medicine at Georgetown University, spoke on the nature and importance of the latest sophisticated immunological tests for measuring human chorionic gonadotropin (hCG) in amniocentesis in early pregnancy. The thrust of his excellent presentation was that over the years, many incorrect decisions have been made in early pregnancy because of inaccurate measurements of hCG. I first met Steve in the late 1970's when he was a postdoctoral trainee in clinical chemistry at the University of Toronto, where I inspected the program for accreditation.

RECENT CHANGES IN MEDICAL EDUCATION

The undergraduate requirements for entrance into medical school have stayed essentially the same; that is, 8 hours of General Biology, 8 hours of General Chemistry, 8 hours of Organic Chemistry, and 8 hours of Physics, each with laboratory work as part of it. Most schools recommend 2 semesters of English, and some schools recommend Calculus or Biostatistics and a course in Genetics and/or Molecular Biology in addition. Admission committees also liked to see a variety of liberal arts and social science courses, such as Philosophy, Ethics, History, Psychology, and other humanities classes. Unfortunately, many undergraduate colleges do not place strong emphasis on the experimental aspects of laboratory work, and it is my impression that the primary goal of premed students is to achieve high grades to help them gain entrance to medical school. A letter to the editor of *Chemical & Engineering News* (Jan 31, 2005, p. 3) is entitled "Test Takers or Scientists?" and a follow-up letter (March 21, 2005, p. 4) states, "Zare has hit the nail on the head" and "The problem he articulated extends to undergraduate education" and "the trend (at many colleges) is to demand that students do more and more simulations and take more and more tests" and not work with real equipment, glassware, and chemicals. During an award talk at the Maryland section of the ACS in November 2004, which I attended at Villa Julie College, Madeleine Jacobs, MS,

Executive Director and Chief Executive Officer (CEO) of the ACS as of 2004, suggested that the name be changed to the Society for Molecular Sciences and Engineering to better reflect the breadth of chemistry as it exists today. To reflect on such a possible name change, a GenChem Editorial Writing Committee, chaired by Jerry Bell, produced, for publication in 2005, a new general chemistry textbook based on an experimental activity approach, starting with flowing water and using it to develop the fundamentals of chemistry (9). The lack of training with experimental equipment at the undergraduate level, along with the absence of hands-on training in the basic sciences in the first two years of medical school, means that current graduating physicians are no longer capable of applying basic research technology to clinical problems without obtaining a PhD degree. Many medical schools, including the University of Maryland and Drexel University School of Medicine (formerly MCPHahnemann University in Philadelphia from which I hold the honorary degree of Professor Emeritus) have dual PhD/MD degree programs.

The entrance examination for admission to any medical school in the United States or Canada is the Medical College Admission Test, or MCAT, administered by the American Association of Medical Colleges. Beginning in 2007, prospective medical students no longer take a "pencil and paper" version of the test, but instead must complete a shorter, more widely available computerized version under a seven-year, \$30,000,000 deal between Thomson Prometric, a Baltimore, Maryland-based testing company, and the American Association of Medical Colleges (10). Because there will be fewer questions, the length of time to complete the test is expected to drop to about 5 hours from 8–10 hours. About 60,000 students worldwide take the exam each year during two weekends. Results are expected to be provided in 30 days or less, down from 60 days in the past.

As early as 1987, Dr. Frank Calia, who taught physical diagnosis to the second-year medical students at the University of Maryland, recognized that students "spent too much time listening passively to lectures, were not utilizing new information technology, and were missing the clinical relevance of their basic science courses" (11). Dr. Calia also felt the faculty could have been more effective in teaching problem-solving. In 1992, Dr. Calia first chaired the committee that was responsible for introduction of the new medical curriculum at the University of Maryland School of Medicine in 1999, the same year the American Association of Medical Colleges set new curriculum standards for all medical schools in the United States (11).

After a trial run or beta site testing at a small number of medical schools in spring 2003, the United States Medical Licensing Examination Committee instituted a new Part III to the requirements for any student graduating from any medical school under their jurisdiction. The examination tests the bedside skills of the senior students by requiring demonstration of their competency in communicating with a patient, taking a family history, performing a physical examination, making a proper diagnosis, and prescribing proper treatment. About 11% of the graduating medical students participating at the beta sites failed the examination. However, as of 2004, medical students

are no longer allowed to receive an MD degree from any U.S. medical school without passing the Part III National Board Requirement. It is expected that this requirement will weed out poor communicators, emphasize competency in medical training, and reduce malpractice rates.

Because medicine has its own jargon, the freshman year at the University of Maryland School of Medicine begins with a one-week course on "Informatics," which introduces students to the use of information technology that will assist their learning, research, and clinical applications (12). Next follows a nine-week, four-day block on the morphological and developmental organization of the human body. This is followed by a one-week interdisciplinary course on "Human Behavior," highlighting the importance of behavior in the prevention, incidence (occurrence), prevalence (frequency of occurrence), diagnosis, treatment, and prognosis (recovery) of wellness and illness. Following this is a nine-week block on "Cell and Molecular Biology," which presents the fundamentals of biochemistry, cell biology, molecular biology, and human genetics, and correlates them with clinical issues. Next is a two-week block on "Cell Function" as an introduction to a six-week block on "Neurosciences" that covers neuroanatomy, neurochemistry, neurophysiology, and clinical neurology, and a final block of eight-weeks on "Functional Systems," providing the student with a basic understanding of human physiology in the areas of cellular, cardiovascular, renal, respiratory, gastrointestinal, endocrine, and integrative physiology. Each block is integrated with clinical applications so that the clinical aspects tie in with the underlying fundamental principles. The general format is two hours of lecture per day and two hours of small group or laboratory per day. Running concurrently with the blocks are "Introduction to Clinical Practice (ICP)" and "Problem-based Learning," both using small-group teaching methods.

Although the 2002–2004 University of Maryland Handbook makes no clear-cut mention of the dissection of a cadaver, a *Baltimore Sun* feature article entitled "Med Students' First Cuts," published September 8, 2003, shows a picture of the Anatomy Laboratory, directed by Larry Anderson, PhD (13). Dissection became a compulsory part of the medical curriculum at University of Maryland School of Medicine in 1840 and is the only way to learn the 206 bones in the body and the location and nature of every nerve, muscle, and blood vessel in the body. Among other instructors in the ten-week course was Dr. Richard Colgan, a family physician who helped students understand the relationship between anatomy and clinical medicine. He demonstrated to the students how cholesterol can render the aorta hard and brittle, how pollution leaves black, grainy deposits in the lungs, and how a failing heart balloons to twice its normal size (one body had a group of staples along the sternum and the knotty scars from open heart surgery). Dr. Colgan tells the students "The dead teach the living," quoting a sign he once saw in an anatomy lab (13).

The integrated schedule at Maryland continues in the second year when students take two major blocks, which include Host Defenses and Infectious Diseases (10 weeks) and an interdepartmental 24-week course in Pathophysiology and Therapeutics, which includes a half day per week training in

physical diagnosis. The second year is characterized again by two hours of lecture per day, two hours of small group or laboratory per day, problem-based learning sessions, and an introduction to clinical practice focusing on physical diagnosis. Year three, formerly designated as junior clerkships, consists of 12 weeks of training in Internal Medicine, 12 weeks of Surgery and a Surgical Subspecialty, 4 weeks of a Family Medicine Clerkship, 6 weeks of OB/GYN Clerkship, 6 weeks of Pediatrics Clerkship, and 8 weeks in a Psychiatry/Neurology Clerkship. Year 4 is only about 32 weeks and includes 8 weeks in Ambulatory Care, 8 weeks of Sub-internship, 4 weeks of Surgical Subspecialties, and 12 weeks of electives. The shorter year and the electives give upcoming seniors the opportunity to choose their specialty area and their three preferences for where they would like to train. It also gives them time to visit prospective sites and prepare for the required National Board Part III where they must demonstrate their clinical competence prior to being eligible to receive their degrees. Many schools, such as Drexel University, employ paid professional "patients" who fake illnesses, while other schools permit their student to hone their skills on computerized patients (14). The University of Maryland Medical System and Johns Hopkins School of Medicine also employ paid professional actors as patients for teaching purposes.

Drexel University College of Medicine in Philadelphia provides students with alternate year 1 and 2 curriculum pathways (14). Both options focus on professional medical education, preparing students to pursue a career either as a generalist or specialist. Also, to help students learn the art and skills of taking patient histories, counseling and educating patients, and providing physical exams, both curricular tracks give early exposure to clinical skills training by using professional patients who fake illnesses.

The Interdisciplinary Foundations for Medicine (IFM) curriculum integrates basic science courses and presents them through clinical symptom-based modules (14). Each first-year module focuses on clinical symptoms and features relevant material from the perspective of several basic behavioral science disciplines. By the end of the first year, the basic and behavioral courses have presented their entire core content, integrating it with related material in other disciplines. In the second year, students learn in lectures, labs, and small group settings. Students who choose the Problem Integrated Learning (PIL) tract, a problem-based tract, learn primarily in small groups, which are supervised and facilitated by faculty (14). There are seven 10-week blocks the first two years. Each block contains 10 case studies, detailing real patient issues relating to the topics of the block. The cases serve as the stimulus and content for students to search out the information they need to understand, diagnose, and treat real clinical problems. Developing the information they need to learn is crucial to the PIL approach. Sharing information, concept mapping, evaluating, and giving and receiving feedback are essential facets of the curriculum. Laboratories and lectures complement the case studies. Each Multidisciplinary Laboratory offers 8 students the opportunity, with an instructor, to view slides via a microscope and monitor on their lab tables. Each lab unit is equipped with networked computers, laserdisc

players, and VCRs. This type of state-of-the-art laboratory enhances team-based learning for both the IFM and PIL students. Drexel University has two primary sites: the Queen's Lane Campus, home of the former Women's Medical College of Pennsylvania founded in 1850 and the Center City Hahnemann (founded in 1848) Campus at 245 North 15th Street, only two blocks from City Hall. In addition, it has primary affiliations with Hahnemann Hospital, operated by the Tennen Healthcare System, St. Christopher's Children's Hospital, and several other Philadelphia and nearby New Jersey Hospital Systems in order to handle its 175–180 medical students per class.

The third year at Drexel is devoted to required clinical clerkship rotations in medicine, family medicine, obstetrics and gynecology, pediatrics, psychiatry, and surgery (14). The clerkships all embody the principles of common curricular objectives at all sites, with students spending 30% of their clinical time in expanded ambulatory care experiences. Each clerkship incorporates the concept of interdisciplinary teaching, with representatives of other departments or service areas, and each clerkship integrates the teaching of basic sciences into clinical material. All third-year clerkships take place in Drexel's affiliated hospitals. The student assignments for the third year are based on a lottery system.

The fourth-year curriculum is structured in the form of "pathways," courses that give students a well-rounded educational experience with some focus on potential careers. Students can choose a discipline-specific or generalist pathway. All students have a pathway advisor. The path is structured so that students take both required courses and electives. The required courses include a subinternship in internal medicine, a clerkship in neurology, and an additional course specific to the pathway chosen. Students also choose 6 elective courses, in close consultation with their advisor. Although fourth-year students complete their required courses at Drexel's affiliated hospitals, advisors usually recommend that their students select electives outside the Drexel system. Additionally, opportunities exist for fourth-year electives at international sites.

Drexel University's precursor, Women's Medical College of Pennsylvania, graduated its first three women in 1851, and Hahnemann accepted its first women medical students in 1941 while University of Maryland accepted its first women students in 1918. However, 2003 was a transition year in which more women entered medical school than men. It is the goal of most women to combine medicine with marriage and children. This is not unusual as I have had colleagues and friends of my generation who were pathologists and one a radiologist, whose husbands were physicians. I also am acquainted with a male laboratory technologist who, in about 1990, became the homemaker taking care of the children so his wife could practice medicine full-time.

The University of Maryland School of Medicine is just one of at least 20 of the nation's 126 medical schools that offers an elective course in Spanish. The program uses foreign students as subjects, such as Sandra Quezada from Chile, and the dozen medical students in their fumbling Spanish must establish her diagnosis and treatment under the tutelage of a Spanish-speaking physician. New York University in New York City has been

teaching medical students Spanish since 1970 and now has a course in Chinese. The University of New Mexico has a course in medical Navajo to meet the needs of students from their region.

All medical schools in the United States use the National Matching Program by which every senior medical student receives one of his or her first three choices of an internship and usually a residency to follow. Most specialties today include the internship year as an integral part of the residency, which varies in the length of the commitment from three to seven years. However, Pathology is an exception and does not require an internship, but many new graduates spend two years each in Tissue Pathology (includes autopsies) and Laboratory Medicine, with optional fellowship training of two years, for example, in Bone Diseases or Blood Banking. On the other hand, Surgery requires seven years of training, and Dermatology, which was formerly a subspecialty of Internal Medicine, now is a specialty requiring direct entry into five years of training and permits dermatologists to surgically remove malignant skin lesions, fatty tissue cysts, etc. Currently, however, plastic surgeons often do such surgery when the lesion is on the face or where it will show in a bikini or other swim dress. On the other hand, older dermatologists trained in three years of internal medicine followed by a two-year fellowship in dermatology use liquid nitrogen (-180°C) to treat precancerous skin lesions and do not have training or privileges in surgery.

Although the match-day system gives most graduating medical students a satisfactory training site for their postgraduate education, there is usually a last-minute rush for a few students to get lined up with a still open internship. In April 2004, a group of young doctors, including a former fellow at Johns Hopkins, vowed to continue to pursue their antitrust challenge to the "matching system" after Congress quietly enacted legislation bringing the challenge to a halt. The young physician opponents feel that residents are underpaid and overworked and were disappointed that Congress did not allow a public debate on the issue. They may have a point; when a resident works 36 hours straight, they are no longer in a position to make sound judgments. Dr. David Axelrod, Commissioner of Health for the State of New York, recognized the overworked resident problem in New York City hospitals, in about 1990, where some medical errors had occurred, and limited their workweek, by law, to a maximum of 80 hours. In spring 2004, the Accreditation Council for Graduate Medical Education (ACGME), in Chicago, took note of the problem and changed the requirements such that no intern or resident may work more than 80 hours per week in any hospital in the United States (15). This change occurred so suddenly that Johns Hopkins had difficulty in making the change in its largest residency program involving 106 residents and lost its accreditation from August until December 2004, although its other 75 residency programs met the requirements. The National Resident Matching Program uses a computer to annually match the 25,000 or so medical school graduates with hospitals and has worked well for over 50 years.

In 2004, the percentage of University of Maryland students choosing primary care decreased from 53% in 2003 to 43% in

2004, mainly because fewer graduates chose pediatrics (16). Roughly 67% of the class of 2004 left the State to attend 103 programs in 27 states, with 22% remaining at the University of Maryland and 11% entering programs at Johns Hopkins or other Maryland hospitals. Although 24 graduates matched in pediatric training in 2003, only 9 graduates matched in pediatrics in 2004. John Winer, of the class of '04, pictured with his young infant son in his arms, was the last to receive his envelope and was the lottery winner with a residency in surgery (seven years) at Brigham and Women's Hospital in Boston, a part of Harvard University (17, p. 29).

A feature article in the University of Maryland Bulletin in summer 2003, entitled "The Passion v. the Paycheck," states that student debt is now a major factor affecting a new graduate's selection of a residency (17). According to the American Medical Association (AMA), the average debt nationwide for medical school graduates in 2001 was almost \$104,000, and nearly 21% carried a debt of over \$150,000. In 2003, the University of Maryland estimated the average projected debt for entering medical students at \$97,000. In 2003, the annual in-state tuition for medical school was \$15,085 and the annual out-of-state tuition was \$28,869. They are cited as averages because inflation leads to annual increases in tuition fees and upper class students paid less during their earlier years. In-state tuition in 1983 was only \$1,800 and out-of-state tuition \$7,322, showing the effect of annual increases. However, tuition is only one part of the debt picture as students must pay for books, diagnostic tools, licensing exams, administrative fees, computer technology, health insurance, room, board, and transportation, as well as clothes, incidentals, and other personal expenses.

In 2003, resident pay was limited from \$30,000 to \$45,000, and under Medicare regulations some of the cost to hospitals can be charged off to Medicare patients. However, the question is "Are medical students choosing to go into higher paying specialties in order to pay off their student loans more quickly, and with less personal sacrifice?" (17, p. 10). As new treatment technologies develop, so does the specialist who is most qualified to utilize that technology; healthcare delivery is in a major state of flux for a variety of reasons including the changing role of various specialists. Radiologists now perform some cancer therapy, and dermatology, formerly a medical subspecialty, requires five years of training and includes surgical training such that dermatologists can surgically remove melanomas. One publication referred to this as the changing sands of medical care.

The very astute Director of the University of Maryland Medical System, Dr. Frank Rapoport (class of 1960), who was in the last class of medical students I taught before leaving the Maryland faculty in 1957, put the University of Maryland Medical System on such sound footing before his retirement that only \$30 million out of a \$530 million budget for 2004–2005 came from state funds. In May 2005, the University of Maryland Medical System filed a preliminary application with the Maryland Health Care Commission for a \$380,000,000 outpatient facility for ambulatory services, which was intended to replace 13 outpatient buildings in

current service. When Edmond F. Notebaert, former Director of the Children's Hospital of Philadelphia, became chief executive official of the System two years ago, he identified as a top priority a new building to pull together the 40 locations in 13 buildings distributed across the campus (18). In the application, he stated that "traveling to numerous locations in different buildings to obtain outpatient care is confusing and problematic, particularly for elderly patients and those who suffer from debilitating diseases." The proposal, which was approved by the Maryland Health Care Commission, calls for a nine-story facility to be built on Greene Street between Pratt and Lombard and is expected to open before 2008. In 2004, Dr. Notebaert tapped Dr. Trent C. Smith, his former associate at Children's Hospital, as the senior vice president for ambulatory services in order to develop "a world-class ambulatory facility." The center will continue the momentum of the development of the west side of downtown Baltimore City, which has included the opening of the Hippodrome Theatre in 2004 and the development of shops and offices. In addition, the University of Maryland is currently developing a very large biotechnology park west of Martin Luther King Jr. Boulevard.

Gerard F. Anderson, Director of the Johns Hopkins Center for Hospital Finance and Management, said that such centers are not profitable for hospitals (18). However, he added "academic medical centers—hospitals and their affiliated medical schools—are building them to provide better training for medical students and residents and better care for chronic patients with multiple conditions." Also, the article noted that Johns Hopkins Hospital has started work on an \$800 million project to replace half of its inpatient rooms, which will have glass walls and face Orleans Street.

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Chapter 10

Selected Topics

One of the most mind-expanding books I ever read is *Biochemical Individuality*, published in 1949 by Roger J. Williams, PhD, of the University of Texas. In Dr. Williams' words, "The wide range of highly significant variations that distinguish real people from hypothetical average people are anatomical, physiological, biochemical, endocrinological, neurological, psychological, etc." His book pictures a variety of stomach shapes and even differences in the bifurcation of blood vessels in different people. Most interesting to me was his use of stick figures to picture the patterns of people in which the head, the neck, two halves of the body, and the arms and legs represent various body chemical constituents that are routinely measured, such as blood glucose, bun, uric acid, amylase, etc. Every adult individual has a unique stick-figure pattern that maintains constancy, except in disease states. Obviously, infants and growing children have their own typical patterns. Because individuals differ widely, we use ± 2 standard deviations as a normal range for body constituents, which theoretically excludes 2.5% of the population at the low and high end of normal ranges. However, not all constituents follow a normal Gaussian curve and a whole science has evolved on how best to develop normal ranges. Although all testing is subject to varying degrees of error, the quality and purity of the standard is the most important source of variation. The problem has been even more difficult in the area of the measurement of enzyme and isoenzyme activity, which I have specialized in. In the early 1970's, we couldn't even agree on whether enzyme activity should be measured at 25° C (room temperature) or at 37.5° C, which is body temperature. Eventually 37.5° C was adopted because enzymes have more activity at the higher temperature, making their activity measurement easier. Dr. Williams' 1949 book, *Biochemical Individuality*, gave major insight into many of the problems the fields of clinical chemistry and hematology would face over the next 40 years.

I remember learning about experiments done by Navy researchers in which they showed that sailors solved intricate puzzles best when their blood glucose was the highest. Kleitman, a PhD physiologist at the University of Chicago, showed in the late 1940's that our normal daily body temperature correlates with one of three patterns: (1) individuals who arise with lots of vigor, but whose energy declines during the day and who have no energy by evening; (2) individuals who start out slowly and whose energy during the day rises to a peak

in the afternoon or occasionally later for others; and (3) individuals who start out slowly and peak during the day but show a second bounce after evening dinner. Over the last half century, our body circadian (daily) rhythms, a field called chronobiology, have been studied extensively, and it is well established that certain body constituents, such as cortisone, are released in characteristic time cycles. Night workers undergo a shift in their sleep patterns and body physiology, which makes it difficult to alternate weekday and night shifts due to circadian rhythms. This effect is also encountered in very long air flights involving multiple time zones.

THE COSTS OF DISEASE

In July 2000, three very intriguing unique manuscripts were published in the recently renamed *Clinical Chemistry: International Journal of Laboratory Medicine and Molecular Diagnostics* (1–3). In the first of these, David ("Dave") E. Bruns, MD, and his colleagues published an article entitled *Toward a Checklist for Reporting of Studies of Diagnostic Accuracy of Medical Tests* in which they spelled out the criteria and information necessary to be included in an epidemiological study (investigation of the occurrence of a disease) to support the diagnostic accuracy of a laboratory test used in medical case-finding, diagnosis, prognosis, risk stratification, and monitoring (1). Their updated checklist enumerates 40 key items that must be included in any publishable study to prove the validity of a medical diagnostic test, whether it is a laboratory test or a CT scan.

The second article, by Donald S. Young, MD, PhD, and his colleagues in Laboratory Medicine at the University of Pennsylvania, analyzed hospital costs related to the 486 diagnostic-related groups (DRGs) of over 1.3 million patient discharges from 60 university hospitals ranging from 252 to 1,273 beds (2). For each DRG, the length of stay, total cost, and key cost components were analyzed, including accommodation (housing, meals, nursing services), intensive care, and surgery. They focused on median rather than mean costs because, due to outliers, mean costs were consistently higher than median costs. In general, surgical diseases cost more than medical diseases, but the five disorders involving organ transplants cost the most. Within the studied population, the DRGs accounting for

the most healthcare dollars were percutaneous (blood vessel) cardiovascular procedures (open heart surgery) and the management of neonates (newborns) with immaturity or respiratory failure. However, the cumulative cost of \$182,800,000 for kidney transplants for only 4,292 patients at the 60 university hospitals resulted in the highest patient cost for a single procedure. Although accommodation costs for transplants were only 12.3% of total costs, which have a median length of stay (LOS) of only 9 days, drug and laboratory costs are exceedingly high. The single best predictor of total cost for most DRGs was laboratory costs. Dr. Young's published data allows individual institutions to focus their cost-reduction efforts based on a comparison of their data with those from 60 other university hospitals in the database.

The third article by the same professional group at the University of Pennsylvania involves *Laboratory Costs in the Context of Disease* (3). In order to determine the contribution of laboratory costs to the overall costs of managing patients with different diseases, Dr. Young and his colleagues studied the costs of laboratory testing overall and in relation to other costs incurred during hospitalization. The mean laboratory costs to manage surgical patients were greater than those to manage medical patients in 19 of the 25 major DRG categories. The median (midpoint with half above and half below) laboratory costs for patients with liver transplants exceeded \$8,000 and the laboratory costs to support other transplants were among the highest. The highest proportion of total medical costs attributable to the laboratory was 18.3% for acute leukemia and for kidney and urinary tract signs and symptoms, both in children. Laboratory costs were found to be less than 1.0% of the total costs for only 15 of 468 DRGs. The highest median daily cost of \$416 was for liver transplant patients. However, several medical conditions had laboratory costs of less than \$30 per day, in spite of lengths of stay that exceeded 10 days in some cases.

Cancer

I very recently became acquainted with the professional journal CURE, *Combining Science and Humanity, Cancer Updates in Research and Education*, in which the summer 2005 issue had two fascinating and enlightening articles (4). The first article was titled *The Dark Side of the Sun and Other Radiation Hazards* by Melissa Weber (4, pp. 25–32). Raymond Tennant, PhD, Director of the National Center for Genomics, recently said “Cancer develops because of permanent changes in a person's genes” (4, p. 29). “Environmental factors including various types of radiation exposure are responsible for gene alterations that scientists just now are beginning to understand.” Skin cancer, associated with radiation exposure from the sun, is the most common type of cancer in the United States and afflicts more than 1 million people annually. Of the estimated 105,750 new cancer patients this year, only a fraction will be teenagers. However, the amount of sun they receive as teenagers probably sets the stage for whether they develop skin cancer as adults. Recently, Duke University chemistry professor, John Simon, collected red and black hair from wig makers and students to determine how the pigments in hair reacted as they absorbed either ultraviolet B rays

(UVB) associated with sunburn or ultraviolet A (UVA) rays that can penetrate and damage skin even without a burn (5). Both UVA and UVB light caused a photochemical reaction with the redheads' pigment called pheomelanin. This reaction causes oxidative stress, in which oxygen molecules called free radicals are formed that damage DNA (deoxyribonucleic acid) and cells in ways that, over time, can accumulate to spur cancer. In contrast, UVB light caused an oxidative reaction with the pigment from black hair called eumelanin (tanning). Unfortunately, skin cancer or melanoma can be devastating and leads to many deaths through metastasis. Although several experimental drugs are in use, early medical attention with surgical removal appears to be the best treatment. Some dermatologists treat precancerous skin lesions with dry ice at -180°C , which freezes them, and if raised above the skin the lesions sometimes dry up and fall off, which has been my personal experience. Only dermatologists who trained after 1999 are qualified to surgically remove melanomas extending into muscle and soft tissues; previously it was a medical specialty. Most melanoma treatment is by general surgeons and plastic surgeons using Moh's technique.

The second article in CURE, by Robiya S. Tuma, was on the *Discovery and Treatment of Chronic Myelogenous Leukemia* (CML) (6, pp. 33–40). In the 1920's, radiation was first used to treat CML, and it was not until the 1950's that the first chemotherapy was developed. In 1957, E. Donnal Thomas, MD, and his colleagues, clinicians at Mary Imogene Basset Hospital in Cooperstown, New York, which is affiliated with Columbia University College of Physicians and Surgeons in New York City, reported the first successful allogenic (matching) bone marrow transplant in a patient with leukemia. In 1960, Peter Newell, MD, and David Hungerford, MD, in Philadelphia, Pennsylvania, discovered the cytogenic marker for CML, which they named the Philadelphia Chromosome. (This is the same David Hungerford, a graduate of the University of Rochester School of Medicine, who is a distinguished Professor of Orthopedic Surgery at Johns Hopkins University and does his surgery at Good Samaritan Hospital in Baltimore). In 1973, Janet Rowley, MD, developed a slide-staining technique to identify this specific chromosome from among the 46 human chromosomes, which made the condition readily distinguishable from other leukemias.

Between 1984 and 1990, several researchers contributed to finding a protein called bcr-abl, identified as the cause of CML. A subarticle by Tara Beere Gibson, PhD, states, “The Philadelphia Chromosome encodes a new set of instructions for making an abnormal fusion protein known as bcr-abl, a tyrosine kinase enzyme that cannot be turned off and constantly stimulates the white blood cells to grow and multiply” (6, p. 38). For the first time ever, we now know the specific biochemical alteration leading to one form of “cancer.” Recently, a German group authored an article titled *Manifold-Assisted Reverse Transcription-PCR with Real-Time Detection for the Measurement of the BCR-ABL Fusion Transcript in Chronic Myeloid Leukemic Patients* (7). Thus, the bcr-abl fusion messenger ribonucleic acid (mRNA) in bone marrow or peripheral blood can be used as a measure of minimal residual disease in patients with chronic myeloid (myelogenous) leukemia (CML).

This test permits the monitoring of effectiveness of chemotherapy (drug treatment) in CML patients.

The first test studies for an experimental drug called Gleevec (manufactured by Novartis) took place between 1990 and 2000 and the first tests in humans took place in 2000 (6). In May 2001, the FDA approved Gleevec for the treatment of CML. It is estimated that 46,000 new cases will be diagnosed in 2005. Frank Giles, MD, a leukemia specialist at the M. D. Anderson Cancer Hospital in Houston, Texas, says, "The transition is, quite frankly, the most dramatic and significant progress that has been seen in any tumor in the last 30 or 40 years" (6). Clinical trials of Gleevec, which are currently in progress include Clinical Trial Phase II by Novartis Pharmaceuticals, Clinical Trial Phase II by Bristol-Meyers, and a Phase I Clinical Trial at the M. D. Anderson Hospital, which uses the experimental drug Zarnestra (Triplifarnib).

A recent article on cancer, published in the July 28, 2005, issue of *Nature* by scientists at Memorial-Sloan Kettering Cancer Center, says their finding helps to further unlock the secrets of metastasis (8). Dr. Gaorav Gupta, one of the two scientists making the discovery, said, "First and foremost, these findings are about the basic biology of metastasis, and the example we used to investigate it is the metastasis of breast cancer to the lung." Immunologically comprised mice were infused with human breast cancer cells from a patient who had widespread metastatic breast cancer. Dr. Gupta said, of cancer straying to a secondary specific site, "Using the (mouse) model, we identified a set of genes that we were able to show mediates this process." He further stated "Basically, the genes are largely composed of those that are involved in the communication of tumor cells in the environment they are trying to live in."

Lung cancer accounts for 20% of all cancer deaths and is the number 1 cancer killer. The National Cancer Institute (NCI) estimates that 162,000 Americans will die this year from lung cancer, and 72,000 will be women (9). Major new studies are exploring whether estrogen plays some role. This is many more deaths than from breast cancer with 40,000 deaths or prostate cancer with 30,000 deaths. Advocate groups, who are currently seeking more government dollars for research, emphasize that 20% of Americans die from lung cancer and 22% of the women are not smokers. They point out that federal funding for breast cancer research in 2004 was \$586 million and \$309 million for prostate cancer, but only \$277 million for lung cancer research, the major cause of cancer deaths. Unfortunately, they do not cite any information on how many women who are nonsmokers developed lung cancer because of secondhand smoke from family members or from the workplace. However, this type of exposure and the objectionable smelly environment has resulted in many states and large cities in recent years forbidding smoking in restaurants, bars, theater lobbies, etc., and in many federal and state government agencies.

A December 1, 2004, *Wall Street Journal* online article by Mark Ingebretsen is entitled *CT Scans Could Help Smokers Fight Lung-Cancer Risks* (10). According to Claudia I. Henschke, MD, in a prepared statement from the Radiological Society of North America, new research suggests that smokers might be able to dodge the deadliest of bullets, lung cancer,

simply by scheduling an annual computerized tomography scan. Dr. Henschke maintains that with annual screening there is a 76–78% chance of a smoker's lung cancer being cured. However, CT scans are very expensive and it is questionable as to whether many health insurance plans will pay for annual screenings for their participant smokers.

Smoking is responsible for approximately 85% of deaths caused by lung cancer and most smokers start as very young teenagers. "Tobacco smoking is the leading cause of preventable death in the United States" (11, p. 1355), and while quitting smoking is difficult, there are many excellent programs, for example the one described by Johns Hopkins professionals (11, pp. 77–88). Distinguished news reporter, Peter Jennings, passed away on August 7, 2005, at age 66 from lung cancer, and his death should have reminded all smokers that smoking often leads to lung cancer.

Lung cancer causes more deaths, some 1.3 million annually, around the world than any other cancer, and the five-year survival rate in Europe is only about 10% due to late disease detection and resection (12). Currently available low-dose spiral CT scans of the chest more effectively detect early-lung cancer in high-risk individuals (heavy smokers); however, the high detection rate of benign lesions has hampered the introduction of large-scale screening programs (11). Although positron emission tomography (PET), a radioisotopic test for which I showed a positive test result in September 2001, can effectively detect lung cancer, it also detects benign lesions. Annual CT scans from December 2001 through June 2004 have shown no changes in my right lung lesions and my pulmonologist at the University of Maryland Medical System discharged me in June 2004 as needing no further follow-up care. However, my benign lesions are due to six pneumonias since 1978, when I was hospitalized in Bryn Mawr Hospital with severe pneumonia. The second and third episodes occurred in the spring and summer of 2002, the fourth and fifth in 2003, and a sixth brief episode in January 2005. I now have bronchiectasis but do not have shortness of breath and attend a health club for physical exercise three times a week. I receive pneumonia vaccinations every five years, but it does not protect against all strains of pneumonia, which is a leading cause of death in the elderly. In order to protect myself, I don't shake hands anymore, try to avoid persons with colds, and use hand sanitizer (62% alcohol) before eating finger food.

My sister, Marge, had never smoked a cigarette in her life and was not subjected unduly to secondhand smoke, but died of lung cancer at age 66 due to five pneumonias in childhood, with permanent lung damage with bronchiectasis at age 28. The medical literature suggests that multiple pneumonias predispose one to lung cancer.

With a family history of susceptibility to pneumonia and several deaths from TB in my father's close relatives, I was not allowed to work my way through college. Instead, my mother became a clerk at the Woolworth's store in our hometown and paid for most of my undergraduate education at Syracuse University, which, with a scholarship, enabled me to graduate debt free. Although I dabbled occasionally with cigarettes in undergraduate college where fraternity rushing parties were called "Smokers," I joined a cooperative working

man's fraternity, where we shared preparing evening dinners, and I never did become a smoker. In October 1947, as a graduate student in medical education at the Syracuse University Medical College (as of 1949 the SUNY Upstate Medical Center), I was immunized along with my medical student colleagues with *Bacillus Calumet-Guerin* (BCG), a vaccine prepared from attenuated human tubercle bacilli and used to immunize humans against tuberculosis (TB).

According to the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, cancer kills more than 1,500 Americans a day; that is, one in every four deaths—or more than a half a million people—each year die of cancer (13). More than 35 years after President Nixon declared a war on cancer in 1971, the American Cancer Society reported recently that cancer surpassed heart disease as the leading cause of death in the United States for people under age 85. On the other hand, Dr. Bert Vogelstein of Johns Hopkins University, who is the leading cancer authority in the world based on the number of citations of his publications, will tell you something different. Over the last 25 years, Dr. Vogelstein's creative discoveries have established cancer as a genetic disease (13).

A new \$500,000,000 per year program, which is intended to turn promising laboratory discoveries in genetics and other fields into drugs and treatments, was announced by NIH Director Elias A. Zerhouni, MD, on October 12, 2005. The new program is intended to take recent scientific advances to the next stage and translate them into practical uses for patients. The program will pay select universities and private institutions to establish departments dedicated to such follow-up work.

On December 13, 2005, Frances Collins, MD, Deputy Director of the National Institutes of Health, and Anna Barker, MD, Deputy Director of the National Cancer Institute, jointly announced to the news media that \$100 million from existing NIH funds would be spent for a human Cancer Genome Project, with the goal of beginning to catalog cancer's molecular underpinnings. The project will start as a three-year pilot program identifying the genes related to two or three types of malignant tumors. If the research is promising and affordable, it will be expanded to study thousands of cancerous tumors. NIH officials described the research as "potentially revolutionary" and asserted that the resulting knowledge could quickly lead to the development of more effective cancer drugs and therapies. Dr. Elias A. Zerhouni, Director of NIH, said "This is really the beginning of an era," and I think we will see an acceleration of discovery.

Often referred to as a single disease, there are more than 200 types of cancers. The mapping of the human genome was completed in 2003. Reaction to the project by various national experts in cancer research has ranged from enthusiastic support to total disagreement. I find most intriguing the recent discovery reported in *Science* by a team of 200 international scientists that 99.9% of our genes are identical for all humans, regardless of national origin. However, the 0.1% that are different result in an identified 3.5 million variations known as "snips" (SNPs), which catalog our individual characteristics. It is hoped that the study of variation of SNPs, which make us differ from one another, will lead to new discoveries such as why and how we differ in individual characteristics, and our susceptibility to

disease primarily in relation to lifestyle and environmental factors. I find this new development mind boggling as to all its implications about the nature of life itself.

In January 2005, the FDA cleared Roche Molecular Systems' (Pleasanton, California) AmpliChip CYP genotyping test, and many experts hailed this as the birth of a new era in personalized medicine (14). Their pharmacogenomic microarray, released to the market in June 2005, detects specific cyto-genetic variations in the cytochrome P450 gene that can provide information on how well an individual can metabolize certain classes of drugs, thereby allowing clinicians to tailor their drug therapies to the individual's genetic makeup. It is hoped that this new type of testing will increase drug efficacy and reduce the number of adverse drug reactions (ADRs) that may account for as many as 2.2 million hospital events and up to 100,000 deaths per year in the United States (14). Although the release of a commercial test system for pharmacogenetic analysis is new, the Associated Regional University Pathologist (ARUP) Laboratories of Salt Lake City began offering tests for CYP2D6 in 2002, CYP2C9 and CYP2C19 in 2004, and more comprehensive tests for all three CYP450 genes in July 2005 (14, p. 3). Gregory J. Tsongalis, PhD, Dartmouth-Hitchcock Hospital Medical Center's Director of Molecular Pathology, initiated a routine program in 2006 that includes all patients admitted to the Hitchcock Teaching Center.

On December 22, 2005, a spokesman for the National Cancer Institute (NCI) said "The rate of cancer cases diagnosed in the United States has stabilized, but the cancer death rate continues to decline, including the four most common types of cancer—prostate, breast, lung, and colorectal." Americans are taking some steps to help prevent cancer, the agency said, and the use of screening tests is at high rates in an effort to detect cancers early. According to NCI Director Dr. Andrew C. von Eschenbach, "The rate of new cases of cancer was 488.6 per 100,000 Americans in 2002, close to the rate of 488.1 a year earlier, which is updated every other year." He pointed out that at the same time, the death rate for all cancers was 193.6 per 100,000, down from 195.7 a year earlier and continuing a steady downward trend.

Breast cancer causes about 48,000 deaths each year in the United States, and with 180,000 new cases diagnosed each year, it's the second most common cancer in women, after skin cancer. Women with inherited mutations in the breast cancer genes known as BRCA1 or BRCA2 have up to an 80% chance of developing breast cancer, while people with defects in MSH2 genes have a 70% chance of developing colorectal cancer (13). Nevertheless, Dr. Bert Vogelstein, the world's leading authority on cancer, says that heredity accounts for just 5% of all cancers and he believes the other 95% happen because cells sometimes make mistakes when they copy their DNA (deoxyribonucleic acid). Although tamoxifen has been used for nearly 20 years to blunt the effects of estrogen, a European study, early in 2005, estimated that 84% of women given Femara (letrozole) after breast cancer versus 81% of those on tamoxifen would be alive with no signs of cancer after five years. A very recent task force study reported that Letrozole (Femara) was more effective than the current gold standard,

tamoxifen, at preventing recurrences of breast cancer in 8,000 women (14). As a result of this study, on December 29, 2005, the FDA approved the use of Femara, which is manufactured by Novartis. It joins already-licensed AstraZeneca's Arimidex and Pfizer Inc.'s Aromasin as aromatase inhibitors (prevent the formation of the aromatic ring characteristic of estrogens and thereby prevent estrogen synthesis).

It also has been shown that pancreatic cancer, a very devastating form of malignancy, is associated with a mutation in the BRCA genes. It is anticipated that further study of molecular biomarkers, which can be identified through pharmacogenetic testing, holds great promise in the early recognition of specific types of cancer in susceptible individuals (15). In the October 28, 2005, issue of *Science*, scientists at the University of Michigan Medical School, led by pathologist Arul M. Chinnaiyan, MD, reported that fused gene fragments, one normal and one that causes cancer, fuse together to form solid tumor prostate cancer. It is an important finding as more than 232,000 men were diagnosed with prostate cancer in 2005 and, according to the American Cancer Society, it is expected to kill over 30,000.

St. Agnes Hospital in Baltimore, which is the closest hospital to our retirement community, has recently installed a landmark innovation in cancer therapy in the form of a new instrument, approved by the FDA in 2002, which integrates a real-time CT-image-guided radiation therapy (IRGT) with intensity-modulated radiation therapy. Timothy Holmes, PhD, medical physicist at St. Agnes, helped conceive the idea of tomotherapy in the early 1990's as part of his PhD thesis at the University of Wisconsin and has overseen installation of the new technology. Dr. Richard Hudes, chief of radiation oncology at St. Agnes since 2001, is in charge of the new sophisticated equipment, which is the 13th unit in the world and the first to be installed in the mid-Atlantic and northeastern part of the United States.

Pheochromocytoma

The inner center or medulla of the adrenal glands, located above the kidneys, secretes the hormones, epinephrine and norepinephrine, that are responsible for an acute physiological reaction summarized by the phrase "fright, flight or fight." When we get this acute reaction, we are frightened, want to run from the situation, or want to fight about what just happened, or some combination of these until we calm down and regain our body control. Hans Selye, MD, Professor of Physiology at the University of Montreal, first described this phenomenon in 1955. The first pheochromocytoma was identified in 1929 by the distinguished Maurice C. Pincoffs, MD, who was Chairman and Professor of Medicine when I joined the faculty of the University of Maryland School of Medicine in 1950, and it was removed by Warren M. Shipley, MD, Chairman and Professor of Surgery. A pheochromocytoma results in the only type of hypertension that is characterized by intermittent increased blood pressure, which is cured instantaneously at surgery.

As a clinical chemist, I was involved, in about 1958, in the measurement of the vanillyl mandelic acid (VMA) metabolites of the catecholamines (epinephrine and norephrine secreted in the urine in pheochromocytoma). A Hycel kit reagent was

available commercially, and I sent the Upstate Medical Center Medical Staff a newsletter calling to their attention the availability of the test and indicating that it detected the rare condition of pheochromocytoma. At that time, it was thought that up to 2% of cases of hypertension might be caused by this type of tumor. Today, we know that pheochromocytomas are exceedingly rare and account for less than a decimal fraction of 1% of the cases of hypertension.

Although such tumors are exceedingly rare, my first cousin Fred Vanderlinde, the second-generation President of the Vanderlinde Electrical Corporation in Rochester, New York, founded in 1922 by my Uncle Ed, developed a pheochromocytoma. My older sister, Dorothy, lived in the suburban Rochester area and visited Fred, in about 1988, and at that time he gave her a summary of his illness. It is a classical description of the clinical episodes characteristic of the condition and demonstrates what such a tumor can do to one's life when it is not promptly diagnosed. My wife and I had lunch in Rochester on July 19, 2006, with Fred's son, Derek Vanderlinde, and at that time he gave me permission to include the two-page summary verbatim.

My statement before the Federal Electrical Contractors (FEC) meeting in January 1986 by Frederic Vanderlinde. For a half dozen years, in me you experienced a person living on excess adrenaline and very little oxygen. It affected my personality and how I treated you.

Seven years ago, after an aortic aneurysm repair, I occasionally experienced a pounding in the head with severe headache. On one occasion Derek rushed me to the hospital but the two minute discomfort had left and I checked out as OK. During a three times per week Y-program of exercise, when pounding began I would lie on the floor for 2 minutes and be OK. Frequently at the office, Derek said, 'You look grey—go home.' I said, I'm OK I'm living on adrenaline! I went without my overcoat in Rochester's cold winters. I could charge my body to heat and be comfortable. Poundings without headaches came more frequently.

In January 1984 the FEC met in Hawaii: upon loading suitcases one day I tossed my pre-breakfast orange juice. For years my personality, effected by hypertension, had been taken for granted with a taste of psychotherapy or love, but these physical symptoms were occurring more frequently with less and less explanation. Last summer, several times after sailing, I experienced pounding and tossing-up. My best friend has a blood pressure kit with an electronic readout. She recorded readings of 200 and 300 during the attacks. In April 1985 the FEC met in San Antonio; I lost a soup luncheon with 'poundings.' I estimated that I had had at least 100 of these head pounding sessions.

To this point my doctor knew what you know except for the 200–300 readings which I had dismissed as false electronic readouts. I had reasoned, if 300 was a true reading, where was the blood clot and attending stroke? Instead, I asked to be tested, first for hyperglycemia, then diabetes, then an ultrasound scan of my heart muscles and valves, etc., and finally we planned a Tread Mill Stress Test for right after the September 1985 meeting of the FEC at The Greenbrier. September 16th: during the Stress Test the symptoms of the poundings reproduced and for the first time, doctors observed the 300 blood pressure readings and immediately put me in the hospital Emergency Department.

In two days, they X-rayed, catheterized my coronary arteries and completed a quadruple coronary bypass. On September 19th they opened again to repair internal bleeding and they also informed me of a tumor in the adrenal gland on the left kidney and the schedule to operate in 30 days.

But by October 1, 1985, I was still in intensive care unit, losing over one pound a day, the blood pressure readings were still occurring in the 200+ range. I was going down hill fast and the doctors agreed to operate, hoping for less risk of my dying. They could not wait two more weeks; the next day with the tumor out and back in ICU, I had a new problem: between hallucinations and reality, the question was: do I take the next breath or accept the golden, easy opportunity of dying? Three times it happened. Each time I was ready to die, and each time the energies from my many friends who believe in parapsychology or spiritualism or prayer provided the indescribable messages that opted for living.

Then I fought to live, but in the hallucinations I believed the hospital personnel were conspiring against me. I pulled out all the tubes and monitors and was about to flee my bed and the hospital.

Some time later I was in a steady state and Dr. Q_____ was at my bedside, sweating and berating me for what I had done. I turned on my left side, away from him and he pummeled me (like cupping except) on my right side instead of my back. I have recently undergone repair of a "surgical hernia" at that location.

By October 5, I had made it to a recovery ward. They had removed the terrible pheochromocytoma, a tumor that secretes catecholamines and causes hypertension. My surgeon, Dr. Seymour I. Schwartz is affectionately known in the medical profession for having written THE book on surgery. Late on a Saturday night, returning from a medical/surgical conference in Virginia, he stopped at my bedside and said, 'I reported your rare case, that your tumor, your pheochromocytoma set a record in output, not an ordinary record but a world record.'

By October 13, my blood pressure had been normal for seven days. They wanted to release me. I was scared; had lost over 30 pounds; I could walk only a few feet, and could not take a shower. Dr. Schwartz assured me that I alone, not Dr. Q_____ or Dr. O_____ (my antagonists) would determine when I would leave. During the next week I began earnest exercise; my walking expanded to over 100 paces and I took my first shower. The next day, October 22, 1985, some thirty-six days after the stress test, I was released.

Today (January 1986) my face and hands are now pink instead of tan and sallow; my heart is really moving my blood. Without the excessive emissions of adrenaline in my system, I am now adjusting to 'normal behavior.' From anger to love, without the excesses of the tumor, these feelings are wonderfully new for me. For those of you who suffered my adrenaline induced emotional outbursts (Steve, John, Steve, Ralph, ...) I sincerely apologize. And for everyone listening, I thank God I am alive and can be with you.

Because I had introduced the VMA urine test for a pheochromocytoma to the clinical staff at the SUNY Upstate Medical Center over 25 years earlier (in about 1958), I am very critical of the fact that it took Fred's clinicians and the Rochester hospitals six years (1979 to October of 1985) to diagnose Fred's

pheochromocytoma. Unfortunately, their failure to make a correct diagnosis in a timely manner nearly resulted in Fred's death on several occasions. Some major medical errors are not acts of commission but acts of omission.

In January 1993, we had lunch with Fred and his lady friend, whom we liked very much, in Ft. Myers, Florida, and at that time I told him I understood the great deal of trauma he went through for a very extended period of time before a diagnosis was made and the tumor removed.

SIDS

A very tragic occurrence is the Sudden Infant Death Syndrome (SIDS) or crib death of what appears to be a perfectly normal infant within a few months of birth. Many studies have been carried out over the last 25 years and various hypotheses proposed (16). In July 2000, Charles Antzelevitch, MD, at the Masonic Medical Research Laboratory (MMRL) in Utica, New York, in conjunction with eight other physicians, several of whom are at Italian universities, reported a molecular link between SIDS and the long-QT syndrome, an EKG abnormality, which is a spectacular finding (16). It appears that the hidden syndrome may continue in some children and result in their sudden death even as teenagers. Dr. Antzelevitch and his group recently identified another defective gene that plays a role in the appalling syndrome responsible for the sudden death of infants, children, and young adults. In a span of one year, they found the cause and prescribed a treatment to correct the genetically induced electrical dysfunction of the heart found in some patients experiencing coronary problems. In October 2005, the Masonic Medical Research Laboratory, in cooperation with the Mohawk Valley Heart Institute, received live heart tissue as the atrial appendage, a byproduct of a heart bypass and valve procedure. It is expected to give Dr. Antzelevitch's research group the opportunity to better understand the normal function of the heart as well as what causes abnormal rhythms (17).

A big question has been how to reduce the clinical incidence of SIDS. Just recently, researchers from the University of Virginia and the Children's National Medical Center pulled together seven published studies involving pacifiers and concluded that one SIDS death could be prevented for every 2,733 babies who drift off to sleep with pacifiers in their mouths. The occurrence of SIDS is rare during the first month of life, increases to a peak between 2 and 3 months of age, and then decreases. Thus the American Academy of Pediatrics (AAP) in November 2005 changed their recommendations regarding the use of pacifiers (18). Consistently higher rates of SIDS are found in black and American Indian/Alaska Native children by a factor of about 2 to 3 times the national average.

Diabetes

Diabetes mellitus is a heterogeneous group of disorders, all characterized by increased plasma glucose (10, pp. 1174-1182). Normal fasting blood glucose is 70-90 mg/dL. It has been

well-demonstrated that the condition can be best treated in patients through the tight control of blood glucose, which in turn avoids its many complications, but the complexities of diabetes are poorly understood. I have said for many years that if we understood diabetes, we would know so very much more about the biochemical reactions and physiological (functional) relationships of intermediary metabolism and body energy production. Although it is possible to write equations for over 1,500 biochemical reactions taking place in our bodies, we certainly don't know their interaction and function. It is well-established that brain tissue utilizes only glucose, the liver is the chemical factory of the body and storage place of glucose in the form of glycogen, and that metabolism speeds up in cancer cells and in fever. Although thousands of journal articles and many books have been written over the past 80 years about diabetes and we can show specific biochemical reaction changes in diabetes, we are still unable to clearly define the kinetic and dynamic interrelationships that take place in the metabolism of glucose (dextrose) and fructose (fruit sugar). Ordinary table sugar is a disaccharide made up of a molecule of glucose and a molecule of fructose, and lactose, or milk sugar, is a disaccharide made up of a molecule of galactose and a molecule of glucose. Starch is a polymer of glucose, which hydrolyzes to maltose (a disaccharide) and then to glucose. Although liver glycogen is also a polymer of glucose, it has much more branching and therefore differs markedly in its properties.

Type 1 diabetes, or insulin-dependent diabetes, occurs world wide and can appear at any age, but it has been called juvenile-onset diabetes because its most serious form occurs in young children (10). Juvenile diabetic patients have been called "brittle diabetics," as they are often difficult to keep in glucose control, possibly because of their physical activity, their ongoing biochemical and growth changes, and hormonal changes in sexual maturation.

Type 2 Maturity Onset Diabetes occurs in middle to elderly adults and can often be brought under control through change of diet, weight loss, and exercise, including walking. Oral hypoglycemic drugs often are effective in keeping it under control, but some type 2 patients may require insulin off and on or regularly depending on the previous factors cited. We have a diabetic friend with whom we regularly played bridge on our three-month winter sojourns in Florida who has an older brother back in St. Louis, Missouri, who is wheelchair bound with severe diabetes, and suffers its dire consequences. However, after seeing what happened to his older brother, our diabetic friend, Bill, stays slender, makes good menu choices, has good medical care by a diabetatologist at Washington University School of Medicine in St. Louis, plays 18 holes of golf several times a week, and walks at least five miles every day.

Insulin is a protein whose amino acid sequence is known, but it cannot be taken orally because the gut would digest it like any food protein. In 2006, the FDA approved Exubera, the first insulin that can be inhaled rather than injected—a novel approach (19). It is manufactured and sold by Pfizer. Concerns linger, however, about Exubera's long-term effects on the lungs and whether it is safe for smokers, children, and patients with lung disease.

Most known body hormones are antagonistic to insulin, including the adrenal steroids such as cortisone and hydrocortisone, the male and female sex hormones. All of these steroid hormones are synthesized from cholesterol and all have a multiple ring structure with various functional groups. Hormonal exceptions to insulin antagonism are the adrenal cortical hormone, adrenaline, which causes our fight, fright, or flight response in emergency situations, and thyroxine, the hormone produced by the thyroid gland in the neck, which controls our rate of overall body metabolism. Today, an injection of cortisone for an acute orthopedic problem in a diabetic patient, either because it is not in the patient's record or the patient forgets or doesn't know about it, can be a near disaster. Another possible exception is glucagon, which stimulates the liver to release glucose into the bloodstream and raises blood sugar (glucose). It is now legal for school nurses in Maryland and New York State to administer injectable glucagon to known juvenile diabetic students who pass out and therefore are unable to quickly take some form of glucose by mouth.

Although fasting levels of blood glucose of 70–110 mg/dL are very desirable, and fairly similar 2-hour post prandial values (after a test dose of glucose or a light meal) are desirable for "normal" individuals, the most important principle for diabetics is to keep their blood sugar below 120 mg/dL as much of the time as is possible. Regular monitoring is possible through the use of any of several home glucose-monitoring systems on the market, which use finger-stick (micro) blood samples (10, p. 1176). One type recently available releases an adjustable lance device prior to collecting a capillary blood sample from the fingertip, and when placed against a test strip fills with blood by capillary action. After placing the strip in an electronic device (micro-processor) along with a control strip of known concentration, it shows the glucose content of the patient specimen in mg/dL. This is modern electronic gadgetry at its best and is fully supported financially by Medicare for patients over 65 years of age, including in-home training in their use and monitoring by nurse practitioners. In the long run, Medicare saves money by preventing end-stage renal disease, and it is in the patients' best interest.

Several commercial devices, using finger stick blood collected in a glass microcapillary tube, have been in use at diabetic clinics, nurses' stations, and for patient self-monitoring for about 30 years. In July 2002, two new computerized devices that help patients track glucose trends on hand-held computers were cleared by the FDA (20). In the May 2000, Health and Human Services Secretary Tommy Thompson warned of the dangers of "pre-diabetes," a condition that increases the risk of heart disease by 50%, and he stated that there are over 17,000,000 Americans with diabetes.

It has been well documented that the secret for avoiding the complications of diabetes is to keep one's blood sugar under control 24 hours a day. We know, by the law of mass action, that blood glucose concentrations that exceed about 150–160 mg/dL are damaging. At high concentrations, molecules of blood glucose attach themselves to various body blood vessels and proteins, and the higher the concentrations and the longer the duration of elevated blood glucose, the more small blood vessel damage occurs. This damaging effect takes place

in diabetics with prolonged blood glucose levels greater than about 150 mg/dL, and no enzyme or chemical reaction is required to attach glucose to various plasma proteins or various small blood vessels, especially those of the eyes and kidneys. It is purely a mass action effect that results from prolonged high glucose levels occurring in diabetics not under good control. Thus diabetic retinopathy occurs in 95% of people who have had diabetes for more than 15 years, but fortunately only a minority of these people will develop significant visual problems as a result (10). However, 35–45% of type 1 (insulin dependent) diabetics develop kidney damage, also called nephropathy, and end-stage renal disease is the most common cause of death in severe diabetics. Glycohemoglobin (HbA1c) is a diagnostic test for the measure of glucose control over the past 4 to 6 weeks and therefore is a better test by far than a single blood sugar determination.

Several large clinical trials, such as the Diabetes Complications Control Trial, the United Kingdom Prospective Diabetes Control Study, and the Providence Health Systems of Portland, Oregon, Study of 3,554 diabetic patients undergoing coronary artery bypass grafting (CABG) have convincingly documented the importance of tight glucose control (TGC) (21). The question asked by the author of the article is whether currently available glucose monitors are adequate to clinically maintain glucose levels between 100 and 120 mg/dL or possibly a target range of 80–120 for diabetics undergoing surgery so as to make them less susceptible to infection. Certainly, a desirable goal for all diabetics should be to maintain their glucose routinely between 100 and 120 mg/dL using a state-of-the-art glucometer. A 17-year federally funded study, published in the *New England Journal of Medicine* on December 22, 2005, found the answer to be “yes; intense control can reduce the risk by nearly half” in type 1 diabetes, the type, which usually arises early in life and involves the death of insulin-secreting cells (22). Dr. Robert Rizza, a professor of medicine at the Mayo Clinic and the president of the American Diabetes Association said “This is truly an important study” and “I usually don’t say that.” Dr. Rizza’s parents, who are deceased, were close friends of ours in the church we attended in Baltimore from 1950 to 1955, and we remember Robert and his sister as youngsters.

A recent survey by the American Association of Clinical Endocrinologists (AACE) shows that two-thirds of Americans with type 2 diabetes are not in control of their blood glucose level, leaving them more exposed to the complication of diabetes (23). The AACE reported that 84% of those polled thought they were doing a good job of managing their blood sugars whether reporting daily blood glucoses or following HbA1c measurements, which give a measure of blood sugar over the past one to two months. The AACE reported that there are over 18,000,000 diabetics in the United States and that type 2 diabetes accounts for 90–95% of all diagnosed cases.

William E. Winter, MD, a distinguished professor in six specialties, but primarily the Director of Clinical Chemistry at the University of Florida School of Medicine in Gainesville, has been involved in diabetes research since 1981 (24). He has found that the vast majority of cases of type 1 diabetes are autoimmune in etiology and that the presence of islet autoantibodies in a

patient’s serum (a lab test) serves as a definitive marker for type 1 diabetes. At least one of four different antibody markers is positive or present in 95% of new cases of type 1 diabetes. Autoimmune diabetes can also present with an initial, noninsulin-dependent course similar to type 2 diabetes. Dr. Winter says patients with apparent type 2 diabetes who have a family history of type 1 diabetes and other autoimmune conditions such as Hashimoto thyroiditis, Graves disease, pernicious anemia, or Addison disease, or who develop insulin dependency should be considered for glutamic acid decarboxylase autoantibodies (GADA) testing. Insulin dependency is a characteristic of “latent autoimmune diabetes in adults” (LADA). LADA, although initially appearing similar to type 2 diabetes, is really slow progressive type 1 diabetes. Dr. Winter concludes that although a glucose measurement remains the first step in diagnosing diabetes, proper classification of a person’s diabetes requires a number of additional clinical laboratory tests (24, p. 16).

In January 1977, I became Professor and Director of Clinical Chemistry at the Hahnemann Medical College in Philadelphia, and during the first month wrote and submitted an NIH grant to study the possible role of chromium in diabetes. About 1960, a former colleague at Syracuse, Richard “Dick” Doisey, PhD, the youngest son of Nobel Prize winner Edward A. Doisey, Sr., PhD, showed that chromium deficiency leads to diabetes in rats and feeding them Baker’s yeast corrected their diabetes. Thus, Dick Doisey’s studies and other published data supported the hypothesis of a glucose tolerance factor (GTF) containing chromium, which is present in food sources such as baker’s yeast and in Pabst beer. Dick studied the well water used at various Pabst brewing plants and found that the one in California had the highest chromium (Cr) content. Subsequently, the company stopped using this well. Dick’s published studies have led to numerous nutritionists recommending the inclusion of small (microgram) amounts of water-soluble chromium picolate in one-a-day vitamin pills, and it is usually included in mineral supplements.

The NIH grant on *The Measurement of Chromium in the Serum and Urine*, which I applied for in January, was approved as of July 1, 1977. The grant provided funding to purchase a \$5,000 Perkin-Elmer 603 Atomic Absorption Spectrophotometer (AAS) for the measurement of chromium in body fluids. Fred Kayne, PhD, a physical biochemist and instrumentationalist, who had been an associate professor at the University of Pennsylvania and was in search of a new career after the closure of the Johnson Research Foundation at Penn, joined my staff at Hahnemann on July 1, 1977, as my right-hand associate. It was a very fortuitous hookup as Fred, trained as a physical chemist, immediately recognized that the background correction was insufficient and substituted a halogen lamp (25). Six months later, Perkin-Elmer introduced the same improvement on their newest AASs. However, we became the first scientists in the world to show that serum chromium levels were only 10% of what had been previously accepted (25).

A previously existing National Institute of General Medical Sciences (NIGMS) grant at Hahnemann supported a postdoctoral trainee in clinical chemistry, and I soon recruited Mark J. Simmons, a new PhD from Indiana University. After

Mark arrived, I asked him if he had any experience with commercial centrifugal analyzers and his reply was, "No; just the one I built for my PhD thesis." Mark was a brilliant addition to our group, and he interfaced our lab computer to our modified AAS for digital processing of the Cr signal output (26). Thus, we were able to measure chromium in standard solutions and in a few microliters (very tiny amount) of serum or urine in the ppb (parts per billion), an ultra-trace level never accomplished before. This is an additional reason why no research group has ever been able to put together a comparable system to confirm our very sophisticated studies.

Trace metal analysis in the parts-per-billion range requires very pure water and superb technology, which we had. Thus, we succeeded in demonstrating that chromium is increased two- to threefold in the serum and urine of diabetics, which we presented in 1979 at an International Trace Metal Symposium held at Sherbrooke University in Quebec (27). After I developed a column chromatographic technique for concentrating the chromium-containing material in urine, our NIH grant supported technician Gary Komar and graduate student, Henry La Boda, who partially characterized a small protein molecule or peptide. The latter is made up of several amino acids, which our evidence showed contained a molecule of trivalent chromium (Cr^{+++}), a very unique novel compound (28). It was demonstrated to be a low molecular weight peptide and made up of several amino acids that contained a molecule of trivalent chromium (28). We postulated at the time that it might be the so-called "second messenger," by which insulin acts on individual body cells, which has never been identified.

Owing to our small diabetic population at Hahnemann, we made arrangements with the Joslin Clinic in Boston as a large reliable source of the needed clinical specimens. However, NIH did not renew our grant in 1981, with the statement that they wanted both phases of the follow-up studies done at the same institution. My personal belief is that they thought we might have hit upon the second messenger, a postulated mechanism for the action of insulin, which several prominent and well-funded laboratories were vigorously researching at the time. Needless to say, neither of these difficult and challenging problems has been resolved as of the present day, even with today's newer AAS and mass spectrometry technologies. We were refused publication in one biochemical journal whose editorial board wrote back, "Prove it is not an artifact," which is almost impossible to do. Additionally, the lack of further funding did not permit us to isolate and attempt to demonstrate a clear-cut clinical abnormality in patients with altered chromium metabolism. I have speculated that chromium deficiency might be associated with nonketonic hyperglycemic hyperosmolar coma (NKHHC), an extremely rare form of diabetes, which is mainly restricted to the infirm and the neglected and undiagnosed diabetics (29, pp. 396–397). Such coma may be one end of a clinical spectrum for patients who suffer uncontrolled osmotic diuresis and diagnosis is usually dependent on laboratory results. However, one anecdotal case, with which I am familiar, provides no real support for this hypothesis.

At least one pharmaceutical company, the Communicable Disease Center (CDC; now the Centers for Disease Control and

Prevention) in Atlanta, Georgia, and the United States Department of Agriculture Trace Metal Research Labs in Beltsville, Maryland, are familiar with our published findings on chromium, but none have had the available resources to further investigate the role of chromium in diabetes, as its deficiency is not a known major clinical problem. More recently, Brian W. Morris, PhD, and his colleagues at the University of Leeds in England have demonstrated that the administration of a test dose of glucose, used for a glucose tolerance test (GTT), results in increased concentrations of chromium in the serum and urine of healthy adults (30). Their studies support our published data showing that chromium plays some unidentified role in diabetes.

A *USA Today* newspaper article published in early 2003 states that nearly one-quarter of retirement-age Hispanics have been diagnosed with diabetes, twice the percentage rate of whites and significantly more than Asians. Also, it points out that diabetes is the nation's seventh leading cause of death and is the leading cause of adult blindness, kidney failure, and the amputation of limbs. According to UCLA's Center for Health Policy Research, it especially poses a serious problem among California's black and Indian populations. Another recent *USA Today* article states that benfothiamine, a synthetic derivative of vitamin B-1 (thiamin), has been found to prevent the structural damage of diabetes in rats. Will it work in humans—a long jump from an effect in rats? Also, a January 12, 2003, article linked diabetes with heart attacks and stated that about 75% of people with type 2 diabetes, the maturity onset type, die of heart attacks or strokes. Although far from a firm conclusion, Dr. Om Ganda from the distinguished Joslin Clinic (for diabetes) in Boston, is quoted as saying, "It really adds to a growing body of evidence that says insulin resistance does contribute to increased risk for heart disease." Lastly, there is no question that obesity plays a significant role in diabetes and it is all too prevalent in the youth of America as well as adults of all ages.

Allison M. Steube, MD, a maternal and fetal specialist at the Brigham and Women's Hospital, a part of Harvard Medical School, suspected that something good was happening to her patients who breast fed their children. She noticed that "Diabetic mothers who nursed their infants required less insulin than others who (were) bottle-fed." She thought that perhaps the act of producing milk protected women from type 2 diabetes, which is dangerously on the rise in America. To find out if her hypothesis was correct, the Boston physician turned to the Harvard-directed Nurses Health Study, which has tracked thousands of nurses over the past 29 years—recording information about diet, exercise, health, and illness. For the diabetes study, researchers were able to track data on 150,000 women who had given birth. When duration of lactation was plugged in versus the risk of diabetes, there was an inverse relationship; that is, the longer a woman breast fed her infant, the lower her risk of developing type 2 diabetes (31). Weight loss and exercise are not the explanation, as shown by controlled studies, but the answer appears to be in the metabolic changes that take place in milk production. Dr. Steube says, "Breast feeding burns 500 calories a day—the equivalent of running four to five miles a day."

An article in the November/December 2005 issue of the *AARP Magazine* (American Association for Retired Persons) is entitled *Diabetes Denial: Five Million Americans Have This Disease And Don't Know It* (32). The article states that 18.2 million Americans have diabetes and 5.2 million don't know they have it. It points out that a nationwide study called the Diabetes Prevention Program was halted in 2001, a year early, because the study had proven that prediabetics reduce their risk of developing type 2 diabetes by more than half simply by losing weight and exercising. Surprisingly, the study showed also that participants over age 60 adapted better than younger participants in sticking to the diet and exercise program and reduced their risk by a stunning 71% (32).

Hypertension (high blood pressure) occurs in diabetic patients 1.5 to 3 times as frequently as in nondiabetics of similar age, and it has been found that the risk of cardiovascular (heart) disease is consistent and independent of other factors (33). The higher a person's blood pressure, the greater the cardiovascular risk, and it is so greatly compounded in diabetics that cardiovascular disease causes 86% of deaths in such patients (33). Therefore, it is very important that such patients be maintained on effective beta-blocker drugs, with blood pressure lowered to 130/80 mm of Hg (mercury) or less, but not all beta-blockers act the same way. George L. Bakris, MD, Professor of Preventive Medicine and Internal Medicine of the Rush University Medical Center in Chicago, Illinois, provided a one-credit course on this subject, toward the AMA Continuing Education program for physicians, through the American Academy of Continuing Medical Education, Inc. The course, which ran from October 25, 2005, to October, 25, 2006, was titled *Evaluating Treatment Options for Patients with Diabetes Mellitus and Hypertension: New Data on B-Blockade* (34). Although the course was supported by an unrestricted educational grant from GlaxoSmithKline, the reported study involved an ethical, randomized, double-blind, parallel-group, multicenter trial in the United States. The conference supplied new findings for physicians on a comparison of the FDA-approved beta blockers carvedilol and metoprolol tartrate (Toprol-XL), which have different pharmacologic profiles in diabetics and in chronic kidney disease patients. The presentation included a flow chart, based on defined clinical and laboratory findings, of how such patients should be treated with diuretics, arterial blood-pressure-decreasing drugs, and angiotensin-converting enzyme inhibitor drugs that act on kidney function.

Metabolic syndrome is a cluster of conditions including glucose intolerance, insulin resistance, large waist circumference, dyslipidemia (abnormal amount of fat in the blood), and hypertension (35). It has been estimated to occur as frequently as 1 in every 4 adults in the United States. Because it is associated with increased risk of cardiovascular disease and type 2 diabetes, preventing this syndrome is a high priority among health professionals. Known multiple lifestyle factors such as smoking status, drinking habits, diet (especially, carbohydrate, fat, and total caloric intake), and physical activity all have been associated with the condition. However, the relative influence of these behaviors in increasing the likelihood of developing metabolic syndrome is a topic under research (35).

According to a January 16, 2006, article in the *New York Times*, researchers at Decode Genetics, a company in Reykjavik, Iceland, have found a variant gene that leads to a sizable extra risk of type 2 diabetes, which is carried by more than one-third of the United States population. According to the CDC, type 2 diabetes accounts for 95% of the 20.8 million diabetics in America; therefore, the finding is of great importance nationally. Because people carry two copies of every gene, it is important whether one or two copies of it have been inherited. The estimated 38% of Americans who carry a single gene have a 45% greater risk of developing diabetes than do those who carry no genes for diabetes. However, according to the Decode researchers, the 7% who carry two genes for diabetes are 141% more likely to develop the disease.

An astounding new development occurred in November 16, 2006, when it was announced that the medication, Avandia, or rosiglitazone, is effective in delaying the onset of type 2 diabetes (36). It took a period of three years and testing on 5,000 people, in the largest clinical trial ever conducted, to demonstrate that the drug is effective in delaying or preventing the progression of pre-diabetes to diabetes by more than 60%. Of the nearly 21 million people with diabetes in the United States, 18 million have type 2, which is caused by the body becoming resistant to insulin or not making enough. Unfortunately, only 70.2% of these, or 14.6 million people, are diagnosed and 29.8%, or 6.2 million, are undiagnosed (36).

Hemophilia

Hemophilia is famous for occurring in royalty, such as the descendents of Queen Victoria and thus the current British House of Windsor. However, it also occurs in common people as a sex-linked genetic factor in the forms of haemophilia A and haemophilia B, associated with defects in blood coagulation. Although these diseases are due to defects in factors VIII and IX of the intrinsic clotting pathway, the affected individuals are prone to excessive hemorrhaging and have critical problems in arresting any blood loss (37). If the bleeding loss is very extensive, such individuals require transfusion.

Porphyrias

While on the University of Maryland faculty from 1950–1957, my mentor in clinical chemistry, Marie Andersch, PhD, who became a life-long friend, stimulated my interest in porphyrias, which are a group of inherited and acquired diseases characterized by red pigments in the urine. Porphyrins comprise the active nucleus of hemoglobin, made up of four pyrole rings joined by methene groups, some of which are red and fluoresce (glow) under ultraviolet light. Porphyrias, such as acute intermittent porphyria (AIP), may be inherited. AIP victims include King George III of the British House of Stuart, who was King of England during the Revolution and thought to be intermittently crazy, a major characteristic of the disease. More recently, AIP has been passed on to the descendents of Queen Victoria (38). Therefore, members of the House of Windsor are subject to porphyria. It is characterized in the acute or active

phase by bouts of red porphyrin excretion in the urine and is accompanied by mental symptoms (irrational behavior) and motor symptoms, for example, temporary paralysis of a limb, with quiescent or latent phases in between. Another acute form, porphyria cutanea tarda (PCT), results in an acute skin reaction on exposure to sunlight, and children with this type must be kept out of sunlight. A third form, the mixed or variegated porphyria (VP), is characterized by the features of both PCT and VP, but the skin lesions usually predominate. Congenital erythropoietic porphyria (CEP) principally features red blood cell effects, while hereditary coproporphria (HCP) results in red coproporphyrins in the urine. The sixth type is characterized by red cell stippling, which also occurs in lead poisoning in which the nearly complete Hb molecule inserts a molecule of lead instead of trivalent iron. Lead poisoning causes what we call basic stippling of the red cells and, additionally, brain damage in young children. Although I first lectured on the topic to the students in Hematology at the Albany Medical Center in the 1960's, the disease entities associated with all six steps of the synthesis of hemoglobin (Hb) were not known. However, they had been identified by the 1980's when I presented the subject in Laboratory Medicine at Hahnemann University.

After I arrived at Hahnemann in 1977, I became involved in advising Dr. Bruce McFagan, the 75-year-old retired head of Ob-Gyn, who was being sued for malpractice for prescribing estrogens to a female patient, and thereby exacerbating this lady's mild porphyria. Most damaging was an affidavit filed by an MD/PhD Professor of Pharmacology at the University of Pennsylvania stating, "Any physician would have recognized that this woman patient had porphyria," which I knew was not true. As a matter of fact, I knew that very few physicians aside from hematologists, oncologists, and some well-trained internists would have made the diagnosis. The case dragged on for a couple of years and I kept telling Dr. McFagan that he would have to get his attorney to challenge the clinical credentials of the academic pharmacologist. However, about 1981, a red blood cell enzyme test for acute intermittent porphyria (AIP), which occurs more commonly in women, was developed by the Pediatric Hematology Staff of Children's Hospital at the University of Pennsylvania, which the patient agreed to take. Fortunately, the test proved to be negative and exonerated Dr. McFagan. My lectures to the second-year medical students included slides showing the fluorescent character of urinary porphyrins and patients with the skin eruptions and blotches associated with the most common defects. Several years ago, when I learned my dermatologist was lecturing to the junior medical students at the University of Maryland on the subject, I gave my slide collection on porphyrias and the associated clinical disease entities to him.

Osteoporosis

The cover of the June 2005 issue of *Reader's Digest* reads "The Killer Disease Doctors Miss" (39). The thrust of the article is that unhealthy eating habits by children put them at an extreme risk of osteoporosis; that is, by drinking a soda or other soft drink instead of a glass of milk it leads to a shortfall of the calcium and vitamin D that is needed to build a strong bone structure.

According to Leon Root, MD, Professor of Clinical Orthopedics at Cornell Medical College in New York, they also are not getting the benefits of vigorous exercise, making them at high risk for not only brittle bones and fractures decades down the road, but for osteoporosis at a younger age than ever before (39). Further, our bodies are in a dynamic biochemical state and each year about 20% of our bones' spongy tissue is replaced.

Osteoporosis is not just a disease of the elderly, but strikes about 8,000,000 women and 2,000,000 men each year, and another 34,000,000 Americans have low bone mass. According to Robert Heaney, MD, Professor of Medicine at Creighton University in Omaha, Nebraska, there is a growing consensus that 200 International Units (IU) of vitamin D for adults under 50, and 400–600 IU for older people is too low (40). He believes that the best protection is offered by taking 1,800 IU daily, because as one ages, one loses bone faster than one produces it (40). Single monthly dose Boniva, for the treatment of postmenopausal osteoporosis, was released to the market by the FDA in March 2005.

The Corporate Medical Director at our Charlestown Retirement Community, Dr. Matthew Narrett, announced on January 12, 2006, the acquisition of the latest sophisticated equipment for the measurement of osteoporosis, the GE Lunar Prodigy. It takes x-ray pictures in all planes of the back, leg, and knee bones in a few seconds and will define in great precise detail a person's bone status. The program is being conducted by JoAnn Caudill, RT (BD), CDT. She is a radiology technologist with specific certification in bone-density scanning, education, and teaching in relationship to nutrition, calcium, and vitamin D intake. Screening of residents started on May 1, 2006, as a major percentage of women have some degree of osteoporosis.

Our retirement community for many years has had numerous programs on the prevention of falls because the most common type of emergency call from residents is as the result of a fall. The Viva program tests our physical, mental, and emotional status on an annual basis, and includes the use of a simple wrist device to measure bone density, with a comparison to age and sex normal values.

Dr. M. F. Holick, a professor of medicine at Boston University School of Medicine, is the leading expert on vitamin D in the United States. He maintains that there is an epidemic of vitamin D deficiency in America for both children and adults, primarily due to the lack of sensible sun exposure and the lack of daily ingestion of 1,000 IU of cholecalciferol, the precursor form of vitamin D. Normal functioning kidneys convert it to calcitriol, the physiologically active form of vitamin D (41). This lack of vitamin D intake results in poor mineralization of the collagen matrix in young children's bones, leading in extreme cases to growth retardation and deformities known as rickets. In adults, vitamin D deficiency induces secondary hyperparathyroidism, which causes a loss of bone matrix and minerals, increasing the risk of falls and often resulting in broken hips. Growing scientific evidence strongly associates vitamin D deficiency with an increased risk of type 1 diabetes, rheumatoid arthritis, hypertension, cardiovascular disease, and some forms of cancer in which increases in serum calcium are observed. Experimental autoimmune encephalomyelitis (EAE), a widely

accepted model of human multiple sclerosis (MS), suggests active vitamin D3 (calcitriol) or its precursor analogs may have therapeutic potential (42).

Extreme Obesity in Teenagers

The Health Report on one of our local TV news channels on August 18, 2005, described a special high school in California that extremely obese teenagers can attend; otherwise they face death from heart disease before the age of 35. One innovative man with foundation financial support operates a “live on the campus” high school that obese teenagers can attend for a minimum of three months with a very demanding 24-hour-per-day regimen of activities. The film showed the student body out running a foot race, with the least fit struggling to keep up. However, this man’s innovative and demanding program is claimed to achieve its goals, usually in three months.

Adult Obesity

According to a report by the Trust for America’s Health of Washington, DC, a nonprofit, nonpartisan health advocacy organization, almost 25 million adults in America are obese and have an increased risk of developing a wide range of diseases, including high blood pressure and diabetes. Obesity is generally defined as being 20% or more above average weight for one’s height and age. We are bombarded daily with ads on weight loss diets, the benefit of exercise and health clubs, and the need for participation in sports ranging from ping pong to golf. Most recently, most of the fast food chains have recognized the need for less fat and for low carbohydrates (carbs) in our diets. In the recent past, changes have taken place in the Department of Agriculture’s daily food chart recommendations and, as of January 1, 2006, all processed food labels were required to cite their trans-fat content. Many food manufacturers have reduced the sodium, total fat, and, in particular, trans-fats (linked to increased heart disease) in their products as a result of the new label requirements, so it pays for consumers to read the labels before purchases are made. Food activists are now pushing for the labeling of food in restaurants, which is not a new concept.

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Health Economics and the Future of Healthcare

There have been many drastic changes in healthcare delivery and compensation since 1900. A recent *Baltimore Sun* article featured Dr. Wilson, *Medicine Woman* (1). Dr. Emily Hammond Wilson, who turned 100 in July 2004, graduated with a medical degree in Georgia in the late 1920's and after further training at Johns Hopkins, served as a young country doctor in Anne Arundel County (1). She administered to blacks and whites alike and, in lieu of scarce cash, received various items in payment including oysters, turkeys, homemade bourbon, which she still enjoys, or a day's work in return. The typical cost for an office visit at that time was \$1.50–\$2.00. In a 1904 family memoir, Mrs. Frances Sidwell Benson, who died recently at 106, recounted that as a young girl, in about 1910, she used to ride with her physician father 16 miles to Frederick, Maryland, to procure quinine and opium, the two most popular drugs of the day (2).

A book, *From Mutual Aid to the Welfare Society: Fraternal Societies and Social Societies, 1890–1967* was recently published, that details the major role organizations such as the Free Masons, Odd Fellows, and early associations and unions played in supporting their members with money in times of health emergencies (3). In 1917, when my father was a conductor on the Rochester, Syracuse and Eastern Trolley System, he received mutual aid funds from the Brotherhood of Railway Employees after being unable to work following surgery for tuberculosis of the left parotid (salivary) glands.

A hospital bill from St. Agnes Hospital, dated May 28, 1943, shows a week of hospital care cost \$24.50 and an x-ray was \$3.50 for a total cost of \$28.00. In 1965, a hospital stay was typically \$41 per day and total healthcare spending amounted to 6% of the U.S. Gross National Product (GNP). In 1976, my 12-year-old sister was hospitalized with a damaged heart from rheumatic fever. The total hospital bill for her hospitalization from late December 1975 in Genesee Hospital in Rochester, New York, until her transfer to Rochester General Hospital for surgery in March 1976 was \$14,000. The Rochester General Hospital bill for the open heart surgical stay and care for a commissurotomy was \$8,000, plus a surgeon's fee of \$1,818 and an anesthesiologist's fee of \$326. All of the expenses, except for \$1,065, were paid by Blue Cross/Blue Shield and most of the latter cost was for a private room at the Rochester General Hospital (4). Today, the typical surgeon's fee for a commissurotomy is \$6,911 and the hospital bill is

\$8,420 at a community hospital, which means the surgeon's fee has increased fourfold, but the hospital fee under DRGs in a Midwestern community hospital has decreased 5.2% due to reduction of the hospital stay from 3 weeks to 3–5 days (5). However, hospital reimbursements in the State of Maryland are controlled by the Maryland Hospital Commission, which permits teaching hospitals, such as the University of Maryland, to charge \$39,000 for the total services provided with only a 6% discount for Medicare patients (6). The surgeon's fee is separate and ranges from \$7,000 to \$9,000.

The many changes in the financing, the delivery (by whom and how), and the delivery sites of healthcare to Americans over the past 20 years were all predicted in the early 1980's. It was my privilege in May 1985 to attend, at Hahnemann University, a five-hour teleconference on "Tomorrow's Healthcare Marketplace: Predictions, Trends, Realities" by Symposiums International (7). The teleconference presented the views of the top national leaders in the healthcare field as well as those of 12 professional, medical, hospital, financial, and think-tank organizations involved in healthcare, and included a senator and a congressman with credentials and experience in healthcare. These astute leaders predicted, in 1985, all of the changes that have taken place in healthcare over the past 20 years, including the effects of new technology, the emergence of HMO's, changes in healthcare funding, such as our current problems with Medicare, and the shifting of care delivery from hospitals to ambulatory care. These changes resulted in a corresponding decrease in hospitals, with fewer large well-managed hospitals predominating and an increased percentage of GNP that would be spent on healthcare. All of this transpired because, as Americans, we want and demand the best healthcare in the world, and the goal of the teleconference was to help institutions like Hahnemann University better prepare for the future.

In 1983, there were approximately 8,000 hospitals and hospital costs averaged \$274 per day and totaled 42% of health costs, which were 10.8% of GNP (8). By 1989, the number of hospitals had shrunk to 6,800, hospital costs averaged \$580 per day, and total healthcare spending was 11.5% of GNP. Costs grew at a very rapid rate during the 1990's and by 2000, the number of hospitals had decreased from about 8,000 to 4,100–5,000 (the number varies with different sources) with the daily hospital cost more than doubling to \$1,380 per day and

overall healthcare increasing to 15% of GNP (8). The principle factor driving up costs is the aging population of America with the elderly living into their 80's and 90's and needing much healthcare during the last year of their lives when 50% of all Medicare costs arise. Several sources have reported recently that the fastest growing population in the United States is the population over 80.

In 1965, overall healthcare costs including both hospital and professional payments were 6.0% of GNP, but by 1980, healthcare costs had escalated to \$286.6 billion and 9.8% of GNP. In the 1980's, healthcare costs increased a modest 1.9% per year between 1983 and 1989 but at 3.5% per year between 1989 and 2000 to reach 15% of GNP. In 2002, health spending rose a whopping 9.3% to \$1.6 trillion, the fourth consecutive year in which healthcare spending expanded faster than the economy, which grew at a rate of only 3.6% (9). Hospital expenditures alone jumped 9.5% to \$486.5 billion or almost one-third of the total gain with much of it due to increased labor costs. For the first time since 1991, the government reported that the growth in hospital costs had exceeded growth in overall spending, partially due to hospital chains such as HCA Inc. (Hospital Corporation of America) winning higher payments from insurers. In a newspaper report, Katherine Levit of the U.S. Centers for Medicare and Medicaid Services stated, "Continued acceleration of health spending—without a similar increase in economic growth—threatens the affordability and generosity of sponsored (company) health-care benefits—and everyone from businesses, to government, to consumers—is affected" (9). How did we get ourselves into such a huge and difficult problem?

Although the complexity of healthcare costs is almost overwhelming, I have found one of the nation's foremost economists, Professor Uwe Reinhardt, PhD, at Princeton University, to have presented a simple explanation (10). Dr. Reinhardt grew up very poor in Germany and then, at age 19, his family moved to Canada; in 1964, he came to the United States to study economics at Yale. He is a proponent of universal healthcare financed primarily through taxation. In his words, "I grew up in countries where healthcare was treated as a social good, where the rich paid significantly more than their health-care costs to subsidize the poor," he says. "I found that a civilized environment." Dr. Reinhardt says the biggest misconception in American medicine is that someone else, namely the employer, is paying their health bill when in reality it is the employee, as there are only three ways a pot of money can be created to pay for healthcare and all come out of households.

First the government can tax us and put it in the pot as illustrated by Medicare for the elderly. Secondly, we can be mandated to buy health insurance and subsidize the poor. Thirdly, business is the pumping station by having employers take it out of our paychecks and put it in the pot. Dr. Reinhardt proceeds to point out that most European countries take X percent of the payroll and, therefore, there is little cheating as occurs with income taxes in the United States and the government quickly and efficiently gets the money to run the health-care system (10). This system is not utopia, as neighboring Canada does not take in sufficient money to meet their health

needs and although price-fixing leads to cheap prescription drugs, people wait for years for some elective surgeries.

Americans today believe that healthcare is a right, not a privilege, and everyone wants the best of care. Unfortunately, although need is infinite, resources are limited and our aging elderly are placing a major strain on the Medicare system by living much longer due to the better healthcare they are receiving. The situation is going to become worse in the future. A recently published report states that Americans turning 65 this year will live, on the average, to 83 years of age (11). Additionally, there are 40–45 million mostly working people and families in the United States making under \$50,000 per year who cannot afford health insurance coverage and there are both young and old citizens who do not have any health coverage, with the number increasing each year (12). Although some with family incomes under fixed limits receive Medicaid, many others including both working poor families and the homeless routinely visit hospital emergency rooms, where they cannot be denied care, and receive very expensive medical care.

About 1980, healthcare economists at Yale University classified all medical and surgical diagnoses into one of 468 categories called Diagnostic Related Groups (DRGs). In 1983, Congress adopted a prospective plan payment for all hospitals, except those privately owned, based on DRGs and paid a fixed price per case based on a single patient diagnosis even when there was more than one on any given admission, for example, an obese diabetic patient having an acute myocardial infarction (heart attack). Early on, this policy led to some abuse and poor medical care by hospital administrations encouraging the discharge of patients and requesting their physicians to readmit them 24 or 48 hours later for treatment of the second diagnosis. However, in the case of patients receiving Medicare or Medicaid, government officials soon caught on and forced hospital administrators to settle for payment of the higher cost DRG. Because there are only a few privately funded or proprietary hospitals in the United States that do not accept some federal funding, this policy affected practically all hospitals. Although DRG's were phased in over a four-year period, the new payment system completely altered the economics of the healthcare system in the United States because there are so many sick elderly people. DRGs forced hospitals to become more efficient and lean and shortened the treatment of all disease entities, even in the case of patients with multiple clinical problems. While many institutions contracted with pathologist-owned and directed laboratory services, others contracted with commercial laboratories to provide complete laboratory services as a package. However, our response at Hahnemann University was the reverse, and we took over the clinical laboratory operation from SmithKline Laboratories at a saving of \$3,000,000 per year (13).

In 1993, three years after I retired, Hahnemann merged with the Medical College of Pennsylvania (MCP) (formerly Women's Medical College), which was part of a major consolidation by the Allegheny Health, Education, and Research Foundation (AHERF), a Pittsburgh-based healthcare company headed by Sherif S. Abdelhak (14). AHERF owned Allegheny General Hospital and several other health facilities, which in

1996 became Allegheny University of the Health Sciences. The newly amalgamated complex, described by the head of Hahnemann's board of trustees as "a system of academic medicine," had assets of \$1.5 billion and encompassed six hospitals, two psychiatric facilities, a research center, and a combined medical school second in size only to the University of Illinois (14, p. 270). Owing to Mr. Abdelhak's mismanagement, the Allegheny University of the Health Sciences went into bankruptcy about 1999. However, MCPHahnemann University School of Medicine with over 150 years of historical survival merged with Drexel University, which has a large Bioengineering Department and fit with Hahnemann's Clinical Staff and Facilities. Recent correspondence, which I received as an Emeritus Professor, has referred to it as Drexel University School of Medicine "in the Tradition of the Medical College of Pennsylvania and Hahnemann Medical College."

On August 4, 1998, Regina Herzlinger, PhD, Nancy R. McPherson Professor of Business at Harvard University Business School, gave the keynote address at the 50th anniversary meeting of the AACCC held in Chicago, Illinois. She is the author of *Market-Driven Healthcare: Who Wins, Who Loses in the Transformation of America's Largest Industry*, published in 1997 (15). Daniel H. Johnson, Jr., MD, President of the American Medical Association at the time stated "Based on remarkable insight into the problems of the healthcare system, *Market-Driven Health Care* can show us how to transform our system into a more cost-effective one by putting the patient in the driver's seat with the doctor riding gunshot."

In the mid-1990's, Dr. Herzlinger recognized the business revolution that has given rise to extraordinary service providers such as UPS, Southwest Airlines, McDonald's, and Federal Express, and that the largest service industry, healthcare, was undergoing the same forces with informed and assertive consumers, powerful new technologies, and ferociously competitive markets that would have winners and losers. She recognized that medicine could not be practiced out of a cookbook and that diagnosis and therapy must meet the unique needs of each individual but there had to be more focused systems, such as Health Maintenance Organizations (HMO's) that could deliver it uniformly in volume with high quality, cost effectiveness, and timeliness. However, the medical care of individual patients, each of whom is unique in not only his or her disease but includes their psychological and social makeups and attitudes as well as treatment options, does not lend itself easily to a production line operation. Under an HMO, physicians often take care of a patient's immediate need only and insist on a return visit with another payment to look at a second problem. Even under employer-based plans and Blue Cross/Blue Shield and similar plans, the relationship between physicians and their patients is under some strain. Some of this is because good physicians are often overworked and because the relationship is buried under insurance paperwork as providers demand full documentation of entitlement to the services provided. This is especially true of Medicaid (state-supported aid for the poor) and Medicare, which covers all patients over age 65 who are entitled to Social Security benefits. Medicare pays for the home care of housebound diabetics by nurse practitioners and it is well-established

that diabetics whose blood glucose is kept under control with monitors and supplies, paid for by the government, never develop kidney damage and end-stage renal disease. This approach provides better medical care and saves the government money in the long run. Women have long been able to have a gynecologist and a family physician for their other medical needs and problems. They now recommend annual physical examinations and authorize annual mammography, so breast cancer may be identified and treated early on. For men, they now pay for an annual PSA (prostate-specific antigen test) and a physical examination to detect or follow prostate cancer.

However, more and more newly graduated physicians are opting for medical specialties with less demanding schedules than Family Medicine (pediatric and adult medicine) and Internal Medicine, such as radiology and pathology, and those paying the most money after the shortest period of training (16). Therefore, fewer new residents enter surgery, which requires a long arduous seven-year training period and perhaps a two-year fellowship in a surgical subspecialty. Some clinicians with large practices are also cutting out certain poor-paying insurers and restructuring their practices to see fewer and better-paying patients. Some institutions including Johns Hopkins, the Cleveland Clinic, and Stanford University Medical Center, among others, provide Boutique Health Services to the wealthy for a fee of \$2,000 for 2- to 3-day executive physicals (17). In addition, Pinnacle Care International, a Baltimore company, reports rapid growth in the area of health advocacy. Pinnacle advises families on doctors and hospitals that are likely to give them the best medical care, arranges appointments, fills out paper work, and sometimes even accompanies patients. This service is not cheap; the lowest or 'silver' level of membership carries a \$10,000 initiation fee and an annual charge of \$5,000. Although Pinnacle caters to the extremely wealthy, the idea is not new and there have been boutique physicians for several years in San Francisco, Los Angeles, Boston, New York, and other big cities where fees seem to be as low as \$5,000 per year for a physician's services. Older physicians feel the pressures the most because they recall the days when medical practice was less frantic and hectic.

Medical school applications in 2003–2004 were about 33,000, more than 14,000 below 1996's peak of 47,000, but most applicants apply to at least three institutions. As of 2003, when 50.8% of applicants were women, there were more women than men in medical schools and many expect to work part-time and combine a career with marriage and a family (16). In areas such as Boston, New York, and California, where the cost of living is high, there are shortages of primary-care physicians, cardiologists, pediatric neurologists (a subspecialty of pediatrics requiring an additional two-year fellowship), and some surgical specialists, such as obstetricians and gynecologists where the malpractice insurance costs are extremely high. Even our state government in Maryland for the past three years has had to hold down excessive increases in malpractice rates. Hardest hit have been the obstetricians with increases to \$100,000 per year for malpractice insurance coverage in Maryland and many northern states. As a result, some obstetricians have fled northern states including New York,

Pennsylvania, and Maryland to set up practice in southern states having lower malpractice rates. Lyric Wallwork Winik wrote an article entitled Intelligence Report: Doctor Dilemma (17). She states that medical school applications have fallen 30% since 1996 because of “the high cost of tuition and other factors” and cites a shortage of cardiologists and neurosurgeons. As a result of these and other physician shortages, 57% of hospital directors say they have had to divert patients to other hospitals (17). Washington, DC, will be the last to feel the crisis because it has the most physicians, 718 per 100,000 residents.

It is well-known that visits to most hospital emergency rooms (ERs) require four- or five-hour waits and most people avoid such visits until the acuteness of the illness demands it. This situation has come about for a variety of reasons including staffing problems due to a shortage of nurses and ER physicians; excessive demand and usage arising as a result of misuse by the poor, uninsured, and homeless who know that they cannot be refused care; and inefficiencies and long waits for x-rays for fractures, etc., for which a radiologist must be called in to interpret the x-ray. Falls, especially by the elderly, are commonplace, which increases the waiting time at most hospital emergency rooms. Nurses and ER physicians frequently “burn out” after a few years and switch to other areas of healthcare or if older, retire. Most hospitals have adopted paperless record systems, that is, sophisticated computer systems, to meet the problem but some tests such as histological (microscopic) examination of tissues by a pathologist must be retained, as well as paraffin blocks of the tissue. Other clinical laboratory tests such as troponin must be performed on emergency patients to rule in or out a myocardial infarction (MI; an acute heart attack). CBC’s (complete blood counts) are necessary for patients with possible appendicitis who usually have an increased WBC (white blood count) or a hematological disorder or are on anticoagulants such as prothrombin. Last month’s issue of my professional organization’s *Clinical Laboratory News*, a free monthly publication supported by its advertisers, contained an article on how to organize the laboratory-testing services required in an emergency room. I was chairman of a committee that addressed the problem 25 years ago and published a manual of guidelines (18).

In 2004, matching program graduates of U.S. medical schools filled 97% of the five-year dermatology training programs, which now include surgical training for the removal of melanomas (malignant skin lesions), but only 41% of the family medicine positions matched (19). There were 2.5 applicants for every family medicine position open, but 14 for every radiology position, which offers regular hours. Owing to the extreme shortage of cardiologists, the American College of Cardiologists is considering reducing the training from six years to five years and cutting out the surgical interventional procedures that aren’t done by all cardiologists. On the other hand, radiology has expanded to include interventional radiologists who use imaging equipment to expertly excise (surgically remove) benign tumors of the uterus without removing it—that is, no hysterectomy (20). The *Journal of the American Medical Association* (JAMA) reported in

2004 that most physicians are still satisfied with their jobs but they reported major unhappiness with the administrative aspects and paper work.

Nurse practitioners, nurse anesthetists, dentists, optometrists, chiropractors, and others have become first-line health practitioners. In addition to four allotropic (conventional) medical schools in Philadelphia, there is a College of Osteopathic Medicine, and Pennsylvania has a number of osteopathic physicians (DO’s) and hospitals, which are generally considered equivalent to other hospitals. Jim Conroy, DO, was a full Professor of Hematology and Oncology and a colleague at Hahnemann who directed our resident training program in Hematology and the Hematology and Coagulation Laboratories. We accepted residents in Pathology, who were DOs, the same as MDs. I asked Roberta Reed, DO, one of our pathology residents, about the situation and she replied that once they left the system for allopathic training, they were not wanted back.

Our Charlestown Medical Center has a podiatrist (foot doctor) who covers our needs as well as those of our two sister communities in Maryland (Oak Crest, northeast of Baltimore City, and Riderwood in Silver Spring, Maryland). While I was at Hahnemann in Philadelphia, I used to give two guest lectures on Clinical Laboratory Testing at the Philadelphia College of Podiatry. Podiatrists also do foot surgery, and the eminent and distinguished William H. “Bill” Sunderman Sr., MD, PhD, had his hammer toe operated on at the Podiatry College.

One of the most controversial areas in allied health professionals is the PhD psychologist who many MD psychiatrists feel is not qualified to treat depression with medications. The federal government found PhD psychologists were trained to provide patients with safe pharmacological care in a six-year demonstration program in the 1990’s in the Department of Defense System. Thus, the underlying issue is not one of drug safety but “politics and an economic issue.” Although medical licensing of PhD psychologists differs in the various states and is in a state of flux, both Maryland and Pennsylvania license qualified psychologists. Master’s degree social workers in Maryland are licensed, but must work nominally under the supervision of a licensed MD psychiatrist.

Many states, including Maryland, license nurse anesthetists and 65% of all anesthesia nationwide is provided by experienced nurse anesthetists. However, Maryland permits a board-certified anesthesiologist to supervise a maximum of four nurse-anesthetists and requires an anesthesiologist to be on duty. Nevertheless, the fight is still being waged in some states. In many states, pharmacists, who now earn Doctor of Clinical Pharmacy degrees after six years, can write prescriptions and work on hospital wards. Because the average hospitalized patient is on 10–12 medications, the clinical pharmacist on the ward looks for drug interactions, which are detrimental to the patient’s welfare, that physicians may not be aware of. There is also a need for such services being provided to homebound patients, as it is a serious problem for the fragile elderly who are often on multiple (10–12) medications with different times for their administration. In theory, their local pharmacist should assist them, but most pharmacists are too busy to have the time.

Our campus pharmacy provides a daily drug delivery service for the elderly needing it, which is fairly costly, with the pills or capsules in individual compartments designating the time each is to be taken, that is, on arising, with breakfast or lunch, etc.

Our retirement community has six full-time internist-geriatricists who are very knowledgeable about medical problems and provide service of 30 minutes per patient on an appointment basis, as well as two nurse practitioners who see patients on a call-in-that-morning basis. A physician is on call around the clock when our Medical Center is not open and the GE Eccentricity Computer System gives any of our staff physicians access to our individual patient records at any time whether in the office, at the hospital, or at home at 1 am on Saturday morning. When a drug was recalled last summer, they were able to identify every patient in our retirement community who was on the drug within a couple of hours. In his 2005 State of the Union address, President Bush called for doctors and hospitals to make better use of technology to store and share medical records. In a subsequent memo, the White House said that computerization is necessary because clinical information about patients is often scattered and unavailable in emergencies. The 15 Erickson Retirement Communities, spread over the United States, are ahead of the curve in that they have computerized patient records.

In 1960's, shortages of physicians increased the role of nurse practitioners. The legislation in 1973 defining managed care organizations and the rising healthcare costs of the 1990's stimulated the availability of nurse practitioners in the hamlets and rural communities where physicians are often not available. The expanded role nurse practitioners play has been accompanied by changes in state nursing laws as needed. Target Stores in Maryland now offer on-site available nurse practitioners within a 20-minute wait-period to care for minor illnesses and answer patient questions. Whereas a child might have to wait a week to see his or her family physician or pediatrician about a sore throat or another minor problem, a nurse practitioner can diagnose the problem and order a prescription with the Target Pharmacy filling it while the parents and family are shopping. People are willing to pay for the service out of pocket, when necessary, as it provides convenience and often neither working parent has to take time off as the service is available during all store hours. Some physicians in some states practice in local shopping centers and are known as "docs in a box," but not all health insurance will pay for such coverage.

Nurse practitioners with a master's degree practice in rural mountain hamlets in the Appalachian Mountains and take on everything from minor surgery to emergency room crises. Even in high-tech hospitals, nurse practitioners have come to play an increasing role, led by pioneer shock trauma cardiac surgeon, Dr. R. Adam Cowley at the University of Maryland, who founded the first of over 800 Shock and Trauma Centers around the world in 1968 and treated his skilled nurse associates as equals on the shock-trauma team (21). Dr. Cowley demanded that new young interns and residents, assigned to Shock Trauma, treat his skilled shock trauma nurses as equals or he literally threw them out.

Many of America's more than 2,000,000 nurses are taking on tasks that were once the purview of physicians. These include administering chemotherapy and, as licensed nurse practitioners, some are setting up their own primary care practices. By 2015, the goal of the American Association of Colleges of Nursing is to have nurses, including nurse practitioners, clinical nurse specialists, nurse midwives, and nurse anesthetists, hold a doctorate of nursing. On the other hand, while the state of Maryland currently has a shortage of nurse educators, Congress has authorized \$248,000 in funding to help the University of Maryland School of Nursing create an Institute for Nurse Educators as a pilot program. A November 8, 2005, press release from the University of Maryland School of Nursing in Baltimore was entitled "US Shortage of Nurses Expected to Hit One Million by 2015" (22). On November 15, 2005, the University of Maryland School of Nursing hosted national award-winning journalist, Suzanne Gordon, for a lecture as part of their celebration of the opening of the School of Nursing's Center of Excellence in Occupational and Environmental Health and Justice (OEJH). Ms. Gordon spoke about the tremendous challenge of retaining and recruiting nurses. She offered innovative and often controversial suggestions on how to alleviate the crisis. Currently, the hospitals across the nation are dangerously short of experienced nurses. The federally funded University of Maryland Center for Health Workforce Development projects a shortage of nearly 13,000 nurses by 2010 in Maryland and a shortage of one million nurses nationally by the year 2015.

Recent research by the Center of Occupational Health and Justice shows that many nurses are frequently forced into a series of 12-hour plus days and nights. In addition, they face roaming shifts, combined with constantly being on call, and high patient loads without adequate time for rest and recovery. Their data show that the end result is a "direct impact on patient complications and patient mortality." Thus, even hospital nurses work in a high stress environment such that 46% of hospital nurses are dissatisfied with their jobs and 22% plan to leave in less than one year. Not surprisingly, this figure is 33% for nurses under 30 years of age who may have received their training more recently and may be newly married or have young children. Although nurses have an enormous amount of responsibility in a hospital setting, some physicians are disrespectful of nurses but control the decision-making process. This situation greatly increases the stress on nurses and impacts heavily on their job satisfaction and morale. Research at the Center has shown that this stress can result in nurses having mental and physical problems including back injuries and heart disease. Ms. Gordon believes that nurses have been unfairly pictured by the media and that whether you live or die in the hospital can be determined by the quality of nursing care you receive; as she says, "they control 90% of the decisions that effect patient care." An additional factor affecting the stress on nurses and patients is the hustle, bustle, and noise in most hospitals as it inflicts pain on the well in addition to the sick. There is nothing new in this observation as Florence Nightingale wrote in her 1859 Notes on Nursing, "Unnecessary noise is the most cruel abuse of care which can be inflicted on either the sick or the well."

Louise Parsons, who founded the University of Maryland School of Nursing in 1889, was a trainee of Florence Nightingale and became the first dean of nursing. Today, the University of Maryland School of Nursing is one of the leading research institutions in the United States, ranks among the top ten nursing schools in the United States, and enrolls over 1,400 students in its baccalaureate, master's, doctoral, and continuing education programs. However, recent medical advances and scientific discoveries have led to an ever-finer carving of medical disciplines into specialties and subspecialties. Recent literature has pointed out the same change but emphasized the new overlapping of medical specialties, which one writer called "The Shifting Sands of Medical Care" (20). It cites dermatologists doing plastic surgery, psychiatrists prescribing drugs, and a radiologist who, after finding a uterine tumor, excised three-quarters of it using his high-tech imaging equipment, leaving only dead cells. Thus, this lady avoided major surgery.

A recent publication by Eleanor D. Kinney, JD/MPH, Professor of Law at the Indiana University School of Law, is entitled "Would a Single Payer System Provide Universal Health Coverage in the United States?" (23). Dr. Kinney states that few policy issues have been studied as extensively or so long as lack of universal health coverage in the United States. Over 110 organized academic centers and foundations are devoted to the problem and it is a top concern of many Americans. The U.S. Census Bureau reported in 2002 that the number of U.S. residents without health insurance increased by 2.4 million or 5.8% to 43.6 million and that at least 15.2% of the population is uninsured at any point in time with more and more companies dropping coverage as healthcare insurance costs rise. In most proposals these days, the federal government would pay for the health of all Americans and probably the most practical strategy would be to increase Medicare. However, currently Medicare is in danger because the population over 80 is the fastest growing population in the United States and the Medicare and Social Security systems are already under severe stress. Hence, as a practical matter, it would be impossible for Congress to pass universal healthcare coverage in the foreseeable future.

The state of Maryland Health Services Cost Commission recently reversed a three-year trend in the major increasing of annual costs in hospital rates. Its proposal of January 11, 2006, allows increases of slightly more than 5% for the next three years (24). It would raise hospital rates in Maryland about half a percentage point a year below the projected national trend.

In 2004, Congress passed the biggest change in Medicare in 40 years when it enacted legislation leading to prescription drug coverage for all elderly Americans effective January 1, 2006. Coverage is offered through private insurance plans that negotiate with drug companies to set prices. The plans vary widely in cost and are very complicated. In general, a monthly fee is charged, with an annual deductible of \$250. Various copays are assessed based on the formulary and the category of drugs and the use of preferred or non-preferred pharmacies. This subsidization continues until one reaches \$2,250. Then one pays 100% of drug payments until \$5,100 is reached; this

is the so-called "doughnut hole." After \$5,100 an individual pays just 5% of drug costs.

Each individual makes a decision on which Medicare D Prescription Drug Plan to enroll in based mostly on the drugs they routinely use, their prices, and the convenience of the pharmacies in the plan in their section of the country. One can change plans once a year in November, if deemed necessary, but one had to enroll by May 15, 2006, for participation in calendar year 2006.

Individuals with good prescription coverage through their present federal, state, or employee pension plans do not need to sign up. Assistance is available to those who meet limited income requirements, such as those eligible for Medicaid. As the plan has gotten underway, there have been many major glitches, especially for low income individuals who have needed immediate refills but have not received proper new identification cards. On Saturday, January 14, 2006, President Bush issued an executive order requiring that insurers must provide a 30-day supply of any drug that a beneficiary was taking and could not charge more than \$5 for a covered prescription.

The theory of this program is that people who have no drug coverage will now get some relief, but only time will tell. Individuals will have to weigh the monthly payment against any savings. Because of their fixed reimbursements, nursing homes have been very concerned about how the drug plan will affect them (25). Medicaid for low-income families varies from state to state as do the prescription plans offered. As predicted, there are many flaws in the Medicare Prescription Drug Plan, particularly as it relates to Medicaid and the poor. Also, there are still many people who cannot afford to buy healthcare insurance; many employers have cut back on benefits or have increased deductibles or increased the employee's share of the cost within pensions. The domestic auto industry, especially General Motors (GM) and Ford, are in major financial trouble as a result of agreeing to unreasonable union demands, including paid-up pensions and healthcare for many years in order to prevent major strikes and shutdowns. It remains to be seen how GM and Ford are going to solve the immediate financial crises they are facing, but the result may be cuts in their healthcare coverage.

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Chapter 12

Quality of Healthcare and Bioethics

“Survey Gives U.S. Health Care System Poor Grade” screams the headline reporting that one-third of United States patients with health problems reported experiencing medical mistakes, medication errors, or laboratory results that were inaccurate or delayed. This new international health policy survey was reported in late 2005 by the Commonwealth Fund (1). The recently completed survey of health delivery in the six highly industrialized nations of Australia, Canada, Germany, New Zealand, United Kingdom, and the United States is the eighth in a series of cross-national surveys of medical care systems. The survey interviewed adults, from each of the six nations, who had been recently hospitalized or had surgery or other health problems, and assessed their views.

Patients in all countries reported safety risks, poor care coordination, and inadequate chronic care treatment, but the United States singularly stood out for high error rates, inefficient coordination of care, and high out-of-pocket costs that led people to go without healthcare. Some 34% of U.S. patients said they had experienced at least one of the four types of errors, that is, mistakes in medical treatment, incorrect medication or improper dosage, and inaccurate or delayed laboratory results. Thirty percent of Canadians reported experiencing such errors, as did roughly 20% of patients in the other nations surveyed. Some 61–83% of patients in each country said healthcare workers did not tell them about the mistakes.

At least 19–26% of patients in all six countries reported communication gaps between themselves and hospital staff and over 16% said they would have liked greater involvement in decisions made about their medical care. One-third of American respondents said that either test results or records were not available at the time of appointments or physicians duplicated tests, which was the highest among all the nations reporting.

As discovered in past surveys, our American healthcare system continues to place undue financial burdens on patients, particularly when compared with other countries. Just slightly over half of adult Americans with health problems said they did not visit a doctor when sick or fill a prescription due to cost concerns. Additionally, one-third of American patients spent more than \$1,000 out-of-pocket for medical bills in the past year. In contrast, 65% of United Kingdom adults reported zero out-of-pocket medical costs. However, it is a known fact that British and Canadian subjects wait years to get elective surgeries under governmental health plans.

Since about 1981, the FDA has required all settings trying out new experimental drugs on normal or diseased patients to have a Bioethics Committee that sets institutional goals and an Institutional Review Board (IRB) that reviews all experimental drugs (new drugs not approved by FDA) being administered to normal or diseased patients. As a clinical laboratory scientist and emeritus professor unaffiliated with the St. Agnes Health Care System, it has been my privilege to be a member of their IRB committee for nearly five years, which meets monthly. Hospitals such as St. Agnes have one board, while large medical institutions have a number of boards or committees; Johns Hopkins University has 18 IRB committees.

Although such committees operate under very stringent codes of conduct, two of the most distinguished medical institutions in the United States have had code violations in the past six years, which have led to fatalities. With the race on for gene therapy, researchers at the University of Pennsylvania in Philadelphia participated in experimentation on Jesse Gelsinger, an 18-year-old with ornithine carbamyl transferase (OTC) deficiency in June 2000.

He was the first person to die in human experimentation, which was the direct result of inappropriate experimental gene therapy treatment (2). In June 2001, Ellen Roche, a 24-year-old technician at Johns Hopkins Asthma and Allergy Center and a healthy volunteer in a study at Johns Hopkins Medicine, funded by the National Institutes of Health, died on June 2, 2001 (3). Thus, two of the finest medical institutions in the world failed to properly protect volunteer research subjects by deviating from authorized protocols and each lost their approval at the time of the crisis. Neither institution had the ban lifted until each had submitted lengthy documentation respecting their handling of research subjects. Thus, under the best of controlled and defined conditions, two people died needlessly.

The Geisinger case is more complicated because the gene therapy involved an 18-year-old youngster, not yet of legal age. It resulted in many institutions worldwide looking at the ethics involving gene therapy in children, some of which were in effect at the time of the incident. The second report brought out the fact that five well-known institutions in the United States had had their licenses suspended for various periods of time between March 1999 and the Johns Hopkins University fatality in June 2001. Ironically, the first two recorded deaths from

human experimentation occurred in the United States at two of our most prestigious medical institutions.

Our IRB committee at St. Agnes Health Care operates in a very stringent manner, even for NIH Cancer Institute protocols. My contribution is to make sure that proper laboratory testing is carried out to protect patients' livers and kidneys even though they are usually on very powerful chemotherapeutic drugs for some type of cancer. Also, I insist on strict adherence to Roberts Rules of Order as provided for in the FDA Code of Regulations. Another member from outside St. Agnes is a stickler on details in proposals and questions whenever a new drug protocol does not provide for payment for any side harm that may arise incidentally. All of the other members of the committee are board-certified medical specialists or licensed healthcare specialists such as nurses and a pharmacist. Hence, all proposals are being reviewed by several healthcare experts from different perspectives, one of whom is the Quality Assurance Officer of St. Agnes Hospital and two members who have no vested interest in St. Agnes Hospital.

The Health Insurance Portability and Accountability Act took effect April 14, 2003, and is commonly known as the Right to Privacy Act. Basically, it seals all patient records except to health professionals involved in any given patient's healthcare. Many healthcare providers, especially researchers and myself as a member of the IRB committee, feel it is a very restrictive and unfortunate piece of legislation as it makes the work of our committee much more difficult. While our IRB committee operates in strict confidence, we must make sure that detailed paper work for all projects, including those organized by the National Cancer Institute but with participants from St. Agnes Hospital, is in compliance with Privacy Act requirements. These include patients being fully informed of their rights to withdraw at anytime and fully informed as to any possible benefits or hazards in the administration of experimental drugs or therapy in comparison with any standard or commonly accepted therapy.

Because of the Privacy Act some hospitals would not give out any information on how patients were doing or if they were even in their hospital. In June 2005, about 40 elderly residents from Michigan were on an excursion to New York State where they were in a boat that capsized on Lake George and a number of them drowned. Because of the Privacy Act, their relatives in Michigan had a very difficult time finding out who had survived and who had drowned. However, the situation was complicated by the fact that the nearest hospital was about 20 miles away in the next county and the Sheriff's Office in charge of the accident probably had no way of knowing that a "Hospital Directory Information" policy had existed from the early 1990's (4). Releasable information is limited to whether or not they are registered as a patient at the hospital.

Unfortunately, during the past five years, there has been almost daily news about medical errors and mistakes. The Institute for Medicine estimates medical errors lead to the death of at least 98,000 Americans and that millions more are injured each year (5). Sometimes, the patient's family is not even told by hospital authorities as they hope to avoid lawsuits. The author of the AARP Bulletin (5), published monthly by the

American Association for Retired Persons, then asks the question: "But how do you fix a system that's more concerned with innovation than safety?" The authors of a study of medical errors in hospitals found that a handful of common complications ranging from injury to a neonate to postoperative sepsis (infection), the two most expensive categories, kill more than 32,500 Americans every year and it is estimated that these deaths add \$9.3 billion annually to hospital charges (6). Also, over the past five years, there have been many bioethical violations by providers of healthcare, health researchers, medical organizations, the FDA, and even some at the National Institutes of Health (NIH). As a professional, I am appalled by all of these violations, which a high percentage of the time, but not always, are due to greed or carelessness leading to poor decisions and wrongful actions.

I recall very vividly how in the late 1980's, the wrong leg was removed from a diabetic patient at Pennsylvania Hospital because the surgeons mixed up which leg was to be removed. Then, another incident happened shortly afterward making me acutely aware of this type of mistake. The recent mix-ups made me so cognizant of the potential problem that when I had ear surgery at Hahnemann in 1990 by the Chief of Anesthesiology and the Chief of Otolaryngology, whom I knew by their first names, I said as I entered the OR, "Look fellows, it's this ear," as I pointed to it. Subsequently, it became common practice to label the skin surface of patients with black or red ink designating the location to be treated or for surgery. The Joint Commission on Accreditation of Health Care Organizations (JCAHCO) mandated a Universal Patient Protocol, effective July 1, 2004, which requires the operating room (OR) team to take a "Time out" before starting surgery (4). This safety measure requires the OR team to make sure it is the right patient, the right procedure, the right site by marking the area at the time, and, if a device or prosthesis is needed, that it is available. All of this is best carried out with the patient and his or her guardian or next of kin. Of course, most important is to make sure the left or right leg or correct side of the body or spinal region is marked properly.

Of the 30,000,000 operations performed in the United States each year, 2% or 600,000 patients, have their recovery complicated by surgical site infections (SSIs) and are a major contributor to patient injury, mortality and healthcare costs (7). The senior author of the study in the introduction to the study says: "Despite evidence of the effectiveness of antimicrobials to prevent SSIs, previous studies have demonstrated inappropriate timing, selection, and excess duration of administration of antimicrobial prophylaxis. We herein describe the use of antimicrobial prophylaxis for Medicare patients undergoing major surgery" (7, p. 174). Elsewhere, it has been suggested that the best protection for the patient is to insist that every person associated with his or her hospital stay, including physicians and nurses, wash their hands with plenty of soap and water, and put on clean gloves. According to several recent reports, doctors' ties are the greatest source of hospital infections and since surgeons in green OR garb do not wear ties, it would appear that same day surgery may have advantages by reducing the exposure to infectious agents. A recent article in

the American Journal of Medical Quality reports that “it’s the process and not the patients” (8). Dr. David Nash said health professionals should do more to promote hand washing among medical staff, take greater care in donning gowns, and use other infection-prevention measures.

After State of Maryland officials learned of several accidents to hospitalized patients brought to their attention as a result of law suits, the legislature passed a corrective piece of legislation. As of July 1, 2003 Maryland hospitals are required to report all mishaps to the Maryland Patient Safety Center and not just quietly bury them in patient records (4).

LABORATORY ERROR

Patient safety came to the forefront in 1999, after the Institute of Medicine (IOM) published its report, “To Err is Human” (9). Ever since, the reduction of medical errors has become a goal in all areas of healthcare. Michael Astion, MD, PhD, Director of Reference Laboratory Services at the University of Washington in Seattle, says that much needs to be done because it has taken five years to get industry organized. However, the Communicable Disease Center (CDC) led the laboratory industry’s effort to improve patient safety by initiating an Institute for Quality in Laboratory Medicine (IQLM) in 2003 (9, p. 6). They have brought together individuals from industry, government, and healthcare professionals with the aim of improving clinical laboratory testing and services. These are the same three groups the National Committee for Clinical Laboratory Standards (NCCLS) brought together from about 1969 to present. On January 1, 2005, the NCCLS was renamed the Clinical and Laboratory Standards Institute (CLSI) with John Zlockie, MS, a longtime friend and colleague, continuing as its operational officer.

A number of issues related to patient safety were addressed at a two-day conference held at the Communicable Disease Center (CDC) in Atlanta, Georgia, on April 28–30, 2006. Although it is hoped that technological innovations will offer solutions, they have not been developed as yet. As mentioned previously, Steven Kahn, PhD, Director of Clinical Laboratories at Loyola University School of Medicine in Chicago, Illinois, reported in December 2004 at a local meeting of my professional society (AACC) that labeling errors, even in blood bank specimens, are the most serious and prevalent source of laboratory error and cost about \$800 per error. While our physician daughter, an authority on blood banking error, stated that the chances of an error are 1 in 10,000, a death did occur in June 2004 at the Sarasota Hospital in Sarasota, Florida, due to a blood transfusion mixup (10). Unfortunately, bar coding of all lab specimens has not eliminated these errors. Linda Sandhaus, MD, of University Hospital Laboratories in Cleveland, Ohio, says that improving the accuracy of patient identification is one of the 2005 Laboratory Services National Patient Safety Goals established by the Joint Commission on Accreditation of Health Care Organizations (JCAHCO) (9, p. 6). The AACC has recently established a laboratory patient safety group under David Astion, MD, PhD (cited above).

A whistle blower’s revelation in June 2004 that over 400 patients tested for HIV (AIDS) and HCV (herpes virus) at Maryland General Hospital in Baltimore may have received inaccurate and unvalidated results has led to numerous repercussions including a Congressional investigation (11). According to our State Health Department authorities, the deficiencies have been corrected but the College of Pathologists (CAP), a recognized equivalent agency, has had to sharpen up its inspections. In addition, the new joint inspections of the JCAHO and the CAP will focus on continual readiness to improve quality by having unannounced inspections as of January 1, 2006 (11). In 1988, George S. Cembrowski, MD, PhD, and I showed that the results on CAP mailed test specimens in chemistry and hematology involved special practices such as running in duplicate, analysis on more than one instrument, delay of testing on a busy Monday or until an instrument is “working better,” etc. These findings were reported voluntarily by lab supervisors and pathologists in a mail survey we conducted in the Commonwealth of Pennsylvania with the proviso that we would not identify any laboratories (12).

Currently, Quest Laboratories, probably the largest laboratory test provider in the United States, has been found by the Maryland Office of Health Care Quality (MOHCQ) to have flaws in some of their specialized laboratory tests such as thyroid stimulating hormone (TSH) and testosterone (13). Although the state has found that none of the test findings resulted in life-threatening situations, the seriousness of the situation is Quest’s failure to address the three problems that had been brought to their attention over the previous two years. After the government cited it on November 16, 2005, for a fourth violation, Quest Laboratories took action. Their spokesman, Gary Samuels, said they had “ordered retraining for all their 1,400 employees and begun advertising a hotline for patient inquiries (800-532-5932).”

President Bush made information technology (IT) investments in electronic medical records of patient records (EMR) a priority during his second term (14). As of April 2005, about 40% of hospital outpatient laboratories and independent laboratories had established paperless test ordering and reporting systems. Our Charlestown Retirement Community adopted the GE Centricity System for all of our 2,300 residents registered in our healthcare system. Thus our patient records are available to our six full-time clinicians 24 hours a day through a secure password on any web-based computer regardless of their location. Physicians at St. Agnes Hospital, such as my cardiologist, have access only to certain screens. This system has now been extended to our 14 sister communities scattered from here to Colorado. St. Agnes Hospital in Baltimore City is the closest hospital to our retirement community and the one by law where we must go for emergency medical care. It is one of the first 25 hospitals in the United States to be completely computerized; notices in its visitor elevators inform the public of this fact. However, a survey reported in April of last year showed only 40% of hospital outreach and independent laboratories had an internet-based system for getting laboratory results to physicians with about an equal percentage expecting to implement systems in 2005 (14).

HOSPITAL COMPUTERIZATION

Adverse drug reactions (AVRs) may account for as many as 2.2 million hospital events and up to 100,000 deaths a year in the United States and hospitals would like to get a better handle on them (15). Target Pharmacy stores have a current advertisement which states: “We’re turning pharmacy upside down, because 1.3 million medication errors every year doesn’t fly with us.” One way they follow through on this is to use different colored caps on prescriptions for each member of a family. Only about 5–9% of hospitals in the United States have electronic drug-order systems because of the large costs in installing them and teaching staff to use them. As I recall, the new Veterans Administration Hospital, connected by a bridge to University of Maryland Medical Center, had physician drug ordering at the bedside when it opened in 1992. One of the available leading electronic systems that permits computer physician order entry (CPOE) of patients’ prescriptions electronically was evaluated by Dr. Ross Koppel and his colleagues, of the Department of Epidemiology at the University of Pennsylvania in Philadelphia, Pennsylvania (16). Although the earliest computerized drug-order system was found to increase the risk of 22 types of medication errors, many of them were probably due to the use of inexperienced physicians and residents performing the entries. Dr. Brian L. Strom, a coauthor and Vice Dean at University of Pennsylvania said, “All of the problems we found are solvable” (16). I found seven editorials criticizing the report in the following issue of JAMA (Journal of the American Medical Association). This early system, one of the first to be marketed, has since been replaced with an updated version by the Eclips Company.

Dr. Peter J. Pronovost, co-chairman of the Johns Hopkins Hospital patient safety committee, is quoted as saying they were phasing in a CPOE system in spring 2005 (16). Dr. Pronovost believed the failures in the University of Pennsylvania system were due to a combination of software and hardware problems. I spoke on January 23, 2006, with Lori Sokoll, MCC, PhD, who is an assistant director of the Johns Hopkins Clinical Chemistry Laboratory who took her Master of Clinical Chemistry degree with me at Hahnemann in Philadelphia. Lori said that their laboratory at Johns Hopkins has the updated and improved Eclips CPOE system and “it is working quite well.”

NEW DEAN OF PUBLIC HEALTH

Dr. Michael J. Klag, the physician who led the reform of the research practices after the death of Ellen Roche in June 2001 and editor-in-chief of The Johns Hopkins Family Health Book (17), was selected out of a field of more than 100 candidates to be the new dean of the prestigious Bloomsburg School of Public Health (18). William R. Brody, MD, President of Johns Hopkins University, called him “the right leader to lead a new chapter in the history of the world’s oldest, largest and most prominent school of public health” (18). As mentioned in Chapter 8 on Public Health, in 1916, staff from the new Johns Hopkins School of Public Health came to train in the laboratory

aspects of public health at the Division of Laboratories and Research of the New York State Department of Health in Albany, New York, at that time the recognized world leader in laboratory aspects of public health. The balance may have shifted in recent years to the federally funded Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, but the two institutions do not have the same interests and responsibilities. In late 1960’s, when I was with the New York State Department of Health, we trained their new clinical laboratory investigators how to perform clinical laboratory inspections and how to handle chemistry, hematology, and drugs of abuse specimens (urine) for the new interstate program. By necessity, specimens were mailed to laboratories engaged in interstate commerce and those needing licenses as they were scattered over all of the United States.

BIOETHICS

In 1972, I was one of 13 professionals to be appointed to the Diagnostic Products Advisory Committee to the FDA, which had been charged with implementing the new regulations. The regulations provided for the labeling of all clinical laboratory testing kits and reagents with manufacturers having to prove their claims. The committee represented all of the laboratory specialties and included two pathologists representing Blood Banking and Hematology, an MD Professor of Microbiology as the chairman, a consumer advocate and two clinical chemists. A statistician was a consultant to the committee. I had been with the New York State Department of Health for seven years and was named to the committee in Clinical Chemistry (and Toxicology) as we had provided national leadership in proficiency testing. The other clinical chemist was Ronald “Ron” Laessig, PhD, who was Director of Clinical Chemistry for the State of Wisconsin, which had a voluntary testing program. Subsequently, I became chairman of the Subcommittee on Clinical Chemistry and the two clinical pathologists, the statistician, and some others met with us. This committee of about eight was the most difficult I ever chaired for two reasons: first, the early 1970’s followed the college student uprisings of the late 1960’s and people were very outspoken and wanted to be heard. Secondly, it met under “sunshine rules” with most of the vice presidents of the major diagnostic and reagent companies who could not speak except when asked, sitting in chairs around the walls of the conference room. I soon learned that it was impossible to bring about a consensus without first hearing out the members of the subcommittee.

My seven years with the New York State program had taught me that the single biggest source of variation between different laboratories’ results was a marked variation in the purity of the standard or benchmark used for calibration. Recognizing this, Ron Laessig, Alfred “Al” Bracey, MS, from the FDA and I wrote a document on “Calibrators” on our dining room table in Albany, which would have taken care of the problem at the time. Subsequently, this document was thoroughly reviewed by the Subcommittee, unanimously approved by the parent Advisory Committee with recommendations that it

be fully implemented by FDA officials as soon as regulations permitted. While the head of the Division of Diagnostic Products and Devices had a strong background in clinical chemistry and did her best to get action on the document, it wound up on the desk of an Assistant Commissioner where it was never acted on.

One of the other objectives of the FDA was to classify all laboratory tests in clinical chemistry and make one of several levels of judgment up to, "Could a person die if the test result was falsely elevated?" There was a similar list for the Toxicology group to act on, which I participated in also. After all of the tests in both lengthy lists were being classified as, "Yes, a grossly inaccurate result could result in a patient receiving inappropriate treatment and cause death," I got very bored. After four years, the challenge was gone and I realized I was wasting my time in spending two work days a month as a consultant to the FDA. In June 1976, I sent them a letter of resignation politely describing their inaction and what a "do-nothing organization" they were. Nevertheless, I received a personalized gold-colored shingle, signed by the Commissioner of the FDA, thanking me for my service.

In 1970's, numerous problems in the toxicity testing of drugs and foods surfaced as an issue of public safety. From 1975 to 1977, the United States Senate subcommittee on health investigated the problems and found shortcomings in the evaluation of Aldactone, manufactured by Searle (19, p. 116). Their investigation showed that rats given the drug in long-term studies had not been examined microscopically after death, despite the fact some had eye lesions, a direct violation of FDA requirements. Also, the FDA found some problems with the records during tests on the sweetener, aspartame, and on the antimalarial drug Flagyl. Although the FDA contended this showed a pattern of poor record-keeping, the Justice Department felt it was not a sufficiently strong case to prosecute. Other known cases contributed to reform when 618–867 audits showed problems in toxicology testing with the huge Industrial Bio-Test Laboratories (IBT). Subsequently, four IBT managers were found guilty of fraud and, with other incidents, led to Congress passing in 1976 the FDA Good Laboratory Practices Law, which was finalized in Federal Code Rules and Regulations in 1979 (19, p. 116). Also, Good Manufacturing Practices (GMPs) were authorized in 1976 to ensure quality standards for the manufacture of drugs.

In 2002, Congress passed the Medical Device User Fee and Modernization Act, which infused much-needed funding to the FDA so that it could speed up its review of 510(k)s and pre-market approvals (PMAs) of *in vitro* (in test tube) diagnostic tests (lab tests) and medical devices. Also, drug companies pay "user fees" to make up a portion of the FDA's costs for reviewing and approving drugs; it has resulted in paying about half of the salaries of the 1,400 physicians, chemists, pharmacists, and other scientific personnel who work for the FDA. Is it a good plan for the FDA to be funded with "user fees" by the manufacturers of diagnostic kits and medical devices and the drug companies, the very companies whose claims on commercial products they must evaluate for clinical efficacy and safety? While common sense says an emphatic "No," it is the route

America follows because of the tremendous amounts of money needed and our inability to underwrite it with governmental funds from taxes.

Americans are taking more prescription drugs than ever before. It has been said, facetiously, that we have a pill for every problem from birth to the grave. In January 2001, *USA Today* ran a cover story with the title "Take One. You'll Feel Better" (19). Alan Rosenberg found that when his son was little, he suffered from a seizure disorder but every time the boy started a new treatment, "he would improve drastically for a short period of time then he would revert back." He didn't think the treatment itself helped his son's seizures and that, "It was just the mere idea of our hopes and trying something new" (20). Therefore, Rosenberg decided to try a placebo, a sugar pill, and found that it worked. As an entrepreneur, he started a thriving business selling placebos. As the author points out, nobody understands how a placebo works but double-blind studies often show significant improvement in the control patients who receive a placebo, and if it equals the effectiveness of the experimental drug then the latter is a dud.

In 2004, Americans spent more than \$235 billion on brand name prescription drugs, many of which could have been ordered as generic (nonbrand) drugs. A retrospective review in 2005 of major drug studies, published in three prominent medical journals over the previous 15 years, showed that nearly one-third of the reports claiming benefits for the new experimental drugs over existing established drugs did not hold up (21). In other words, the benefits claimed for one-third of new drugs were not true. This is a shocking revelation; as consumers, who are we to trust?

An issue just as important is, how safe is a new drug or device? In June 2004, David Graham, MD, Safety Officer of the FDA, complained of the extreme pressure being put on him by the Commissioner's Office. After being warned that his job was in jeopardy, Dr. Graham blew the whistle on the FDA and spoke publicly of the many studies showing that patients taking Vioxx were twice as likely to suffer a heart attack (21). No doubt the over 20 million people taking the drug agreed with Dr. Graham, who had suspicions about the drug for some time.

Amid rising concerns as early as 2000 that its pain killer drug Vioxx, Merck's most important new drug, posed heart risks, Merck officials overruled their top medical scientists (22). Indeed, the death of a 79-year-old woman from a heart attack, who was otherwise in good health, had brought about a lawsuit. While the mounting evidence showed there were serious concerns with the drug, company records reported to the FDA contradicted the actual findings. Merck's chief medical officer quit in 2002 due to his feeling that the company was being dishonest. However, the drug was not withdrawn from the market until September 30, 2004, after a second study, called Vigor, clearly showed the deaths from heart attacks of eight people who were taking Vioxx. This major disaster, due to greed and a major bioethics violation, has had profound effects on the company's finances and stock value. In June 2003, a company that makes balloon-like devices to treat aneurysms was fined \$92 million for covering up thousands of incidents in which the devices' malfunctioning might have been involved in 12 deaths and 57 surgeries (23). As consumers, we

must rely on the FDA to carry out its charge both for drugs and devices. Outside advisors with expertise often furnish information to the FDA and can make recommendations but may be biased due to vested interests.

Recent years have seen numerous acts of scientific dishonesty, the most flagrant of which is the Korean scientist who fabricated and published information on stem cell lines that never existed. Scientists at the University of Minnesota published an article in the British journal *Nature* last June showing that 33% of scientists had confessed to violating one of ten types of scientific misconduct ranging from not including negative information and plagiarism to outright falsifying data (24).

In December 2003, it was revealed that many of our high-level scientists at the National Institutes of Health (NIH) had accepted millions of dollars in fees and stock options for consulting activities in connection with research on potential drugs and therapies, which sparked Congressional concern (25). Consequently, both the House and Senate launched inquiries into the conflict-of-interest allegations. NIH Director Elias S. Zerhouni, MD, acknowledged to Congress the seriousness of the allegations and the need to conduct a thorough review of the situation. As director, the responsibility was his to take action on the charges if he found they were true. Initially, after such activities were proposed to be banned completely, NIH scientists rose up in anger and protest. However, after six months of review Dr. Zerhouni, the former vice dean for research at Johns Hopkins University, issued a ban requiring only about 200 of the most senior NIH officials to sell stock holdings valued at \$15,000 or more in any biomedical company. However, the ban forbids NIH scientists from accepting consulting fees from drug makers and device manufacturers.

For many years, pharmaceutical companies operated under bioethics that did not permit them to advertise drugs in news ads and on television. A half-hour show on PBS (Public Broadcasting System) on January 25, 2006, featured Daniel Troy, former chief legal counsel for the FDA, and Howard Blumenthal, MD, Professor of Medicine at Harvard Medical School. Drug companies spend \$21 billion a year, of which \$7 billion goes to physicians directly or indirectly in the form of drug samples, literature to physicians on new drug products, gifts up to \$100 in value, and both company-sponsored and independent medical education. Is this completely ethical? Does self-regulation of physicians work?

There are many health industry practices that create conflicts of interest and the current influence of market incentives in the United States is posing extreme challenges to the medical profession. In January 2006, the leaders of 11 major academic medical centers in the United States called for reforms that would ban some common practices, regulate others, and make a concerted effort to disclose physicians' financial relationships with manufacturers of drugs and devices (26). Their proposal has been endorsed by the Association of American Medical Colleges (AAMC), the approval agency for all medical schools in the United States and Canada. This major proposal, published in the January 25, 2006, issue of the *Journal of the American Medical Association* (JAMA), brings the need for reform of the relationship between physicians and the

pharmaceutical companies to the attention of a majority of the nation's physicians. The academic medical center leaders have proposed to "take the lead in eliminating the conflicts of interest that still characterize the relationship between physicians and the healthcare industry."

The headlines in a feature article of our *Baltimore Sun* newspaper for Sunday, May 7, 2006, screamed IMPROPER SALES OF MEDICINES TARGETED: Drug Firms Have Paid Fines of \$3.5 Billion Since 2001 for Wrongful Promotions (27). The article states that a Civil War-era law to root out fraudulent army contracts has been quietly employed by whistleblowers and federal prosecutors in recent years for cracking down on pharmaceutical companies wrongly promoting their drugs and that they have paid \$3.5 billion in fines since 2001. It states that intensive marketing has led pharmaceutical companies to give televisions to physicians, sell them drugs at undisclosed discounts, and take other improper steps to encourage them to give patients drugs they don't need, which in fact may be harmful to their patients. Thus, to avoid prosecution, drug companies have had to hire compliance officers, re-train their sales staffs, and create hot-lines so employees can alert them to wrong doing. Federal law permits companies to promote drugs only for uses approved by the FDA.

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