

Charles Armstrong, M.D.:  
A Biography

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“Give Dr. Armstrong a mouse and a syringe, and he can do research.” Quoted by Dr. Robert J. Huebner to the author. Dr. Charles Armstrong in the mid-to-late 1950s. Courtesy of the National Library of Medicine.

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## Armstrong – Acknowledgments

The author was the fortunate recipient of the cooperation and steadfast support of Ms. Mary Emma Armstrong, Dr. Armstrong's daughter, in writing this biography. She contributed a treasure trove of documentation that she had collected and maintained conscientiously for many years. She had compiled three large loose leaf notebooks containing personal papers, correspondence, newspaper clippings, magazine articles, book chapters and other descriptive material detailing various aspects of her father's life and activities. In addition, she had kept a brief autobiographical sketch written by her father as well as the oral autobiographical interview conducted by Dr. Wyndom Miles of the National Library of Medicine about a year before Dr. Armstrong died. She also outlined her father's curriculum vitae and kept account of personal family matters. The author had frequent and generous access to all of the above material.

Mrs. Harriet Huebner, the widow of Dr. Robert J. Huebner, provided additional items of source information. Dr. Huebner, a young associate, confidant, and a successor Chief of the Laboratory of Infectious Diseases, was unable, due to illness, to complete a short biography of Dr. Armstrong authorized by the National Academy of Sciences for one of its volumes of *Biographical Memoirs*. Dr. Huebner was suffering severe intellectual impairment caused by rapidly advancing Alzheimer's disease. Mrs. Huebner contributed a large packet of reprints covering many of Dr. Armstrong's major discoveries along with some of Dr. Huebner's very sparse marginal notes and commentary.

The author wants to credit the help of Mrs. Marjorie Ciarlante of the National Archives at College Park, Maryland for providing access to the files of RG (Record Group) – 90 that contained information about Dr. Armstrong’s early years in the United States Public Health Service and the Hygienic Laboratory.

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## Introduction

I first became acquainted with Dr. Charles Armstrong in January 1948. It was during the year of my internal medicine internship in 1947-1948 at the Robert Dawson Evans Memorial Hospital (then Massachusetts Memorial), now University Hospital, a component of Boston University Medical Center. Influenced during my previous training by charismatic teachers of laboratory and clinical microbiology, I became attracted to the possibility of pursuing a career in the study of infectious diseases. Fortunately, I encountered a benefactor in the person of Dr. William Lane Hewitt who was then a Fellow in Medicine at the Evans. He was working on the wards of the hospital, and he was also assisting Dr. Chester S. Keefer in the analysis of the therapeutic value of the antibiotic, streptomycin, in the first 3000 cases. They were performing this project under a producer's grant to the Committee on Chemotherapy, Division of Medical Sciences of the National Research Council. Dr. Hewitt also held the rank of Surgeon (equivalent to a Naval lieutenant-commander or an Army major) in the Commissioned Corps of the United Public Health Service. He had also worked at the National Institute of Health for about six years (2). During the course of our professional association, which was extremely cordial, he became aware of my interest in infections.

Initially, he suggested that I start a project in my "off-duty hours" with the hospital's chief bacteriologist to see if I could help isolate "L-forms" (cell wall-deficient bacteria that did not grow in conventional bacteriological media) from a patient with blood culture-negative infective endocarditis (infection of a heart valve). This project,

however, was short-lived since successive culture plates became contaminated with common skin bacteria.

About the same time, I had to confront the problem of deciding how to plan my training for the coming few years. Competition for residencies and fellowships at this time was keen because of the preferential acceptance of the many young medical officers returning from their World War II service who wanted to complete their training before returning to civilian practice. In view of this situation, I decided that since I had graduated from medical school at an age several years younger than most of my classmates, I could afford to spend several years acquiring some laboratory experience in infectious diseases prior to entering a residency training program.

When I discussed this with Dr. Hewitt, he suggested that I might be interested in and profit from working at the National Institutes of Health in the Division (later Laboratory) of Infectious Diseases. As mentioned previously, he had worked in the Division, knew most of the prominent investigators and was personally friendly with Dr. Armstrong, the current Chief of the Division. I did not know at that time about Dr. Armstrong's prominence as an investigator in microbiology, especially in virus diseases. Dr. Hewitt described in glowing terms the scientific accomplishments of Dr. Armstrong. Hewitt stated that, despite the modern custom of building huge bibliographies, Dr. Armstrong had written only a modest number of research publications but that most of them were of original research that made major contributions to the knowledge of infections. Dr. Hewitt offered to arrange an interview for me with Dr. Armstrong at the National Institutes of Health in Bethesda, Maryland.

At this juncture it is worthwhile to describe the historical evolution of the Division (later Laboratory) of Infectious Diseases (3). This organization was the most direct descendant of the original Marine Hospital Service research laboratory established in August 1887 at the Marine Hospital on Staten Island, New York. Its function was to assist the Public Health Service in diagnosing infectious diseases among passengers on incoming ships. Detached from the Hospital and moved to the Butler Building in Washington, D.C. in 1891, this “Laboratory of Hygiene” became known as the Hygienic Laboratory. Authorized in 1901 by Congress to investigate “infectious and contagious diseases and matters pertaining to the public health,” the research of the Hygienic Laboratory focused primarily on bacteriology and pathology, the two major fields of 19<sup>th</sup> century medical interest (3). In 1902 a reorganization of the Public Health Service divided the Laboratory into four divisions; infectious disease research became located in the Division of Pathology and Bacteriology. On February 1, 1937, the Division was renamed the Division of Infectious Diseases, becoming one of the eight Divisions and one Office (of Comparative Studies) defined in the National Institute of Health reorganization of that date. The NIH moved to the Bethesda campus from 1938 – 1941 as the construction of the buildings was being completed. During this period the Division had the assignment of administrative jurisdiction over the Rocky Mountain Laboratory in Hamilton, Montana. The Division incidentally carried on the heart and dental research of the Public Health Service (3). Almost coincidental with my arrival at NIH, in the reorganization of 1948 that created the (plural) National Institutes of Health, the Division became the Laboratory of Infectious Diseases, one of the four original components of the National Microbiological Institute (NMI) also established at that time (the other three



were the Laboratory of Tropical Diseases, the Laboratory of Biologics Control and the Rocky Mountain Laboratory). The Rocky Mountain Laboratory received equal administrative status as part of new NMI, and the heart and dental activities were placed in their own newly created Institutes. In 1955 the NMI morphed into the National Institute of Allergic and Infectious Diseases (NIAID) with many resultant changes both in LID and NIAID. During the period of 1948 to 1952 when the organizational changes occurred or were in the process of occurring while I was at NIH, the only thing that penetrated to my level of awareness as a junior officer was just the changes in the office stationery.

In January 1948 I was able to meet with Dr. Armstrong. I was then in rotation at the Forest Hills Hospital, part of the Massachusetts Memorial (Hospital) complex. This phase of my internship was a mix of medicine and surgery without obstetrics or pediatrics. I had to maneuver three days off continuously from a Thursday to a Saturday with a report back to duty on a Sunday. To compensate for this “vacation time”, I had to work three extra weekends. I took a roomette on the night train from Boston to Washington, D.C. Arriving at Union Station, and, ignorant of local geography and unacquainted with the local transportation system, I asked a bemused information clerk about “the train to Bethesda”. I finally made my way by taking the streetcar (long-since gone) from Union Station to Friendship Heights in Chevy Chase, Maryland and then the bus up Wisconsin Avenue through a semi-rural downtown Bethesda to the NIH-Naval Medical (Hospital) bus stop.

Miss Virginia Burlingame, Dr. Armstrong’s gracious and efficient secretary, greeted me initially at the Laboratory. (She later confessed to me that she enjoyed greeting the young

and “handsome” doctors who came to work in the Laboratory (1)). I met Dr. Armstrong shortly thereafter in his office in Building 7, The Memorial Building. He impressed me immediately with his warm, friendly but dignified and humble personality, especially so, since Dr. Hewitt had enlightened me about his multiple research accomplishments. After a cordial introductory conversation, Dr. Armstrong asked me about my interests and what I might want to do at NIH. I replied that I had no specific interests but that I wanted to acquire some laboratory skills working with rickettsias and viruses and to see what might develop. This answer was probably one that he found satisfactory. He suggested then that I meet with some of the other investigators in the Laboratory.

I had very pleasant meetings with Drs. Robert Huebner, Karl Habel, Carl Larson and Dorland Davis, all with established research reputations. I ran into a “buzz saw” encounter with Dr. Byron J. Olson (opinionated and dogmatic) who castigated me for not knowing what line of investigation I wanted to pursue. Fortunately, we had no further exposure to one another, to the mutual advantage of each, during the time that I was at NIH.

At the end of the day’s visit, Dr. Armstrong asked me with whom I should like to work. I was torn in my decision between Drs. Huebner and Habel. The research achievements of both men impressed me. Initially, I felt that I wanted experience working with rickettsial organisms, but on the other hand I thought I would learn more virology under Dr. Habel’s supervision. In view of Dr. Huebner’s recent successes with rickettsialpox and his current activities with Q fever, I opted to begin my work with Huebner and try to learn virological investigation on my own. Dr. Armstrong seemed pleased, and he approved of my decision. (Huebner was one of his favorite people,

probably the most favorite.). We shook hands, and he told me immediately that I could start working at the Laboratory on August 1, 1948. He said that official notice would be sent to me around June 1948. He advised me in the interim to apply for a Public Health Service Post-Doctoral Fellowship since that would be my official position at NIH. I was one of the first persons in that category after World War II.

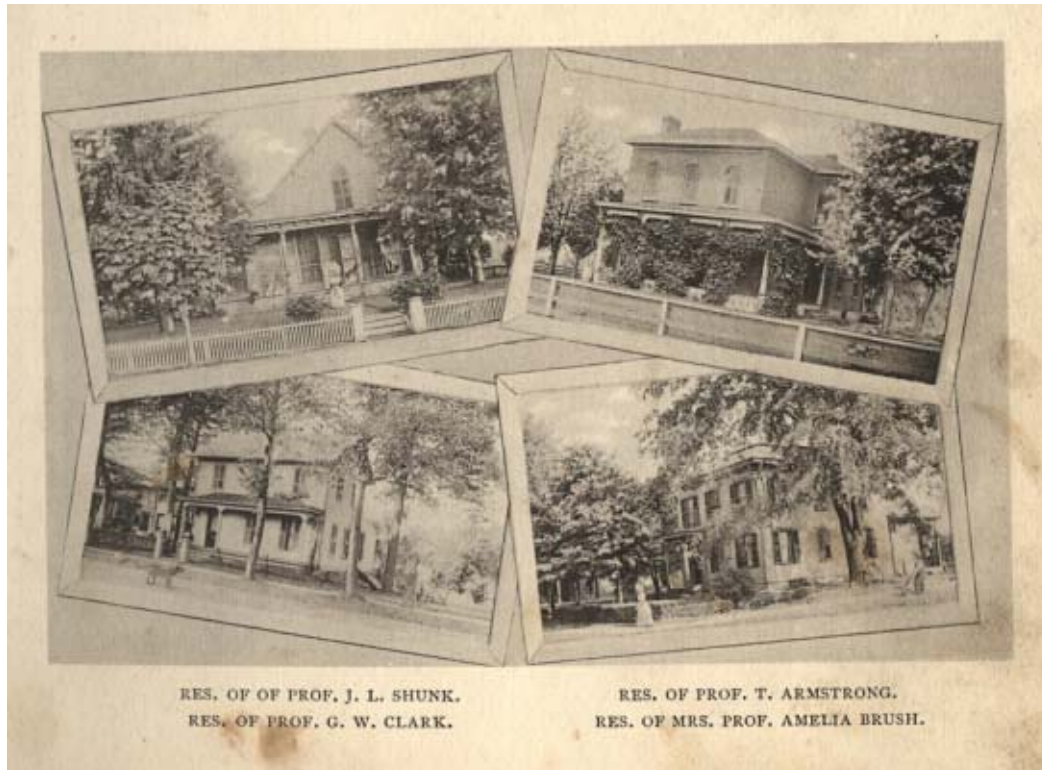
After this initial inspirational exposure to Dr. Armstrong, I returned quite exhilarated to the drudgery of my internship and the remainder of a snow-laden winter in Boston. However, as spring approached without further communication from NIH, I became apprehensive about the status of the oral commitment to me. Friends and family suggested that I should “protect my flank” in order not to be left dangling without an appointment on June 30, 1948 at the end of my internship. Hearing about some good residencies still available locally, and heeding the above well-intentioned advice, I applied for an assistant residency in internal medicine at the Veterans Administration Hospital (then in Framingham, Massachusetts) on the medical service of Dr. Maurice B. Strauss, the prominent nephrologist. My concerns were entirely without foundation. In early June 1948, true to his word, Dr. Armstrong sent me a telegram instructing me to report to my assignment August 1, 1948. The following day I received a telephone call from Dr. Strauss offering me the assistant residency for which I had applied. I thanked him for his kind offer but explained that I had made other arrangements more in keeping with my basic interests.

In my years in and out of the preparation for and the practice of internal medicine and infectious diseases, I have encountered many brilliant and talented faculty members, investigators, clinical colleagues and administrators some of who became role models for

me; but among this group there were very few truly heroic figures. Dr. Charles Armstrong was one of my heroes. During the height of his career when he was investigating deadly outbreaks of virulent disease causing infectious organisms with great personal risk to himself, he became infected repeatedly with these microbes some of which caused life-threatening illnesses. The media, especially the newspapers, printed day-by-day accounts of his laboratory activities and the status of his health during the illnesses he acquired when he was studying some of these dangerous organisms. His investigative exploits were also the subject of magazine articles and book chapters by medical science writers such as Paul DeKruif. In the 21<sup>st</sup> century, like the Biblical Pharaoh of the Book of Exodus “who knew not Joseph”, the modern public and scientific community “knows not” Dr. Charles Armstrong. I have, therefore, undertaken to write his biography in order to keep alive the record of his accomplishments and the memory of him as an innovative scientist and as a remarkable human being.

## The Early Years: Family Background; Education

Dr. Charles Armstrong was born in Alliance, Stark County, Ohio on September 25, 1886, the youngest of four children of Theodore and Emma Maria (Bertolette) Armstrong. His father, Theodore, was the only son of Robert Armstrong, a country practitioner of medicine at North Benton, Ohio. Grandfather Robert Armstrong never graduated from medical school. He gained his experience as an apprentice to an established medical practitioner. This was a usual custom in Ohio and, indeed, in most of the United States in the early half of the 19<sup>th</sup> century. Despite the lack of modern diagnostic and therapeutic modalities and formal training, Charles Armstrong described his grandfather as a person of common sense who had a sense of duty and of service to the constituents of his practice. Charles Armstrong had no first hand knowledge of these traits since his grandfather died “worn out” when Charles was a child of about 4-5 years. However, grateful patients were frequent visitors to the home of Theodore and Emma Maria Armstrong and often discussed with them the work and character of Grandfather Armstrong. It was not clear to Charles Armstrong just what effect or influence, if any, these often repeated testimonials might have had on his choice of a career. However it is certain that the stories of hardships, of travel in all kinds of weather by buggy, saddle or on foot and of not sleeping in his bed for weeks at a time did not deter Charles from studying medicine. It was, however, possible that these considerations, among others, did serve to influence his decision to enter the United States Public Health Service rather than to risk general medical practice.



Residences of Professor Theodore Armstrong and neighbors, late 19<sup>th</sup> century, in Alliance, Ohio. Courtesy of Mary Emma Armstrong.

Charles Armstrong described his father, Theodore, in some detail.

Biographical Sketches (2) of “Lexington Township” (Ohio), of undetermined date, provided additional details of Theodore’s life. The sketch (2) outlined these facts about him. “Theodore Armstrong, A.M., Professor of Penmanship and Assistant Superintendent of the Commercial Department of Mount Union College, Mount Union, Ohio was born June 12, 1848 in North Benton, Ohio. He is the oldest son of a family of 10 children born to Dr. Robert and Amy B. (Woodruff) Armstrong. His grandfather Armstrong came to Ohio and was one of the first pioneers of Mahoning County, as were the Woodruffs, ----. When moving from New Jersey to Ohio, their team being heavily laden with their effects, the grandmother, Mrs. Woodruff walked on foot the entire distance. [EAB – This was a remarkable feat of endurance for the pioneers opening up the United States Northwest Territory in the late 18<sup>th</sup> and early 19<sup>th</sup> centuries. They covered distances of 400 – 600

miles over unpaved roads and trails and several ranges of the Appalachian Mountains in animal driven carts and wagons.] Dr. Robert Armstrong was a prominent physician and had a very extensive and lucrative practice in Mahoning county and vicinity. The subject of this sketch, Theodore, received a liberal common school course, and in the fall of 1865, he entered Mount Union College (3). He was appointed (a) tutor of a class in 1868, in the meantime pursuing his own studies. Being of frail constitution, he was compelled to give up his college work for a short time. Upon finding his health recruited by outdoor exercise, he returned and graduated in the scientific course in Mount Union in 1870, and in 1871 graduated in the classics. He was then appointed Professor of Penmanship and Assistant Superintendent of the Department of the College. A 'Professorship of Penmanship' was not an unusual faculty position at that time. The manual typewriter was not invented until 1873; a legible written hand, therefore, became a necessity to provide documentation in commercial, legal, official, domestic, and literary communications. May 1, 1873 he married Emma Maria Bertolett [perhaps a schoolmate at Mt. Union College], daughter of Zachariah and Mary Bertolett of North Benton, Ohio. They have two children living – Mary I. and Bertolett. [This sketch was written before the birth of Dr. Charles Armstrong.] Professor Armstrong has a very commodious home which he has taken great delight in beautifying, doing all the work himself as recreation in his leisure hours.”(2)

Charles Armstrong had a slightly different perspective of his father's career at the college. Following graduation and graduate work at Mount Union College, Theodore Armstrong specialized in commercial law, bookkeeping and penmanship – subjects which he later began teaching at the school (in 1873), then a struggling religious

(though non-sectarian) college. During the most productive portion of his life, as a teacher, he received a salary of less than \$1000 per year, part of which money was at times returned to keep the school operating, especially during the lean years that followed the Civil War.

In order to supplement his meager teaching salary and to support his family, Charles' father began farming as well as the raising and selling of blooded brood mares, racing horses and Shetland ponies. In winter, the care of the stock and during the summer the planting and harvesting of crops with which to feed the stock, supplied an abundance of work for the whole family. The trustees and faculty of the religiously strict institution in which he taught frowned upon Theodore Armstrong's interest in the breeding of fine horses, but his less puritanical ideas made him popular with his students. In fact, on several occasions when the school's "temperance" committee of the faculty was about to conduct a sudden raid on the students' favorite tavern, Theodore Armstrong warned the students to give the appearance of studying their texts rather than debating the quality of the tavern's alcoholic beverages (1). When Charles Armstrong was about 10 years old, his father gave up teaching to devote his whole attention to the farming and livestock business. Charles Armstrong speculated that with this exposure in his early domestic life, he naturally developed an interest in the care and treatment of ill animals.

The livestock business brought many visitors to the Armstrong home that was just outside the corporate limits of Alliance; the visitors included horsemen and traders who were always invited to stay for meals and to spend the night. In addition to these visitors, town friends of the Armstrong siblings, both boys and girls, were usually present during the day attracted by the opportunities to ride the horses or the ponies. Dr.



Armstrong described the home as far from the quiet work-a-day farm home. The dwelling was an ample, nine-room, brick house in a pleasant location, surrounded by trees and with three large barns nearby.

Dr. Armstrong did not elaborate at length about his mother; he described her as a hard-working woman, and, like his father, she was a good disciplinarian who maintained a congenial atmosphere about the home and whose first consideration was always her family.

The family background described established Charles Armstrong as a representative descendant of the pioneering farming stock that settled northeast Ohio in the early 19th century.

In an oral interview (1), he described his early education. He did not start public school till he was eight years old. His birth was difficult; he suspected that he might have had a mild arrested hydrocephalus (delayed closure of the bony suture lines of the skull due to cerebrospinal fluid accumulation). He felt that his head was disproportionately larger than the rest of his body when he was born and continued so for the next several years. His father was dubious about whether Charles would be normal or not, and Father Armstrong kept him from going to school until he was eight. By law, Charles should have started school when he was six but his father happened to be on the local Board of Education, and he exerted his influence to delay Charles' registration in school. Dr. Armstrong always felt cheated and somewhat resentful for having to delay the start of his education for two years. He started grammar school in an old-fashioned, not a one room, but a four-room schoolhouse; however, each room hosted two or three classes. He learned his subjects quickly and readily. It helped that his first teacher was his aunt,

his father's sister, who was an excellent teacher and who gave him a little extra attention. He had no academic difficulties. After finishing grade school, he went to Miles Junior High School, then, he progressed to the 3-year high school in Alliance from which he graduated in 1905. In high school he received minimal training in the sciences, primarily astronomy and physics without laboratory work; an indifferent teacher taught these high school courses through texts and lectures. He went for one year to the Mount Union College Preparatory School. In this school he had a dynamic instructor who provided courses in geology followed by biology, chemistry and physiology along with minimal exposure to laboratory bench experiments. He then went to Mount Union College for four years graduating with a Bachelor of Science degree in 1910. While in college he received the Yost Prize for scholarship. At college the courses in which he excelled, and enjoyed most, were the natural sciences including biology, geology and mathematics; he was not fond of and had little aptitude for classical or modern languages.



- 1) Mount Alliance High School Class of 1905. Charles Armstrong is seated second on the right in the second row. Courtesy of Mary Emma Armstrong.

Mount Union College (3) was “typical of many other small liberal arts colleges in the Midwest during the 19<sup>th</sup> century. It evolved from a modest beginning in a single building to a modern campus of the 20<sup>th</sup> century. During the early years it was known as a seminary. Actually it was a small struggling academy, like most other schools of that day; but this term was used to indicate the religious emphasis. The seminary was a success, and it acquired a college charter in 1858.” The school was traditional but also innovative. It “was not sponsored or founded by any religious denomination – but it did gain the patronage of the Methodist Episcopal Church during the Civil War years.” Limited finances plagued the early days of the College, but, with time, and, especially after World War II, the school expanded, the finances and endowment improved, and the

campus provided a hospitable environment for students of both sexes. Dr. Armstrong remained a lifelong enthusiastic and loyal alumnus of his College. In 1933, the College bestowed upon him an honorary Doctor of Science degree.

With his attraction to the sciences and with the family precedent of his having a grandfather who was a respected family physician, it was predictable that Charles Armstrong might decide on a medical career. While he felt a strong desire to attend medical school the year after graduation from college, he was in debt and lacked the funds to start his medical education. Instead, for one year, he accepted a position as Superintendent of the Greentown Ohio Special School District, employment that combined administration with the teaching of high school science and mathematics. This was a profitable experience for him. While he was in this job, he became better acquainted with the woman, a college classmate, Miss Bess Rich, who taught with him, and who later became his wife. As Dr. Armstrong described her, she was a congenial and understanding helpmate. That same year he also accumulated enough money for the entrance and annual tuition fee for Johns Hopkins University Medical School - \$240.



Mrs. Elizabeth Rich (Bess) Armstrong, graduation picture, Mount Union College, 1910; Ms. Mary Emma Armstrong, around 1950. Courtesy of Mary Emma Armstrong.

He applied to Johns Hopkins (4) because it had the “the best reputation in Ohio, and it wasn’t much more expensive than other medical schools”. Dr. Armstrong’s regional chauvinistic minimalist assessment of the Johns Hopkins Medical School is amusing, particularly in view of its outstanding reputation from the time of the School’s founding up to the present era. Johns Hopkins (1795-1873), an American financier and philanthropist born in southern Maryland, left \$7 million in his will to be divided equally between the Johns Hopkins University and the Johns Hopkins Hospital both of which became incorporated in 1867. Instruction at the University began in 1876, and the Hospital opened in 1889. The School of Medicine opened in 1893. It accepted only college graduates who had at least one year’s instruction in the natural sciences. The

School was also the first to afford its students the opportunity to further their training in an affiliated teaching hospital. “Modern American medical education started at Hopkins over a century ago when the founding physicians of the Johns Hopkins University School of Medicine created a revolutionary medical curriculum that, for the first time, integrated a rigorous program of basic science education with intensive clinical mentoring” (4). The founding physicians were the “Famous Four” who provided the core of the outstanding early clinical faculty. They were Sir William Osler, Professor of Medicine, Dr. W.S. Halsted, Professor of Surgery, Dr. William H. Welch, Professor of Bacteriology and Pathology, and Dr. Howard A. Kelly, Professor of Obstetrics and Gynecology. In 1910, when Abraham Flexner, the American education reformer, wrote Bulletin #4, *Medical Education in the United States and Canada* exposing the inadequacies of most proprietary schools for the Carnegie Foundation for the Advancement of Teaching, he endorsed the Johns Hopkins model of medical education (4). Subsequently the American Medical Association and the Association of American Medical Colleges laid down standards for course content, qualifications of teachers, laboratory facilities, affiliation with teaching hospitals, and the licensing of physicians that survive to this day (5).

Johns Hopkins School of Medicine accepted Charles Armstrong for admission in the fall of 1911, and he entered his studies with enthusiasm. At the end of his freshman year he returned home to Alliance, and he was determined to continue his medical studies without interruption. He was able to do this by working summers. The first summer he worked with a railroad construction gang digging trolley post-holes. Thereafter, he secured more lucrative employment in a foundry assembling railroad car couplers. This was heavy work but he had always been used to hard work on the family farm. The

foundry job entailed piecework, so he was able to make \$4 to \$5 per day before the summer was over. Through a loan from relatives, supplemented by his summer savings, he was able to return to Johns Hopkins for his second year. The following summer he worked as a teacher of biology and geology in the summer school program at Mount Union College. With additional summer work and loans from his family he was able to graduate from Johns Hopkins with his class in 1915. On the whole, his medical school experience was an enjoyable one. After graduation he took and passed the Maryland State Board of Medicine examination to practice medicine.

He had expected to go into the practice of medicine. In view of this goal, he applied for and was accepted in 1915 into a 2-year rotating internship at New Haven General Hospital, the teaching hospital for Yale Medical School, New Haven, Connecticut. Here he found the contacts with patients, fellow interns, residents, students and faculty most stimulating. He finished the first internship year and started the second year when he suddenly came face-to-face with fiscal reality as he began thinking about starting a medical practice. He was in debt for his education, and he had no money saved from his meager internship salary. In order to start a practice he would have to establish an office, purchase an automobile, pay salary for one or more nurses, and he would need a wife. Contemplating the further borrowing of additional major funding seemed to him like an almost impossible obstacle to his plans for practice. One evening while he was in the midst of trying to resolve these conflicting decisions, he saw an announcement on the hospital bulletin board of examinations to be given within a week for applicants seeking admission to the Commissioned Corps of the United States Public Health Service. Applications were to be addressed to the Surgeon-General. A letter of inquiry from Dr.

Armstrong to the Surgeon-General brought a telegraphic invitation to report for examination at Ellis Island, New York in four days. Dr. Armstrong went to the Superintendent of the New Haven General Hospital and explained the reasons for his desire to take the examination for the Public Health Service. Immediate acceptance into the Service if he passed the examination, he also explained, would mean that he could not fulfill his internship obligation for the remainder of the year. The Superintendent generously told Dr. Armstrong that if this was what he wanted and needed to do, the Hospital would not hold him to the completion of his full two years of internship. Dr. Armstrong borrowed enough money to get himself to New York to take the examination that he passed successfully. Another intern from New Haven took the same examination and failed.

In his personal papers (1), he described details that he remembered of the examination process. It was a very rigid examination lasting 5 days. There were four days of written examination and one day of oral quizzing including possibly a physical evaluation of the applicant. The examiners questioned Dr. Armstrong sharply about his feet since they thought he might have exhibited a tendency to flat footedness. They finally decided that his feet were fine, and he passed the physical requirements for a commission. The examining board for the fifth day oral examination consisted of 5 Public Health Service officers dressed in full uniform. They asked him questions for several hours, then assigned him a hospital patient to examine and diagnose. One of the examining physicians, a Dr. Cobb, asked Armstrong, "Well, what's he got"? Armstrong's patient had obscure signs and symptoms that he could not explain. Armstrong's response was, "Damned if I know". Dr. Cobb replied, "Oh, don't feel bad about it. We don't know



either”. With this final repartee the examination concluded. Several weeks later the USPHS informed Dr. Armstrong that he had passed the examination, held the commission of Assistant Surgeon as of October 16, 1916 and told to report for duty at the Immigration Station, Ellis Island, New York.

Several weeks later, on November 8, 1916, he received a letter from Dr. J. Morris Stevens, Chief of the Department of Obstetrics and Gynecology of New Haven Hospital (1). “My Dear Armstrong: Your kind letter of October 28<sup>th</sup> has not been answered on account of one of those high pressure periods with which you are familiar. From what you say, I regret extremely that we did not have the conversation in question months ago. But, of course, neither of us felt free to speak. However, I do trust sincerely that you will like your new work, and I believe you will. As I understand, the Government Service offers opportunity for promotion, and I know it will come to a man of your serious purpose and diligence; for, after all, the people who win out are those who do their work day after day, and whose excellence is that they are dependable. Dr. Morse and Dr. Morris join me in the best wishes for your future. Sincerely”. With these prophetic words of encouragement, Dr. Charles Armstrong began his lifelong, illustrious career in the United States Public Health Service.

#### Armstrong – Notes – The Early Years

- 1) Information gathered from personal papers, a short autobiographical memoir, and an extensive oral interview conducted by Wyndom Miles of the National Library of Medicine in October 1966 (transcribed in August 1977) provided much of the information recorded in this and subsequent chapters. Dr. Armstrong’s daughter,

Miss Mary Emma Armstrong provided three large loose-leaf binders filled with personal papers, pictures, newspaper clippings and other printed materials documenting her father's activities.

- 2) History of Starke County, Ohio, Perrin [?] 1881.
- 3) Web page of Mount Union College, Alliance, Ohio  
<http://www.muc.edu/geninfo/history.htm>.
- 4) Web page of Johns Hopkins University School of Medicine.  
<http://www.hopkins.medicine.org/medical=school/>; Microsoft® Encarta ® 98  
Encyclopedia
- 5) Encyclopedia Britannica; Microsoft Encarta Encyclopedia, 2006.

## Initial Assignments

When he accepted his commission in the Public Health Service, Charles Armstrong selected access to an exclusive and elite group of individuals. Dr. Ralph Williams (1), writing Chapter 9 entitled *Those Who Carry On* in his history of the United States Public Health Service, described the origin, the physical and professional requirements of applicants for admission, the mission and the administrative details of the Commissioned Officers Corps of the USPHS. The U.S. Public Health Service began its existence when it was established as the United States Marine Hospital Service (1798-1902) in order to provide medical care to merchant seamen and Naval personnel. During its existence this organization also began performing other public health functions. Its name changed to the United States Public Health and Marine Hospital Service from 1902-1912. Since 1912 to the present it has enjoyed its current title. It has existed as parts of several government departments and agencies including in succession up to the present: the Department of the Treasury, Federal Security Agency, Department of Health, Education and Welfare (HEW), and Department of Health and Human Services (HHS).

A Supervising Surgeon (the first Surgeon General of the USPHS) of the Marine Hospital Service, Dr. John M. Woodworth (1871-1879), when appointed initially, decided that one of the important problems confronting him was the development of a mobile corps of carefully selected medical officers to staff the Marine Hospitals and to perform other health duties. Prior to their appointment, officers of the Marine Hospital Service were selected on a somewhat random basis with scant emphasis on the on the

presence or absence of professional qualifications. By and large, in that 19<sup>th</sup> century era of non-standardized training in medicine, the level of professional proficiency of physicians was quite variable trending toward the lower scale of competency. Very frequently the positions were filled with political appointees, and the changes in Federal administrations often resulted in the replacement of these medical officers.

The experiences of Dr. Woodworth (2) “while a medical officer in the United States Army during the Civil War impressed upon him the effectiveness of a mobile corps of physicians who were required to maintain their physical and professional fitness, and who were subject to a definite form of discipline. During the term of his office (1871-1879) he worked closely with state and local health authorities in dealing with outbreaks of epidemic diseases. He frequently responded to requests from states and localities by assigning medical officers from the Marine Hospitals to cooperate in handling outbreaks of smallpox, yellow fever, and other epidemic diseases. These experiences emphasized the value of an officer corps sufficiently flexible to enable the directing head to send officers as necessary to meet such sudden exigencies as epidemics, public disasters or other similar emergencies. The events of that era and the accomplishments of the Service in dealing with them laid the foundation upon which was created the Commissioned Officers Corps by the Act of January 4, 1889. This Act established by law the adopted policy of a mobile corps subject to duty anywhere upon assignment, a policy that had been pursued by Dr. Woodworth since he assumed charge of the Bureau of Marine Hospital Service in 1871.” The successors of the Service, as exemplified by the USPHS Hygienic Laboratory and the Division (later Laboratory) of Infectious Diseases, maintained these functions continually until the emergence of the

Communicable Disease Center, (currently the Centers for Disease Control and Prevention), created in 1946 when the latter took over the investigation of epidemics of infections and the isolation of emerging infectious pathogens.

In this fashion the nascent Public Health Service inaugurated in the Federal Government the first merit system exemplified by the appointment of civilian officers for employment in the Marine Hospitals. This program was in operation for 10 years prior to the adoption of the United States Civil Service System in 1883 and was the precursor for the establishment of the Commissioned Corps in 1889.

The Commissioned Corps, initially, was small and chosen selectively, consisting entirely of physicians, most of who had served as Union medical officers during the Civil War. As developments expanded in hospital activities and public health, it became necessary to include in the Regular Corps scientists (generic), nurses, dieticians, physical therapists, veterinarians and sanitarians (3) The Act of July 1, 1944 provided authority for these appointments. The various categories of professionals were selected by examination by members of their respective professions. Professional qualifications, evidence of good physical health, personality and other personal attributes that would “render them effective in dealing with the public, with other governmental agencies, and with representatives of other nations” (3), formed the basis for selection or appointment to the Regular Corps.

During times of war, the officers of the Regular Corps, by Executive Order, were assigned to the United States Armed Forces, usually the Coast Guard or the Navy, or, individually to specific duty with the Army. During wartime, the members of the Commissioned Corps were required to wear the dress and field uniforms of the services

to which they were assigned. The uniforms displayed the designations for rank and included the distinctive Public Health Service device or logo. This logo, designed by Surgeon General John M. Woodworth in 1871 (4), included a fouled anchor (representing a seaman in distress) and the Caduceus (a winged wand with two entwined serpents) of Mercury (Greek god of commerce and thieves) that represented the combined operation of the Marine Hospitals in the care and treatment of merchant seamen and their relation to maritime commerce. The Army Medical Corps adopted the caduceus as its service logo in 1902 (5). In some professional medical organization the preferred symbol is the Staff of Aesculapius, the Greek god of medicine and healing. This consists of a knobbed wooden staff with a single entwined snake (5).

The ranks in the Public Health Service with their equivalent ranks in the Navy, Coast Guard and Army are as follows:

PHS Medical Officer	Navy, Coast Guard	Army
No Rank for Medical Officers	Ensign	2 <sup>nd</sup> Lieutenant
Assistant Surgeon	Lieutenant, Jr. Grade	1 <sup>st</sup> Lieutenant
Senior Assistant Surgeon (formerly Passed Assistant)	Lieutenant	Captain
Surgeon	Lieutenant Commander	Major
Senior Surgeon	Commander	Lieutenant Colonel
Medical Director	Captain	Colonel
Assistant Surgeon-General	Rear Admiral Lower Half	Brigadier General
Chief of Bureau	Rear Admiral Upper Half	Major General
Surgeon-General	Vice Admiral	Lieutenant General

The ranks also carried a title designating the profession of the PHS officer; e.g., Senior Surgeon, Senior Veterinarian, Medical Director, Veterinary Director, etc. Some non-medical officers received an admission rank equivalent to Ensign with the designation “Assistant”. During war time periods or emergencies, personnel in the Reserve Corps were occasionally called to active duty depending on need.

Charles Armstrong's experience has already described partially the entrance examination for the Regular Corps. After 1905, following the report of Dr. Abraham Flexner and the adoption of accreditation requirements for United States medical schools, the Public Health Service felt that graduates of these medical schools were competent professionally. The PHS held examinations competitively for the best candidates to fulfill the "mission" of the Commissioned Corps. The Service, thus, placed emphasis on physical health, personal appearance, personality and the ability to pass a comprehensive written and oral examination lasting many days on the full range of medical science and clinical aptitude.

"The mission of the Commissioned Corps of the Public Health Service, as seen by a majority of its officers, was conceived as a 'mobile group of skilled specialists' prepared to undertake research whenever required, ready to perform professional and administrative duties, capable of responding to emergency needs and assisting other Federal agencies as well as State and local officials in the solution of their medical or public health problems"(1). Thus, Charles Armstrong, M.D., on October 16, 1916, was about to embark on a lifetime career in the elite, carefully selected, exclusive group represented by the Commissioned Corps of the United States Public Health Service.

#### Early Duty Stations in the Public Health Service

Charles Armstrong's first assignment, after receiving his commission, was directly to the Immigration Station on Ellis Island in New York Harbor. For six weeks he spent full time examining newly arrived immigrants. Immigration in the years prior to

World War I was extremely active. From a professional standpoint, he was grateful for the experience of seeing a wide variety of ailments originating in many lands; these were primarily eye (trachoma) and skin afflictions that he had either never, or rarely, encountered while he was in medical school or during internship. He spent his entire days doing the physical examinations and evaluations of the immigrants' eligibility for entering the United States.

He found some of the immigrants' plights tragic because some family members passed their physical examinations and were eligible for admission, and other family members did not pass the physical or mental requirements for entry. This situation gave rise, in many cases, to desperate circumstances because immigrants frequently came with limited funds; the option for stranded families, with some members ineligible for entry to the United States, was to return back to their country of origin or to their port of embarkation. Alternatively, the eligible immigrants would enter the United States, and the non-eligible family members would go back. When immigrant children were ineligible because of health reasons, the entire family would frequently have to return to the point of origin. In many instances, immigrants arrived sick with medical, emotional, intellectual or contagious illnesses. The Medical Department quarantined the ones with contagious illnesses (6) until the end of the period of communicability, and then the doctors released them from confinement. The Medical Department admitted those patients with treatable illnesses who required hospitalization to the USPHS Marine Hospitals. When these patients recovered, they were either allowed to enter the United States or they were deported. The Immigration and Naturalization Service (INS) (6) bore the expense for the hospitalization of sick immigrants. Prior to World War I there were



no provisions for pre-arrival examinations for immigrants. The flow of immigrants decreased significantly during the war years, 1914-1918. After the war, in order to alleviate the disruption of families and inconvenience to immigrants caused by refusal of entry to the United States, the Congress (7) passed the Immigration Act of 1924. This Act legislated the provision of medical inspection for prospective emigrants at the time of visa application at United States Consular Offices abroad. This plan was actually put in place (8) in 1925, initially in Great Britain and the Irish Free State, and was extended later to include the major United States Consulates in Western Europe and Italy.

Charles Armstrong served at Ellis Island for six weeks before being transferred to duty with the United States Coast Guard (9). The time was late 1916 when the United States was slowly drifting into a state of war with Germany (World War I, April 2, 1917); the United States shared outrage with Great Britain, France and their allies because of Germany's policy of unrestricted submarine warfare against ships of all nations dealing with Germany's enemies. Armstrong's new assignment took him to the Curtis Bay Coast Guard Depot in Baltimore Harbor, Maryland and to the Coast Guard Cutter ITASKA. The Itaska was in dry dock being repaired and equipped for sea duty. Before the repairs were complete, another Coast Guard Cutter, the SENECA was ready for sea. This ship needed a medical officer, so Armstrong was transferred to the Seneca. She was actually a more suitable ship for handling medical care than the Itaska. The Seneca was roomier, of 1200 tons displacement and contained a well-stocked and equipped sick bay with 2 bunks. She was armed for anti-submarine warfare in anticipation of the impending belligerency.



Assistant Surgeon Charles Armstrong, USPHS, aboard Coast Guard Cutter SENECA, while assigned to the United States Navy, 1916-1918, during World War I. Courtesy of the National Library of Medicine.

The Seneca's first sailing orders with Armstrong aboard were for iceberg patrol in the North Atlantic. The Coast Guard and Navy were still very sensitive to the hazard of floating icebergs and their threat to merchant shipping since the sinking of the Titanic in April 1912. The crew was issued cold weather gear, and the ship's galley was stocked with high caloric food in anticipation of patrolling in the frigid North Atlantic. At the last moment the orders were countermanded; the ship and crew were ordered to sail to Cuba and to patrol the Straits of Florida because of rumors of German submarines in those waters. Since there was much shallow water, and extensive coral reefs, around Cuba, the Seneca could not approach close to shore; the Skipper decided to explore the Cuban shoreline with a small launch that was attached to the mother ship. Armstrong persuaded the Skipper that a medical officer should accompany the launch since "something might happen". For the next several weeks Armstrong had an enjoyable trip around the Cuban shoreline looking for German submarines. Armstrong and the launch crew encountered no hostile activities except for some irritable locals who menaced them on shore by brandishing their machetes at them.

With inconclusive search results for German submarines in Cuban waters, the Navy then assigned the Seneca to convoy duty. A new convoy was starting up near Gibraltar, and the Navy directed the Seneca to join the convoy going from Gibraltar to South Wales. Armstrong served aboard the Seneca for 23 months; during 17 months of his sea duty (1917-1918), the Seneca was transferred to the United States Navy and was engaged in the guarding of convoys of merchant ships on the high seas. The Seneca became part of the Patrol Squadron based on Gibraltar. Her regular run was between North African ports, Gibraltar, and Milford Haven, South Wales. This was Armstrong's itinerary back and forth until almost the end of World War I. While Armstrong was on the Seneca, there were 13 separate attacks by German submarines on the convoys that the ship was trying to protect. Several merchant vessels were lost during these attacks. Despite the hazard of lurking submarines prowling the waters, the danger that the protecting ships feared most was the possibility of collision between ships on dark nights; all ships had to steam with their lights extinguished or be otherwise rendered invisible.

Armstrong felt (10) that his experience at sea was a complete cipher from the standpoint of gaining further medical experience; however it did provide him opportunities to visit "interesting places" in Cuba, Europe and Africa. The experience also helped teach him some of the rudiments of military protocol that he found to be useful later in the Public Health Service. On board ship he found that his practice consisted of healthy, young men, pre-examined and found fit for duty in the Coast Guard. If they became seriously ill, he sent them ashore for treatment since the ship's infirmary could not handle major medical or surgical illnesses. The infirmary really functioned primarily as a first aid station. His main medical chore in port was the examination of

food stores as they came aboard to make sure they were fit for consumption. At sea, his main medical function was to remove cinders from the eyes of the sailors who had been on “watch” duty. The Seneca was a coal burning ship. The watch stations on board were higher than the ship’s smokestack; smoke and hot cinders frequently filled the eyes of the sailors who had “the watch”. Armstrong became quite expert at removing these cinders while he and the sailor would be on a heaving deck in a rolling sea. The sailor would be pinned against a stanchion, Armstrong propped against a wall, and they would both roll with the movement of the ship. Sometimes the cinders would be hot when they landed in the eye would burn in and then be difficult to dislodge.

On one return trip from Great Britain to Gibraltar in 1918, the Seneca was asked to transport a prisoner from Plymouth, England. This prisoner, who was to be incarcerated in Gibraltar, was not feeling well. The trip from Wales to Gibraltar by “slow” convoy took 9-10 days. En route, two thirds of the Seneca’s crew became ill. The infirmary could hold only two men; the remaining sick crewmen were strewn in the gangways and on the decks. There were just enough well sailors to keep the engines hot and the boilers going. To help out, Armstrong even volunteered to take a turn standing watch, a task not in his normal duties. Arriving in Gibraltar, Armstrong hoisted the yellow quarantine flag and wired ashore saying that there was an unknown illness on board, most likely influenza. The reply from shore was, “Come on in, everybody has got it here”. The shipboard epidemic on the Seneca caused major morbidity among the crew but, fortunately, there were no fatalities; it was Armstrong’s only experience dealing with major illnesses while he was on sea duty.

The worldwide influenza pandemic of 1918-1919 was responsible for Armstrong's return to the United States. Toward the end of World War I, the pandemic was producing major morbidity and mortality in the United States, and the USPHS requested that the Navy release many of its Regular Corps Medical Officers to help affected communities deal with local epidemics. The Navy acquiesced to this request since it felt that that the war would not last much longer. So, on August 16, 1918, Assistant Surgeon, C.C. Charles Armstrong, USPHS, received orders (11) that "he was detached from duty on board the USS Seneca, CG, and from such duty as may have been assigned to him, and he was to report to the Commanding Officer of the USS YANKTON for temporary duty on board that vessel. Upon arrival of the Yankton at a port in the United States, he was to regard himself detached from temporary duty on board that vessel, he was to report to his home and report by letter to the Surgeon General, US Public Health Service".

The USS Yankton (12), originally named Penelope, was a steel-hulled schooner, built 1893 in Leith, Scotland. She was acquired by the US Navy in May 1898, and commissioned May 16, 1898 at Norfolk, Virginia. Her displacement was 975 tons; length, 185 feet; beam, 27 ½ feet; draft 13 feet 10 inches; speed, 14 knots; complement, 78; armament, 6 3-pounders, 2 Colt machine guns. She partook in the Spanish-American War patrolling and engaging the enemy in Cuban waters. In 1907-1908 she accompanied the Navy's "Great White Fleet" on the "round the world cruise" as a fleet tender. In World War I she headed for Gibraltar to join the Patrol Forces protecting Allied shipping from German U-boats, and she came under hostile fire during combat. The Yankton, according to Armstrong, had been the extravagant yacht of a well-known French actress

[?]; the Navy converted the ship to a gunboat and the Yankton had achieved some recognition in battle.

Armstrong had some memorable encounters with the current Captain of the Yankton who had achieved a reputation of his own. He was notorious because of excessive strictness with subordinates and rigid adherence to rules of military conduct and discipline. He had the reputation of running a “hell ship”. All branches of the Armed Forces were acquainted with his reputation, and fellow officers warned Armstrong about him. Armstrong faced his new, but temporary assignment with trepidation. Upon arriving on board, Armstrong reported to the Captain and inquired about the hour for holding sick call. They settled on the time of 9 am. The Captain said, “That will be all right, but I want to tell you one thing. If the men come to see you sick, I want a complete record of what his complaint is, what you find is the matter, what your treatment is, and what your advice is and everything. The reason for this is that these men someday will probably be asking for some pension. It is very important to them to do this”. Armstrong took command of the infirmary sick log, and he promised to follow the Captain’s instructions faithfully.

The Yankton left Gibraltar for the trip home but, for unknown reasons, the ship received orders to proceed to Lisbon, Portugal, possibly for a good will tour. Armstrong said that the Chief of Naval Operations was trying to make the Navy “dry” (alcohol-free) and encouraged strict disciplinary action against liquor and drunkenness on United States naval vessels. The Captain of the Yankton was especially vigorous in meting out punishment, including incarceration and court martial, for anyone on board with liquor in his possession, either in the bottle or on his breath. As added punishment, he would also

restrict shore liberty when the ship was in port, and he would require the offending crewmen to stand watch, adhering to the same schedule used when the ship was at sea.

Arriving in Lisbon, the Yankton anchored in the Tagus River, the Captain apparently had been invited to an elaborate celebratory event on shore. Resplendent in his full dress uniform, and leaving the ship in the polished, brass-enhanced Captain's launch, the Captain headed for the city in the evening. After Armstrong retired for the night, the officer on watch awakened him around 1 am and said, "Did you see the old man last night?" Armstrong replied, "No". "Well", the watch officer said, "He was 'pie-eyed'. He held on to the gangplank or he'd have fallen overboard". About 2 am Armstrong had a call to come to the Captain's cabin. When Armstrong entered the cabin, the Captain was sitting on his bunk "pale as a sheet" and retching. Armstrong observed that the smell of alcohol on the Captain's breath would have ignited if he had put a match to it, and the Captain was terribly sick. Armstrong said, "I'd like to wash your stomach out but the infirmary does not stock a stomach pump. The best I can do is to give you something to make you vomit". Armstrong gave the Captain some warm salt water that worked quickly. He also administered aspirin tablets and some coffee. He remained with the Captain until the patient was feeling better, and he then left until he would see the Captain at 9 am that morning to let him inspect the medical log.

When Armstrong first reported for duty on the Yankton he was the beneficiary of serendipitous misinformation. He had to use the head (toilet). The Officer of the Day directed him to a toilet that he was supposed to use. Armstrong was impressed with the toilet's neatness and its well-stocked supply of soap, towels and abundance of hot water. After 2-3 days, he discovered that this was the Captain's private toilet. In the morning,

after treating the Captain's alcoholic debauch, Armstrong was conflicted about presenting the medical log for the Captain's inspection because he had not reported treating the Captain's "medical" condition. He was indecisive about making a report that would reflect badly on the Captain's long and otherwise exemplary career in the Navy. As both men looked wordlessly for several minutes at the innocent appearing medical log, Armstrong finally said, "Captain, I owe you an apology". The Captain replied, "Why so"? Armstrong responded, "I have been using your bathroom but I did not know it was yours. I had been misinformed. The information given me was that it was to be my bathroom. Right now it is yours, and I have no business being there. I'm sorry. It won't happen again." The Captain said, "Well now, I want you to continue using it as you have. If you run out of soap or towels, just let me know, and I'll see they are provided." Armstrong protested that he didn't think he would like to do that, but the Captain retorted that if Armstrong didn't continue using the bathroom he would feel very badly. This conversation seemed to defuse a delicate situation associated with Armstrong's treatment of the Captain's early morning medical "emergency". Armstrong continued using the Captain's bathroom, and they both maintained a cordial, sober relationship for the remainder of the homeward journey.

An unexpected windfall resulted from the above episode and the Captain's role as "grateful patient." When the ship was about 11 hours from New York City, the Captain called Armstrong into his office for the following conversation:

Captain: "You told me you were from Ohio."

Armstrong: "Yes."

Captain: "What part?"



Armstrong: "Alliance, Ohio."

The Captain said he was acquainted with the location, used to go through there often, but never stopped.

Captain: "Are your parents living?"

Armstrong: "Yes."

Captain: "How long since you saw them?"

Armstrong: "It has been about 2½ years."

Captain: "I think you need a vacation. I'm going to write your orders that when you get to New York to leave at your convenience for Alliance, Ohio, you are to take 9 days leave of absence. At the end of that time, you wire your proper station of the Public Health Service of your whereabouts and tell them you await orders. Now remember! Nobody can repeal this order because this is an order from the Navy."

Dr. Armstrong was very appreciative of this gesture of kindness from the Captain. Dr. Armstrong remembered roughly the time frame of these events in his autobiographical interview (13). Official documents from the Navy, the history of the USS Yankton, and the Public Health Service provide precise times of his leaving the Seneca, returning to New York and then home (14). He was detached from the Seneca on August 16, 1918, and he was told to report for duty to the Commanding Officer of the USS Yankton on August 17, 1918. Upon arrival of the Yankton at a port in the United States, he was to regard himself detached from temporary duty on board that vessel. He was to proceed to his home and report by letter to the Surgeon General USPHS. The Yankton left Gibraltar August 19, 1918 for repairs in the United States. She steamed via Lisbon, Portugal and Ponta Delgada in the Azores and reached the New York Navy Yard

on September 5, 1918. Armstrong was detached from the Yankton on September 11, 1918. A letter came to Armstrong at 805 West State Street, Alliance, Ohio from the Treasury Department, Bureau of the Public Health Service dated September 17, 1918 ordering that upon completion of leave of absence granted, he was to proceed to Washington, D.C. and report to the Bureau (14). The letter contained transportation requests and authorization for expenses for carrying out the instructions.

On September 28, 1918 Surgeon General Rupert Blue (14) sent the following official order, “ Sir, Having reported at the Bureau in Washington, D.C. after detachment from the revenue cutter Seneca you are hereby directed to proceed to Boston, Massachusetts and report to Surgeon L. L. Lumsden at the State House for duty in connection with the control of the epidemic of influenza now prevailing at Fore River Shipyard, Massachusetts.

“ Your status while on this duty will be that of special temporary duty, and, in proceeding to points near Fore River, you will be allowed your transportation expenses in connection with the discharge of your duty, and an allowance of \$4 (EAB – Four!) per diem in lieu of subsistence. Respectfully.”

Thus began Armstrong’s career – chasing outbreaks of the 1918-1919 influenza pandemic in the United States and the assisting of state health authorities with local outbreaks of illness.

#### Notes – Initial Assignments

- 1) Williams, R.C., Chapter 9: Those who carry on, pp. 490-552.
- 2) Ibid. Pp. 490-491.

- 3) Ibid. p.493.
- 4) Ibid. p.516.
- 5) Microsoft, Encarta Encyclopedia, 2006.
- 6) Williams, R.C. p.100.
- 7) Ibid. p. 108.
- 8) Ibid. p.109.
- 9) Personnel orders among the Armstrong papers. Military orders in the Public Health Service during the early years were transmitted on plain official stationary to junior officers by superior officers or more frequently by the surgeon general.
- 10) Recorded in autobiography.
- 11) Among Armstrong personal papers.
- 12) USS Yankton, Schooner, originally named Penelope.  
<http://www.greatwhitefleet.org.yankton/oo/history.htm>.
- 13) Wyndom Miles, oral interview.
- 14) Among Armstrong personal papers.

## Influenza; Botulism

Upon reporting to the Bureau in Washington, D.C., his superiors discussed with Armstrong his future career interests in the Public Health Service. The Service was giving young officers returning from wartime sea duty with the Navy some choice in picking their new assignments. The choice was clinical duty in a Marine Hospital or participation in some of the ongoing field public health activities. At this time period the primary field activity was the study and control of the scattered outbreaks of influenza in the United States. Armstrong, whose prior training and experience had been oriented to clinical medicine, changed his career aspirations. He decided that he would rather concentrate his future professional activities in the field of public health where he could help the many, rather than treating individual patients where he might benefit only the few. Having made this career-determining decision, from which he did not deviate, Charles Armstrong embarked on his initial post-war assignments.

Armstrong's experiences during the influenza period have to be considered in the context of the Public Health Service's response to this devastating pandemic (1). His initial encounter with influenza was aboard the Coast Guard Cutter Seneca. The world wide pandemic was called the "Spanish Flu" after the area where the initial cases were noted. The public adapted the name from the Italian sobriquet "un influenza di freddo", an attempt to attribute its occurrence to cold climatic conditions. It was similar to many previous pandemics but was of extremely greater prevalence and associated with a frightening increase in morbidity and mortality. It was estimated that world wide 20 million influenza-related deaths occurred. In the United States there were millions of

cases and around 500,000 deaths. The very young, old and infirm patients were the most vulnerable to a fatal outcome, but, surprisingly, many apparently healthy young adults succumbed to the disease. The usual clinical manifestations were fever, chills, aching, weakness followed by dry cough, sore throat, nasal stuffiness and burning of the eyes. The excessive mortality was due to the super-imposition of severe influenza with viral or virulent bacterial pneumonias (often caused by the streptococcus or staphylococcus). According to Dr. Thomas L. Rivers, then a young medical officer stationed in September 1918 with the Army's Permanent Pneumonia Board at Camp Pike outside Little Rock, Arkansas (2): "The soldiers who suffered most of all were the big, white farmer boys from the Mid-West and Negro troops from rural Louisiana and Mississippi. While they were healthy enough, they just had no immunity. The scrawny fellows from the big city slums, by and large, escaped because they had acquired immunity before they got to camp."

In 1918, the virus of influenza had not been identified (1933), and vaccines and antibiotics were still 20-25 years in the future. The only treatment available, beside divine intervention, was rest, fluids, adequate nutrition, temperature and cough control and good nursing care. In a later "flu" epidemic in 1968, a local medical-science newspaper reporter, during a telephone interview, asked the author about the nature of illness caused by influenza. After a lengthy technical explanation, the reporter asked the author, "What is influenza really like"? The author's reply was, "Well, with influenza you think that you are going to die and afraid that you wont". This was the statement printed and emphasized in the newspaper report (3).

The United States Public Health Service became actively involved with measures to combat, control and study the influenza pandemic of 1918 (1). The PHS became aware through newspaper reports in the summer of 1918 and from official reports from overseas health departments of the prevalence of the so-called Spanish influenza in foreign countries. The Service also recognized that, because of the widespread prevalence of the epidemic, it would be impossible to prevent the occurrence of the disease in the United States. The epidemic actually appeared in three waves in the United States: early spring 1918, late summer 1918 and fall-winter 1918-1919.

Medical officers of the Service, as exemplified by Armstrong aboard the *Seneca*, were among the first to observe the early stages of pandemic influenza. These officers were attached to Coast Guard vessels, based on Gibraltar, performing convoy escort duty up the coast of Spain and across the Bay of Biscayne to England. They watched the beginning of the epidemic in Spain and its progression to England and France. The officers saw practically all ships of the entire British-American-Italian fleet tied up at one time or another in the harbor of Gibraltar with many crew members ill with influenza. This was as described by Armstrong in the previous chapter.

The medical officers, including Armstrong, found that the most effective measures to help the sick crewmen were to take temperatures of the entire crew company twice a day, to place at bed rest every one with even a fractional degree of temperature elevation, and to keep them at rest until they were fever-free for a full day. Medical quarantine officers were cautioned to be on alert for typical cases among crew, passengers and vessels entering the United States from European ports so that cases of influenza could be brought to the attention of local health officials.

Reports received by the Public Health Service in early 1918 indicated that influenza was occurring in New England. On September 18, 1918, Surgeon General Rupert Blue sent telegrams to all State Health Officers requesting information concerning the prevalence of the disease in their respective states. Replies to this request indicated that the disease was present in New England, along the Atlantic Coast as far as the Virginia Capes, and in a few foci in states east of the Mississippi River.

On September 26, 1918 the State Health Officer of Massachusetts requested aid from the Public Health Service because the disease was spreading very rapidly over the entire state, and he was unable to furnish physicians and nurses to the involved communities. This request prompted the September 28 letter (orders) from the Surgeon General to Armstrong dispatching him to Massachusetts and to the epidemic raging in the Fore River Ship Yard. The Surgeon General also sent a number of other medical officers immediately to Massachusetts for duty in cooperation with the State Health authorities.

A major problem in combating the epidemic nationwide was the lack of medical manpower, since many physicians and nurses were already serving in the Armed Forces. The Public Health Service, likewise, had limited availability of medically trained personnel. In addition, when the epidemic struck, there were no Federal funds to hire additional physicians, nurses and ancillary professionals to help the states. To alleviate the problem, the Congress, almost immediately, in the following resolution (1), appropriated \$1 million in an attempt to meet the need:

(Public Resolution No. 42 – 65<sup>th</sup> Congress)

(H.J. Res. 333)

Joint resolution to aid in combating “Spanish influenza” and other communicable diseases.

Resolved by the Senate and the House of Representatives of the United States in Congress assembled, That to enable the Public Health Service to combat and suppress “Spanish influenza” and other communicable diseases by aiding State and local boards of health or otherwise, including pay and allowances of medical and sanitary personnel, medical and hospital supplies, printing, clerical services, and rent in the District of Columbia and elsewhere, transportation, freight, and such other expenses as may be necessary there is appropriated, out of any money in the Treasury not otherwise appropriated, \$1,000,000 to be available until June 30, 1919.

Sec. 2. That the Secretary of War, the Secretary of the Navy, and the Secretary of the Treasury are authorized and directed, respectively, to utilize jointly the personnel and facilities of the Medical Department of the Army, the Medical Department of the Navy, and the Public Health Service, so far as possible, in aiding to combat and suppress the said diseases.

Approved October 1, 1918.

With additional funds now available, the next hurdle to be surmounted was to ferret out the needed personnel. The public health establishment appealed to the American Medical Association and other professional organizations to encourage their members to apply for duty with the Public Health Service in order to combat the epidemic. A significant bottleneck was finding adequate registered nurses many of who were already committed



to duty with the Armed Forces. Given the extent of the epidemic, it was impossible, generally, to provide enough physicians and nurses to treat individuals, but in areas where this could be accomplished, all personnel worked devotedly in treating the patients. “Probably the most important accomplishment was organization of the local resources in advance of the height of the epidemic. Plans were made for opening emergency hospitals as needed, volunteer nurses were organized, emergency kitchens were established, and, in this way, many communities were able to take care of themselves when the epidemic reached them” (4).

The volume of calls for assistance increased daily from all sections of the country, and the Public Health Service decided to appoint a Director of each state. In many instances the State Health Officer took on the position of Field Director and, in this capacity, directed the activities of Public Health Service personnel within his state. In other instances, an officer of the Service was detailed to cooperate with the State Health Officer in directing relief, and the PHS placed these officers on duty October 15, 1918. All requests for aid were funneled to the State Health Officer in charge and he made the judgment about how personnel and resources were to be allocated within the state.

Each state made daily telegraphic reports to the PHS Bureau of the progress of the epidemic and the need for assistance. In this way the PHS was able to maintain an overall picture of local needs and could determine where personnel could be sent to be of greatest use. “During the influenza epidemic, 64 commissioned officers, approximately one-third of the Corps, were assigned to full time influenza duty. Between October 1, 1918 and June 30, 1919, the PHS employed 1,085 additional physicians, 703 nurses and nurses’ aides and 328 clerks to deal with the epidemic. Many of these epidemic workers,

including Charles Armstrong, moved from state to state serving in as many as three areas”.

By December 1, 1918 the epidemic had reached the peak and had begun to subside. A second wave in the spring of 1919 did not reach the same degree of prevalence of the 1918 outbreak, but requests for help still came to the Service, and, unfortunately, many of the requests could not be honored. Also by February 15, 1919 the \$ 1 million dollars appropriated by Congress was exhausted, and little or no aid was available during the second wave of the epidemic.

The paper work associated with the epidemic was a problem because many of the recruited clerical help were unfamiliar with the arcane regulations for registering information and the forms for disbursing compensation to the newly hired medical and nursing personnel. Also, many of the regular clerical workers were stricken with influenza and unable to give assistance for long periods. Eventually all the pay vouchers were processed, and the funds were distributed in the proper amounts.

The suddenness and intensity of the epidemic and the thin availability of the Regular Corps of Commissioned Officers of the PHS prompted the establishment of the Reserve Corps of the PHS. After influenza became epidemic, the Congress passed the legislation establishing the Reserve Corps, but the authorization came too late to be of any value during the outbreak of 1918 (1). The Public Health Service, in cooperation and aid to the states, was able to accomplish much good in helping to alleviate some of the suffering of the affected communities despite limited resources, personnel and effective therapeutic or preventive measures.

During this chaotic period, Armstrong started his influenza-related activity with the trip to Fore River, Massachusetts in late September 1918. He performed whatever duties he was required to accomplish. On November 9, 1918 Surgeon General Rupert Blue (5) sent him a letter instructing him “to report to the Director, Hygienic Laboratory (Washington, D.C.) for duty in connection with investigations in regard to the prevention, etiology and treatment of influenza. On receipt of instructions from the Director, Hygienic Laboratory, you will proceed for this purpose to such places in the field as may be necessary.” It was apparently during this trip to the Hygienic Laboratory that he came under the tutelage of Dr. Wade Hampton Frost (6) from whom he learned the principles of epidemiology. Dr. Frost was one of the pioneers in the discipline of epidemiology whose lifelong work helped establish epidemiology as a distinct field of medical research. A 1903 medical alumnus of the University of Virginia, Dr. Frost (1880-1938) was a Surgeon (Major) in the USPHS from 1905 to 1929. In 1919, the Service assigned him as a resident lecturer to the new Johns Hopkins School of Hygiene and Public Health. In 1929 he resigned from the PHS in order to serve full time as Professor of Epidemiology at Johns Hopkins. From 1931 to 1934 he was the Dean of the School of Hygiene and Public Health. Dr. Frost was a pioneer in the study of water pollution. He also conducted important research in poliomyelitis, yellow fever, influenza, diphtheria and tuberculosis. Dr Frost taught and directed Armstrong’s work on influenza until Armstrong’s appointment as a USPHS Epidemiological Aide to the State health Officer of Ohio in 1919.

After Armstrong’s interlude at the Bureau in early November 1918, he maintained an active travel schedule to various outbreaks of influenza in scattered locales. These

included as determined by travel orders (5): Whitworth College, Brookhaven, Mississippi in November 1918, Baltimore, Maryland in December 1918 (followed by a 10 day leave of absence), and Springfield, Illinois in January 1919. His instructions January 18, 1919 for the Springfield, Illinois field study (5) were as follows: “Under authority of Bureau letters of November 9 and December 18, 1918 you are herewith instructed to proceed to Springfield, Illinois to confer with the Commissioner of Health of that State relative to the census of influenza in certain localities in Illinois to be undertaken by the State Department of Health.

“As the State Department of Health is undertaking to make its surveys uniform with those of the Public Health Service, you will consult with them in regard to coordinating all necessary details.

“Upon completion of this duty you will return to Baltimore to continue your duties there.

“Authority for your travel under these instructions is contained in the Bureau letters above cited. Respectfully, W.H. Frost, Surgeon in Charge” (5).

On February 17, 1919 (5) he received orders after completion of his duties in Baltimore to proceed to Dr. Frost’s office in Washington, D.C. for further temporary duty in connection with investigations of influenza. On March 8, 1919 Dr. Frost instructed Armstrong to proceed to LaPlata, Maryland and other localities in Charles County, Maryland for the purpose of collecting special data relative to the prevalence and mortality of influenza in that County (5). Upon completion of this duty he was to return to Dr. Frost’s office. If necessary, Armstrong was to return to Washington, D.C. from

time to time during the progress of the work for conference. Upon completion of his duties in LaPlata, he received about 3 weeks' leave in May and early June 1919.

Interspersed with Armstrong's frequent trips and occasional periods of leave were the valuable teaching sessions spent with Dr. Frost learning the rudiments of epidemiological investigation. In his autobiography (7), he credits Dr. Frost with stimulating his interest in the value of epidemiology in the study of infectious diseases, and Armstrong applied well the epidemiology lessons he learned in many of his future investigations.



Portrait of Dr. Charles Armstrong, age 33 years. Made by Bachrach and Company Washington, DC, in 1919. Courtesy of Mary Emma Armstrong.

In later years, Armstrong had an opportunity to reflect on some of the frenetic activity associated with the Public Health Service's attempt to compile statistics and to

keep track of the influenza outbreak of 1918 and 1919. In his oral autobiographical interview (8), he stated that a major statistical observation that the PHS tried to accumulate was the incidence of influenza among older patients and its relationship to excess mortality in the community. This statistic is a currently accurate method used by health authorities to chart outbreaks of influenza and to assess the outbreak's severity. Armstrong was of the opinion that the reporting of cases in 1918-1919 by the local and regional health officers was insufficiently refined and accurate for reporting reliably the occurrence and severity of outbreaks. Armstrong observed that local newspapers first reported information about outbreaks quickly and accurately suggesting that early reporting by the official health organizations required improvement. Epidemic information and reporting has improved and become highly refined over the years; this is exemplified by the current activities of the Public Health Service Centers for Disease Control and Prevention (CDC) and its publications, especially the Morbidity and Mortality Weekly Reports (MMWR).

After the completion of his leave in June 1919, Surgeon General Rupert Blue sent orders to Armstrong on July 1, 1919 (5) directing him to report to the Bureau in Washington, D.C. for a temporary period of about 10 days or 2 weeks for special duty preparatory to being detailed to Columbus, Ohio as Epidemiological Aide to assist the Health Officer of that State. At this particular time, the PHS was interested in improving the collection and reporting of statistics for communicable diseases, and it detailed young Commissioned Corps officers as epidemiological aides to many state health officers. During this period at the bureau, the preparation undoubtedly included intensive instruction supervised by Dr. W.H. Frost in the practices of epidemiology and the

collection of data in anticipation of the new assignment. On July 21, 1919 the Surgeon General sent additional orders to Armstrong (5):

“Having completed your course of instruction at the Bureau, you are directed to proceed to Columbus, Ohio for the purpose of assisting the Health Officer of Ohio in establishing an endemic index for the reportable diseases.

“In the establishment of this system you are authorized to travel whenever necessary to points within the state and whenever practicable to proceed to such points as may be necessary to assist in the prevention and control of communicable diseases. You will be allowed a per diem of \$4 in lieu of subsistence as provided by Section 13 of Public Act 161 approved August 1, 1914 for a period of not to exceed three months from the date of arrival at Columbus, after which time you will be allowed a per diem of \$4 in lieu of subsistence when absent from Columbus in the performance of official duty.

Respectfully”.

On arrival in Columbus, Ohio, Armstrong reported to the new State Health Officer, Dr. Finley. Armstrong described Dr. Finley as a very good, competent health officer to whom the State government gave wide latitude to enforce strict public health measures and to establish whatever facilities (e.g. safe water supplies) that would best serve to ensure the health of the citizens of Ohio. Rigid adherence to these principles apparently conflicted with the interests of the officials who appointed the health officers, and they refused to appoint Dr. Finley to a second term of office (8). Armstrong had a good relationship with Dr. Finley who gave him the chance to engage in several career-advancing field study opportunities. These studies resulted in Armstrong’s earliest publications that he believed



were instrumental in his assignment to the Hygienic Laboratory in Washington, D.C. in 1921.

## Botulism

The first study (9), culminating in Charles Armstrong's initial scientific manuscript, "Botulism from Eating Canned Ripe Olives", appeared December 19, 1919. The author's (EAB) first acquaintance with this study occurred in medical school bacteriology class in 1944 when the dynamic Professor, Dr. Alice B. Marston, described, in exquisite detail, the lethal potential of small amounts of ingested botulinum toxin. The author's re-acquaintance with the study occurred while reviewing the Armstrong bibliography.

Botulism (Latin – botulus – sausage; ismos – condition) is a neuro-paralytic (nerve involvement with paralysis) intoxication involving the central nervous system (usually brain stem and spinal cord) caused by the toxin (poison) produced by the anaerobic (grows without oxygen) spore-forming bacterium *Clostridia botulinum*. Eight different antigenic toxins can be produced by different strains of the organism; the most common are usually types A, B, or E. The organism is widespread in nature occurring in soils vegetables, marine sediments and the intestinal tracts of domestic animals. Botulism occurs most frequently from the ingestion of inadequately prepared food, less frequently from traumatic wounds (e.g. during wartime), or uncommonly as a condition known as infant botulism. The spores are heat resistant but the toxin is heat labile; temperatures of 80C (178F) for 30 minutes or 100C (212F) for 10 minutes render the toxin inactive. Improperly canned commercial or home-canned foods (fruits and vegetables) cause the

majority of outbreaks when anaerobic conditions and non-acid foods allow the germination of spores, growth of the vegetative forms of the bacterium and toxin production. The foods incriminated most frequently include meats, sausage and a variety of fruits and vegetables.

Clinical symptoms and signs include fatigue, weakness, dizziness, headache, and sore throat initially, followed by the nervous system manifestations of double vision, trouble speaking and swallowing, loss of voice, and descending muscle weakness. Death is usually from heart or respiratory failure. Treatment management is primarily the use of specific antitoxin, supportive treatment for breathing difficulties and meticulous nursing care. Antibiotics are used as adjuncts to destroy any residual vegetative forms of the bacterium.

Armstrong reviewed the knowledge up to 1919 of major outbreaks of botulism. In a footnote, he also described 5 deaths in Detroit, Michigan reported after his description of the Ohio outbreak. He indicated that the Ohio and Detroit outbreaks were both due to eating California packed fruits – ripe olives.

Armstrong described in detail (9) the outbreak of poisoning that developed in a group of people who were in attendance at a banquet held on the evening of August 23, 1919, at a country club near Canton, Ohio. About 200 people from Canton and the surrounding towns were present at the banquet. Following the dinner, 14 cases of poisoning occurred – 11 among guests and 3 among employees of the club. Five guests and 2 employees died. The guests who became ill were all members of a party given by Mrs. I.W.G. (who died) of Sebring, Ohio and had been served at a separate table, thereafter described in the

manuscript as the “Sebring table”. The two waiters who attended the table and the chef were also affected.

Following appropriate and accepted epidemiological practice, Armstrong described the menu of foods served at the banquet: cantelopes, turkey, turkey stuffing, tomatoes and mayonnaise, crackers, scalloped corn and pimentos, browned potatoes, green olives, celery and pickles, rolls, butter, ice cream, cake, water and coffee. The Sebring table received the above foods with the exception of the green olives, celery and pickles. In place of these foods, the waiters served the Sebring table ripe olives, chocolate candy, Newport creams, and candied almonds, all of which were furnished by the hostess.

Armstrong took a detailed food history from among the ill persons who ate at the Sebring table. He asked specifically about each food item eaten at the table. Suspicion fell almost immediately upon the ripe olives, furnished specifically by the hostess for her 18 guests, as the cause of the illness. The waiters for this table set the olives out in three serving dishes, placed at equal distances in the middle of a long rectangular table, separated by flower arrangements in vases. The guests at this long table, in this manner, had easy access to at least one dish containing the ripe olives. During the course of the dinner various diners, who tasted the olives, commented on peculiarities of the taste, odor and consistency of the olives with a variety of uncomplimentary terms. Memory refreshment occurred about the quantity of olives eaten by the various diners when suspicion arose that olives might have been the cause of the illness following the dinner. Of the 14 persons who became ill, all had eaten the olives. Some of the guests who did not become ill apparently tasted but did not eat the olives. There was a rough correlation among the 7 fatal cases between the hours elapsed from the dinner to death and the number of olives

eaten. One patient who ate 5 to 6 olives died in 54 hours. A woman who ate ½ olive died 171½ hours after the dinner. In the 7 non-fatal cases there was a correlation in declining illness severity with the ingestion of from 2 olives to 1 bite. Armstrong speculated that some variation in illness and death with the number of olives eaten occurred because one of the waiters serving the Sebring table washed two of the olive-containing serving dishes, but not the third, prior to putting the dishes on the table.

Among the waiters at the club, there was a custom of collecting the remaining delicacies after the diners had finished eating; the two waiters poisoned collected the left over olives and ate some of them. Later, the waiter who survived carried the olives to the chef with the request that he try one of them because they “didn’t taste right” to the waiter. The chef ate 2 olives and later died.

Armstrong provided the following epidemiological summary for this investigation (9):

“1. The ripe olives were known to have had a peculiar taste and color, and, in the light of the epidemiological data and circumstances under which the poisoning occurred, it did not seem possible to hold any other article of the menu to be the vehicle of the poisoning.

“2. The limitation of the poison to the diners of the Sebring table, to the waiters of this table and to the chef, is explained by the theory that the ripe olives were the poisoning agent.

“3. Fourteen of the of the 17 who ate or tasted the ripe olives were definitely ill.

“4. None were ill who did not eat the ripe olives.

“5. Severity of the illness in each case was, in general, proportionate to the number of olives eaten.

“6. The fact that some of the olives were washed before they were eaten and some were not, of our ignorance of the relative toxicity of different olives, of the effects of other articles of food or drink on the poisonous substance, and of individual immunity or susceptibility, together with numerous other factors of unknown effect, would seem to furnish various possibilities for explaining why some recovered after eating more ripe olives than others did who died”.

Armstrong reached the following epidemiological conclusions: The poison which caused the death of 7 persons and the illness of 7 others, under the circumstances described, was contained in a jar of ripe olives supplied by the hostess to her guests. He listed the various ways that a poison could have entered the jar; by deduction, he concluded that the poison in the olives must have been formed in the jar by the action of microorganisms.

Fortunately, 6 olives and a small amount of brine from the original jar were recovered; a waiter had placed them in a club ice chest until the investigators retrieved them for examination on September 3, 1919. Six olives and the brine were delivered to Dr. John G. Spenser of Cleveland, Ohio, a chemist, for examination. The olives were light brown in color, soft, macerated and had a putrid odor suggestive of feces. Dr. Spenser’s chemical examination showed “zero volatile, irritant, corrosive, alkaloidal, glucosidal or putrefactive poison”. A portion of the turkey served at the meal, also submitted to Dr. Spenser, as a control, for examination, gave entirely negative chemical and bacteriological findings.

The State Department of Health received 2 of the olives and about 5 milliliters (1/6 of an ounce) of the brine for study. Utilizing the facilities of the Health Department Laboratory, Armstrong and his co-authors, R.V. Strong, a bacteriologist and Ernest Scott,

Professor of Pathology, College of Medicine, Ohio State University performed investigations to determine the nature of the “poison” and the probable bacterial organism that produced it. Small amounts of brine or a suspension of olives proved lethal when injected into guinea pigs. A jar of olives of the same brand and shipment as those at the banquet furnished material for controlling these experiments. The control animals remained well. The test brine also proved fatal when fed to guinea pigs. Brine passed through bacterial filters regularly killed the animals. The same filtrate heated to 80C for 30 minutes proved to be harmless.

Armstrong and co-authors next tested the olives and brine for “anaerobic spore bearers”. They inoculated the test material into appropriate bacteriologic media, heated the mixture at 60C for 60 minutes, and incubated the mixture under anaerobic conditions at 37C and at room temperatures. Within 2 days the tubes at 37C showed evidence of bacterial growth, and the tubes at room temperatures showed growth in 5 days. Growth could be transferred from these initial tubes to subsequent tubes, and the organisms from initial tubes and transfer tubes were identical. The germ isolated showed the appearance, anaerobic growth, and biochemical reactions consistent with *Bacillus botulinus* (now *Clostridia botulinum*). “Sisco of the Harvard Laboratories” (9) confirmed the identification. Armstrong and associates mixed ripe unspoiled chopped olives in tubes along with brine of the same brand as the original jar adding no additional ingredients. They autoclaved these tubes at 15 pounds pressure for 30 minutes, cooled the tubes rapidly, inoculated the mixture with the test brine and grew the mixture under anaerobic conditions as before. After 3 days they detected growth as indicated by gas formation and bubbles accumulating in the ground olives at the bottom of the tubes. The bacterium

growing in the tubes produced abundant spores and lethal toxin. In this experiment the investigators showed that the olives could support growth of the organism and the production of botulinum toxin.

Armstrong suspected that alcohol might possess the property of destroying botulinum toxin. The epidemiological data that supported this suspicion was the recovery of two patients after eating one or two olives. These two patients had partaken alcoholic drinks more or less freely during the evening. By mixing various dilutions of toxin with ½ milliliter of 95% alcohol and injecting the mixture into guinea pigs, Armstrong found that he could protect guinea pigs against 20 times the lethal dose of raw toxin.

Armstrong also wanted to test the immunological properties of blood from persons who had had previous exposure to botulinum toxin. He collected blood from several of the recovered patients. Comparing blood from these patients with blood from normal controls, he found that the controls contained approximately the same quantity of antibodies that could agglutinate the bacillus as the blood from the patients. He also found that blood obtained from recovered patients did not neutralize the lethal effect of toxin. From other studies that he conducted, Armstrong concluded intuitively that illness and death occurred from preformed ingested toxin and not by new toxin formation within the gastrointestinal tract by ingested organisms. It was possible that the ingested toxin, though lethal, did not occur in sufficient antigenic quantity to stimulate a strong immune response. These findings followed the conclusions of other previous investigators (9) cited by Armstrong in the manuscript.

Armstrong also examined some of the patients clinically and tabulated a summary of physical signs and symptoms. Pathology examination in the patients and guinea pigs was

consistent with observations published previously in the medical literature by other authors. He stated that the diagnosis in a single or index case might present difficulties since initial signs and symptoms could mimic other medical conditions. The occurrence of other cases in an outbreak helps to clarify the diagnosis. Mortality in outbreaks has varied and occasionally reached 100 per cent. The prognosis, according to Armstrong, was that that patients who escaped death could expect complete recovery, but it might require weeks, or even months, in the more serious cases. During this recovery period, bronchopneumonia was the most feared complication. Weakness was the symptom that was slowest in disappearing from the survivors.

The mortality in 1919 was as high as formerly indicating the unsatisfactory status of the availability of specific treatment. Treatment, as one would expect in 1919, was largely symptomatic and empirical. Gastric lavage and induced emesis was used to remove residual offending food from the stomach. Purgatives and colonic irrigations were advocated. The therapeutic manuals also recommended strychnine to “improve the action of the of the damaged nervous system. Cardiac and other stimulants were to be used as indicated”. Emphasis was on the maintenance of adequate nutrition and fluid intake when possible. In 1919, treatment such as specific antitoxin, antibiotics, and nutritional and mechanical respiratory support for patients with botulism was not available. The employment of these modern therapeutic measures have helped decrease the mortality currently when the diagnosis is suspected or confirmed early in the course of illness. Occasionally, the diagnosis can be made, even in the absence of laboratory evidence of botulinum toxin in the blood or feces, especially, when the illness occurs in the midst of an outbreak of similar illnesses and a compatible epidemiological background.



Armstrong proposed some recommendations for the prevention of botulism. He wrote: “1). The ideal of prevention would be a process of canning which effectively kills all spore-bearing organisms. However, the great resistance of *Bacillus botulinus* (*Clostridia botulinum*) to heat or other agencies (as shown by Burke (9)) emphasizes the danger that a few spores may occasionally survive almost any process of canning. 2). Thorough cooking of all canned food before serving or sampling would render foods infected with *Bacillus botulinus* harmless in so far as the presence of preformed toxin is concerned. 3.) The rejection of canned food which show even minor changes of taste, odor or consistency. Several of the (above) patients ate of the olives even though they tasted ‘off.’” These recommendations are still applicable at the present time.

Armstrong concluded his publication with the following summary: “1). The epidemiological investigation pointed to the ripe olives as the vehicle of the poison. 2). The olives and the brine (in which they were canned) were found to be highly toxic for animals, both when fed and when injected. 3). The organism isolated from the olives and brine seemed, from its morphology, cultural characteristics, toxin formation and pathological lesions produced, to be a strain of *Bacillus botulinus*. 4). Antitoxin and agglutinins could not be demonstrated in the blood of recovering patients 45 days after the dinner. 5). Alcohol had the property of neutralizing the toxin when mixed in vitro. 6). It would seem that *Bacillus botulinus* did not produce its toxin under usual conditions in warm-blooded animals”.

This study, and the outstanding publication (9) resulting from it, is remarkable considering that Armstrong’s prior professional training consisted of just a medical school curriculum education, a truncated medical internship, wartime service treating

healthy young men aboard a Coast Guard cutter, chasing after influenza illness statistics for several months and a few weeks of instruction in epidemiology. In this initial manuscript, Armstrong demonstrated the qualities that would presage his future research activities. He possessed a keen intellect and exhibited enthusiastic intellectual curiosity. He was a careful observer, industrious, and paid meticulous attention to detail. He thought logically and could reason deductively with great skill. At this early stage in his career, he was already dedicated obsessively to strictly controlled, epidemiological observations and laboratory experimentation. He acquired comprehensive knowledge about the subject he was investigating including reviews of known information about the subject. He had the ability to collaborate seamlessly with his co-authors. He had a lucid writing style. Dr. William Hewitt (who introduced the author to Charles Armstrong) described his observations of Armstrong in the laboratory in the 1940's when Armstrong's reputation was recognized internationally. Hewitt said (10) that Armstrong "was not a 'flashy' worker at the laboratory bench; he did not publish an extensive bibliography, but each research paper represented a major scientific contribution". In the portion of the oral autobiographical interview, conducted by Wyndom Myles (8) describing the botulism incident, Charles Armstrong presented another aspect of his personality. He possessed a well-developed sense of humor. The following informal monologue by Armstrong, slightly modified, described some of the social aspects, anecdotal details and rumors associated with the outbreak: "The first event of any importance I had (participated in as an Epidemiological Aide to the State Health Officer) was in an outbreak of olive poisoning in Canton, Ohio. A lady had given a party to which she had invited some of the wealthy and most important people of the area. It was held in

a country club. I think there were 9(?) deaths and several sick who had recovered. I was sent to make a study of the epidemic. It was in the time of prohibition, and the rumor got out that it was the liquor – (that) it was wood alcohol. Since botulism dulls vision and gives speech difficulty and wood alcohol gives blindness, too, - so there was not much evidence (of the possibility of botulism initially). There was also a nasty rumor that got started that Colonel Rybreck, who was a military man was there and he died; and that Mrs. Garrison (the hostess) was in love with him, but she was married and couldn't get him so she poisoned him. Well, I went over and began to review the patients. Many of them were from Alliance and Salem, and I stayed at home (in Alliance). The newspapers did not know where to reach me so I wasn't hindered or bothered by them too much, I made a thorough study, I thought, and wrote up the report, and everything pointed to olives. The olive people from California sent their head lawyer in to see Dr. A.W. Freeman (State Health Commissioner) and he sent for me; the lawyer had a suit of \$100,000 damages for this (botulism) publication. Dr. Freeman listened to him (He had a habit of blowing smoke rings.), he was a master of blowing smoke, just kept blowing them, and blew one around the ink well. He kept this up and when the lawyer got through, he (Dr, Freeman) handed him this report and said, 'Read that'. (The lawyer had not read the report previously.) The lawyer read the report, asked 2 or 3 questions and gave up the idea of suing us. The outcome was (that) the company spent a half-million to revamp the whole process of canning, and hired a man by the name of Meyer (possibly Dr. Karl F. Meyer, a famous California microbiologist and botulism expert associated with the Medical School, University of California San Francisco) to do the work for them, and there never was a case of botulism due to olives since that time. That worked

well'. The foregoing is a very modest account of a major accomplishment by Charles Armstrong in his initial excursion into infectious disease investigation.

### Influenza on Kelleys Island

Armstrong supervised the study of another outbreak in Ohio that was a model of the application of epidemiological methods to the investigation of infectious disease outbreaks in an isolated community (11). The performance of this study was an additional factor prompting the invitation to his assignment to the Hygienic Laboratory in Washington, D.C. Influenza became epidemic again in parts of the United States in early 1920. On February 4, 1920 Acting Surgeon General J. C. Perry (5) sent Armstrong c/o State health Officer, Columbus, Ohio the following order: "Sir, Bureau telegram of January 30, 1920 as follows is hereby confirmed. 'Proceed Washington reporting to Frost for influenza investigations'! In accordance with the above telegram you will proceed to Washington, D.C., reporting to Surgeon W.H. Frost at the Bureau for temporary duty in connection with studies and investigations of influenza. Etc ---." The return to Washington, D.C. was to attend the conference of Public Health Service officers in February 1920 for discussion of the desirability of making a series of intensive epidemiological studies of influenza in rural communities. The conference decided that the epidemiological aides in the various states should undertake such studies as opportunities might present. On the recommendation of State Health Commissioner, Dr. A.W. Freeman, the conference selected Kelleys Island, Ohio for making a study because of its exceptional isolation and because of the severity of the 1920 influenza epidemic

that had been occurring there. Despite the small size of the population, Armstrong realized that he would need additional professional help to carry out the detailed investigation required to study the outbreak adequately. He received the assistance of Ross Hopkins, Assistant Epidemiologist, Ohio State Department of Health who was a recent graduate of the new Johns Hopkins University School of Hygiene and Public Health.

Armstrong introduced the report with descriptions of the community's geography, demography, and general features of the community. Kelleys Island, a political subdivision of Erie County, Ohio is located entirely in Lake Erie, about 12 miles north of Sandusky, 5 miles from Lakeside and about the same distance from Put-in-Bay. The island has an area of about 2000 acres, is of limestone formation, and rises only a few feet above the level of Lake Erie.

During the influenza epidemic of January and February 1920 there were 689 persons upon the island, all of who were white (Caucasians). The Kelley Island Lime and Transport Company operated a limestone quarry and crusher on the island, employing from 100 to 300 men, - the smaller number being employed during the winter when the lake shipping traffic was impossible. Grape growing, peach culture and fishing were the other chief occupations on the island. From the nature of the industries it was apparent that there was a demand for labor during the late spring, summer and fall months. This demand was met by the influx of many people each spring who found employment, for the most part, in the quarries, and who returned to the mainland at the approach of the closed season for lake shipping navigation. The winter population, however, during the 1918 and 1920 outbreaks was composed almost entirely of established families who had

lived on the island for several years and thus constituted a community whose members were almost universally acquainted with one another – a condition of some advantage, perhaps, in tracing exposure, contacts and other epidemiological relationships.

Armstrong described the following general considerations about Kelleys Island. Housing conditions on the island were good, the homes were well separated, of better than average construction, and the number of houses was far in excess of the requirements of the winter population. During the winter months, communications with the mainland was limited; crossing over (the lake) at this time of year was not only difficult, but dangerous as well. Mail was delivered to the island daily (in season), conditions permitting, by carriers who resided on the island and who, during the winter months, carried the mail between the island and Lakeside, a summer resort that was almost entirely deserted in winter. The island possessed no public water supply, sewer system, theater, moving-picture theater, restaurant, village pump, streetcars, or other means of public conveyance. One central school for both grammar and high school pupils, one church conducting worship regularly during the winter of 1918 and 1920, and another holding services at intervals, 5 general stores, a butcher shop, a confectionary parlor, two pool rooms, and a post office afforded possible places of contact for the general public. Ice boating, sleigh riding, ice fishing, dancing and parties were the chief winter amusements of the younger people.

The epidemic of 1920, according to Armstrong, began sharply on January 24, reached a peak on January 31, and then fell somewhat less sharply until February 16 when new cases practically ceased to appear. Tabulation of the incidence of cases yielded a sharply rising double-peaked distribution curve with a more gradual fall off. The study began on

February 19, 1920 and the investigators carried it to completion as rapidly as they could visit the families and secure the desired information.

Upon arrival at the island, Armstrong told the assembled inhabitants the purpose of the visit, and he requested the islanders to remember, or to mark upon their calendars, the dates on which various members of their households became ill. The dates of onset as secured in the household canvas were checked, as far as possible, against the school records and the time sheets of the Kelley Island Lime and Transport Company; these records were kindly placed at the disposal of Armstrong and Hopkins for this purpose. These checks together with the cross checks secured through contact, histories, and other sources between individuals rendered Armstrong and Hopkins quite confident of the accuracy of their data.

The authors, wholly conducting the house-to-house survey by themselves, began on February 19, completed the survey on March 7, and secured (obtained) a record of every person on the island. They completed in 7 days a re-survey, begun on March 21, for the purpose of locating new or recurrent cases. Following the recent conference with epidemiological aides from several states, referred to previously, Surgeon W.H. Frost, of the USPHS, had prepared special forms for use in recording epidemiological data.

Armstrong and Hopkins used these new forms in gathering the information during their survey. They used Form I to collect the household record, general sanitary conditions and similar information; they used Form II to obtain an individual record of contact and symptoms of illness for each member of the household. In the 1920 epidemic on Kelleys Island, they based the diagnosis of influenza in individuals primarily on clinical illness, exposure to known cases and the realization that epidemics were occurring throughout

the country. Laboratory confirmation was not available; influenza virus was not cultivated in animal hosts until 1933 (12). A retrospective history of individual illness in the 1918 outbreak on the island served as the basis for suspicion of prior experience with influenza. Control measures in 1918, such as restricting gatherings and group activities, were not invoked in 1920 because of the loss of public health machinery occasioned by an interim change in Ohio legislation (13) (Ohio Griswold Act). The attack rate in 1920 was higher than in 1918, possibly due to the lack of suggestions for restricting the congregation of large groups during the epidemic.

The attack rate among the people on the island during the course of the 1920 epidemic was 53.5 per cent – 369 persons affected among the population of 689 people. There were two fatalities including the island's only physician. In January communication with the Ohio shore became more difficult. Formation of ice in early January hampered travel by boat, and, later in the month, shore to island travel could occur only when the ice thickened to support the weight of people and finally automobiles. The island was effectively isolated except for occasional persons crossing the ice in late January and February. Sporadic "typical" cases occurred in early January – on the 3<sup>rd</sup> and 12<sup>th</sup>. With the appearance of illness in the patient on January 24, the epidemic exploded rapidly. The authors found that the school was a major source for the dissemination of infection. Influenza spread rapidly among the students who brought illness home to their families. Graphs constructed by the authors showed a peak for the incidence of illness in the students, followed by a second peak a few days later representing the incidence in non-school attending family members. The incidence of illness in students decreased when the school was finally shut down on January 30.



Various parties and social gatherings occurred during the epidemic attended by variable numbers of persons some of who attended more than one gathering. The largest was on January 29 when 30 people attended a masquerade dance. The attack rate in this group was 77 per cent. The authors were uncertain about the contribution of these gatherings to the attack rates since many of the attendees at these events were exposed to multiple potential sources of infection in the community.

The authors evaluated other possible sources or factors contributing to the spread of the infection including milk, water, insects, crowding, economic status, housing conditions, and general sanitation. These factors did not appear to influence the acquisition of illness. A factor that they thought did influence the incidence of infection was immunity acquired during the earlier epidemic of 1918. Of the 136 cases who were ill in 1918, there were 27 re-attacked in 1920, or an attack rate of 19.8 per cent for this group; this contrasts with an attack rate of 62.4 per cent in the group of population not affected in 1918. The authors postulated that this difference indicated the presence of a relative but not absolute immunity some 15 months following the previous infection. They cited other studies in the published medical literature (11) that demonstrated similar findings.

After tabulating the detailed data on the population of 689 persons present on Kelleys Island during the 1920 influenza epidemic, the authors provided the following summary:

- 1). The public school, which remained in session without medical supervision of any kind during the early portion of the 1920 epidemic, served as a center for the spread of influenza upon the island. They did not mean to infer that prompt closure of this school would have prevented the 1920 epidemic, but it did seem probable that it would have delayed it.

- 2). It seemed probable that the measures of suppression as applied during the epidemic of 1918 were partially successful at Kelleys Island, where, the authors admitted, conditions were rather ideal for such procedure.
- 3). Milk and water had no apparent relation to the spread of influenza upon the island in 1920.
- 4). The apparent influence of crowding, housing conditions, economic status and general sanitation seems to have been exerted in opposite directions during the two epidemics (1918 and 1920).
- 5). The incubation period most frequently observed appeared to have been from 1 to 4 days.
- 6). A relative immunity seemed to be apparent 15 months following the 1918 epidemic. Armstrong and his associate, Ross Hopkins, thus using a strictly epidemiological approach without laboratory support, were able to trace the course of an influenza epidemic in an isolated community and derive meaningful conclusions. It is apparent that they accumulated massive amounts of data from the 689 persons with which to construct the charts, tables and maps that appeared in the manuscript. In the 1920's, this accumulation of data represented a labor-intensive effort since the authors did not have the benefit of calculating machines or of late 20<sup>th</sup> century computers. In recording the data for tabulation, they might have had available punch cards that could be manipulated by hand with a thin metal stylus and a special type of punch. The cards were about 8 or more inches square with a double row of perforations on each side. A master index card contained the key to the data that was being studied. The punch could remove one or two perforations depending on the depth of the cut, and the removal of these perforations

would allow the recording of two separate items of data. A separate card would be used to record data on one individual in a study. To examine a specific item of data, a group of cards would be stacked together upright, and the stylus would be passed through the perforations or punched-out areas representing the data. Since the perforations had been punched out to record the data, the stylus would lift out of the stack the cards that were negative for the data. The cards not lifted out could then be counted to get the numbers for the specific data information. The major time consuming task was recording or punching the data into the cards. Research studies generating large amounts of data used this system or variations of the system until the advent of mechanical and electronic methods of calculation.

In the autobiographical interview with Wyndom Miles (8), Armstrong had some interesting reminiscences about his experiences while doing the study: “Another opportunity I had was an epidemic of influenza in 1920 in Kelleys Island. (Ohio). It was the second wave of the epidemic (after 1918); they had pretty much escaped the first one. It was an isolated place and we thought that was a place to make a thorough study. I was sent up there and started in. I saw that it was going to be more of a job than one man could handle, so I asked for an assistant. They [perhaps the Ohio State Health Department?] sent Ross Hopkins, one of the first graduates of Hopkins Medical School (JHU School of Hygiene and Public Health). He was a very good worker. When I went out (to the island), I went in a truck loaded with sugar, and it was very cold weather. We went out over the ice. The driver suggested I not bundle up too much and sit on the back of the truck. When we came to a crack in the ice, the driver had 2 big planks which we’d lay across the cracks and drive over. The day Hopkins came out, there was some thawing

of the ice. He hired a boy who had an iceboat to bring him across, but they fell through the ice. Hopkins crawled out of the water, and he was rushed to the hotel, got some warm clothes. When we [?] got word of what happened, we and some of the islanders decided on a celebration. They had a bottle for the celebration. Hopkins, I suppose, never had a drink of whisky in his life. He poured out a tall glass of the stuff. The islanders thought he was going to finish it, but after a sip (an undetermined amount), Hopkins settled down (into peaceful oblivion) much to the amusement of the assembled revelers.

“Hopkins was a great help. We made our study and prepared a thorough report. The first case was a man who lived by himself. He had no contact with anybody on the island except that he received something from his mother and we thought some of that had become contaminated. About this time a man by the name of Nelson Dry [?] had a party, a dance and nearly all on the island was invited. Within 3 days we began to see cases all over the island. We asked the first case if he was at the dance, he was; did he dance with a certain girl, he had; we traced practically every case back to this one man. We could also trace the secondary cases, and it became a very common thing and gave us information as to incubation period and was as an elucidating epidemic as had occurred. [EAB – Armstrong’s memory many years after the events occurred do not quite coincide with his published account of the epidemic, but the memories represent major features of the epidemic that were of significance to him.] That kind of stirred up interest in my work, and I was invited to come to the Hygienic Laboratory”.

Charles Armstrong, following the investigations of the botulism outbreak and the 1920 influenza outbreak on Kelleys Island, had indeed laid a solid scientific foundation for

himself that warranted the Public Health Service's decision for stationing him at the Hygienic Laboratory.

#### Notes – Influenza, Botulism

- 1) Williams, R.C. Discussion of Public Health Service's involvement with the 1918 Influenza Pandemic contained in pp.167, 546, 548, 597-602.
- 2) Benison, Saul, 1967 *Tom Rivers. Reflections on a Life in Medicine and Science.* An Oral History Memoir. The M. I. T. Press, Massachusetts Institute of Technology, Vail-Ballou Press, Binghamton, New York. Pp.58-59. Herewith referred to as "Rivers."
- 3) The Washington Post December 15, 1969.
- 4) Williams R.C. Ibid. p.600.
- 5) Personnel orders among the Armstrong papers.
- 6) Wade Hampton Frost. Websites University of Virginia and Johns Hopkins School of Hygiene and Public Health; NIAID Intramural Contributions, p. 35.
- 7) Armstrong autobiographical notes.
- 8) Wyndom Miles, oral interview.
- 9) Armstrong, C., Story, R.V., and Scott, E., December 19, 1919. Botulism from eating canned ripe olives. *Public Health Reports* 34:2877-2905.
- 10) William L. Hewitt, personal communication to the author.
- 11) Armstrong, C. and Hopkins, R. July 22, 1921, An epidemiologic study of the 1920 epidemic of influenza in an isolated rural community. *Public Health Reports* 36:1671-1702.

12) Horsfall, F.L., Jr. and Tamm, I., 1965 *Viral and Rickettsial Diseases of Man*, Fourth Edition, J.P. Lippincott Company, Philadelphia, Montreal. Chapter on influenza viruses p.689 written by Thomas Francis, Jr. et al. Hereafter referred to as “Horsfall.”

13) State of Ohio Griswold Act of 1920.

## Typhus, Dengue, “Devil’s Grip”

Charles Armstrong reported to the Hygienic Laboratory (1) following the completion of the study of the influenza epidemic on Kelley’s Island. He embarked on a career typical of many of his illustrious predecessors and contemporaries. He combined research at the laboratory bench alternating as necessary with expeditions into the field to study local epidemics. He started his work at the North Laboratory, the structure located at 25<sup>th</sup> and E Streets NW Washington, DC, often called popularly “the Red House on the Hill.” This research laboratory, opened in 1904 with a staff of 13 persons, shared a site with the United States Naval Hospital, and the shared site had the designation as Government Reservation No. 4 on the original Pierre L’Enfant design for Washington. The Laboratory focused initially on commercially produced serums and vaccines (then in their infancy) for licensing. The Hygienic Laboratory researchers also investigated and helped control epidemics of yellow fever, typhus, trachoma and bubonic plague for which in the early 20<sup>th</sup> century effective vaccines and antibiotics were not available.

As noted previously (1), the Hygienic Laboratory was the embryonic progenitor of the 20<sup>th</sup> and 21<sup>st</sup> century National Institutes of Health. The Division of Infectious Diseases, later the Laboratory of Infectious Diseases, NIAID, was the direct lineal descendant of the Hygienic Laboratory. Some of the renowned and accomplished predecessors of Armstrong were the Directors, Drs. Joseph J. Kinyoun, Milton J. Rosenau, John F. Anderson, and George W. McCoy. Other distinguished members of the laboratory were Drs. Charles W. Stiles and Wade Hampton Frost. Dr. McCoy and Dr. Joseph Goldberger preceded and were contemporary with Armstrong. Some of his

primary contemporary associates included Drs. Edward Francis, Alice Evans, Margaret Pittman, James P. Leake, and Sara Branham. For the accomplishments of these physicians and scientists, the reader is referred to Williams (1), Harden (1), and *NIAID Intramural Contributions* (1). Charles Armstrong began his career in the Hygienic Laboratory primarily with several field epidemiological studies.

Typhus Fever on the San Juan Indian Reservation, 1920 and 1921 (2).

The organism, *Rickettsia provazekii*, causes epidemic typhus (3). *Rickettsia* are small, obligate (need living cells to grow), intracellular, gram negative (take basic dyes) pathogens, held back by the usual bacterial filters, and readily seen under the microscope when prepared by special stains. They require an insect vector to infect their usual hosts. Epidemic typhus is spread to humans by the feces of infected body lice, either by rubbing into the abraded skin or by aerosol into mucous membranes. Lice infect the human population by louse transfer from person to person. Typhus epidemics have been recognized for millennia, and usually occur with major population upheavals such as wars, famine, floods, and other natural disasters. Hans Zinsser's book, *Rats, Lice and History* (4), provides a historical perspective of the human worldwide experience with typhus and bubonic plague. Typhus is a serious febrile disease associated with confusion, characteristic rash that spreads from the trunk to the extremities, and high mortality if untreated. The advent of the tetracycline and chloramphenicol antibiotics provided highly effective treatment and resulted in a marked reduction of mortality and morbidity.

The classical methods of prevention and control involved the destruction of bodies and clothing infested lice by rather cumbersome and labor intensive methods.



During World War II, effective louse control of the epidemics in the Mediterranean Theatre was achieved by the use of the chemical insecticide DDT (dichlorodiphenyltrichloroethane). During the outbreaks, the Armed Forces Medical Services sprayed large numbers of the populations at risk by periodic liberal application of DDT into the peoples' clothing using hand-operated dusters. This procedure gradually eradicated the incidence of infection along with whatever measures of personal hygiene that could be accomplished.

Unfortunately, the lice became gradually resistant to DDT. DDT also tended to accumulate in the tissues of living creatures resulting in adverse health effects. In 1962, Rachel L. Carson, in her book "Silent Spring" (5), described the adverse effects on the regional ecology of the environment caused by the widespread use of chemical insecticides. This was one of the influences that led to the banning of DDT use in the United States in 1972. Currently, other insecticides (malathion 1% and temafos [Abate] 2%) are effective for short-term use.

It is interesting to compare the methods described by Armstrong in controlling the epidemic on the reservation where his group was dealing with an isolated, widely scattered population in a predominantly semi-desert environment. Case finding was challenging, and environmental and cultural factors had to be appreciated in order to accomplish successful control.

During the latter months of 1920 and during the first half of 1921, 63 cases of typhus with 27 deaths (@ 43% mortality) occurred on the San Juan Reservation. The reservation comprising almost 6,000 (5,884) square miles lies in the 4-state corner area of New Mexico, Arizona, Utah and Colorado. The area, as described, was primarily semi-

desert which, however, at the time supported a scanty growth of grass sufficient to maintain sheep. The scarce availability of water accounted for the backward and impoverished condition of the native population of about 7,000 (slightly more than one person per square mile). With the exception of a few Government employees and traders, the inhabitants were Navajo Indians (6).

As described by Armstrong in 1922 (2): “ The Navajo is nomadic in his habits and never lives in villages. These habits are imposed on him by the necessity of supplying his sheep with fresh pasture and water and of keeping them away from his neighbor’s flocks. His abode, or “hogan,” is a primitive structure, ranging from a mere shelter of cedar boughs in summer to a log building covered with earth for winter use. The hogan is usually crowded, filthy and unhygienic since the Indians lack knowledge of even the most primitive rules of sanitation. Owing to the scarcity of water for domestic purposes, bathing is uncommon and quite unknown to many. Left to themselves, the Indians of San Juan Reservation are 90 to 100 percent infested with vermin, usually both head and body lice being found.”

The origin of the epidemic in 1920 was a subject of speculation. The region, situated between Mexico and the mining areas of Utah and Colorado at the time, may have served as a pathway for itinerant laborers, some of whom may have carried the infection from Mexico where typhus was endemic. Another possibility may have been occasional Navajos who may have wandered beyond the reservation boundary and been exposed to persons harboring infected body lice. On returning to the reservation, these wanderers may have brought typhus back to the reservation.

Agency and missionary physicians variously diagnosed cases occurring prior to May 1921 as severe influenza, “black measles” or typhoid fever. Drs. Waller and Tappan of the United States Public Health Service (USPHS) correctly identified the epidemic as typhus in May. They based their diagnosis on the sudden onset, the characteristic fever, the mottled and petechial (small red spots) eruption appearing on the fifth to the seventh day of the disease, the profound stupor, the foul condition of the mouth, the recovery by crisis (sudden drop in temperature and clinical improvement) in many cases, the age distribution of the fatal cases (very young and very old) and control of the disease by destruction of the louse infestation in exposed persons. “Dr. John G. Griffin, the Agency Physician at Shiprock, New Mexico, and Dr. George H. Davis, the medical missionary at Red Rock, probably died of the disease, each believing, however, that he had influenza” (2).

Inasmuch as the Navajo at that time had no accurate method of recording time according to the Gregorian calendar, the exact onset of the earliest cases was difficult to establish. Cases probably began occurring around November 1920 and followed at intervals throughout December 1920, January, February, March, April, May and June 1921. Infection tended to occur in three main foci: River Agency, Red Rock and Tosito located at 30-35 mile intervals approximately from each other at the apices of an equilateral triangle in the reservation.

The first known case of typhus occurred in the Red Rock district involving a 55-year old “medicine man.” Early in November he went to Farmington, New Mexico where he “sang” over a patient and was away about one week. Three or four days after his return home he became ill and died on December 10, 1920. Before his death, at intervals,

other family members of the “medicine man”, including his youngest daughter, aged 16, followed by his oldest daughter, aged 20, his oldest son, aged 23, the next oldest son, aged 21 and his widow, all became ill. A 4-year old son escaped illness. The onset of these illnesses in the family probably occurred in November, December and January.

During the illness of the first case (the “medicine man”), the family hosted the customary “sing.” A brother-in-law of this case and his wife attended and remained throughout the ceremony, probably 15 days. The husband became ill 3 days after their return to Shipwreck, New Mexico in December. He died January 10, 1921. From the original episode, the disease spread to a total of 63 known cases with 27 deaths. Spread from these earlier cases was usually traced to the association with “sings.” The last case developed June 13, 1921, and the last death occurred on June 27, 1921.

The chronology of the development of cases was estimated to have occurred as follows: November, 1; December, 6; January, 8; February, 2; March, 3; April, 21; May, 10; June 12 for a total of 63. The chronology of deaths as determined by Agency records occurred as follows: December, 2; January, 4; February, 2; March, 2; April, 2; May, 11 and June, 4 for a total of 27. Thirty-seven males were involved with 19 deaths (51.4%), and 26 females were involved with 8 deaths (30.8%) for an overall mortality rate of 42.8 percent. The cases occurred unevenly in the three epidemic locales.

#### The Eradication Campaign.

Several factors helped to limit the extent of the epidemic. The Navajo families were separated widely from one another, living in groups of one to three hogans often many miles from their nearest neighbors. The Navajos customarily did a limited amount

of visiting, usually confined to members of their own clan. In addition, by the time the epidemic had reached the stage where it might have been expected to spread rapidly, the arrival of spring and warm weather had its usual limiting effect on the spread of typhus. Despite these favorable circumstances, however, there were many obstacles to surmount in eradicating the disease and controlling the epidemic. Some of these circumstances include: The almost complete absence on the reservation of equipment to combat the lice; the distance from markets; the scattered and constantly changing locations of the Navajos' dwellings, with the attendant difficulty in locating cases; the absence of roads; the high percentage of louse infestations among the locals; the scarcity of available water and fuel; the complete ignorance of the natives with respect to the spread of the disease; and the natural fear and superstition which they held toward any new procedures, such as bathing, together with the tendency to conceal cases because of these fears. Fear of the unknown was also a major factor in concealing this information from the personnel dedicated to eradicating the disease.

On June 24, 1921, because of problems of interstate quarantine involved, the Office (now Bureau) of Indian Affairs, upon recommendation of DR. R.E.L. Newberne, Chief Medical Supervisor for that Office, requested the USPHS to assume full control of the situation. The Office of Indian Affairs and the Chief Medical Supervisor continued their close and efficient cooperation under the new arrangement.

Dr. Armstrong arrived at the epidemic locale on May 31, 1921. The other physicians on the scene included Dr. Newberne, Dr. J.S. Perkins, Special Physician of the Indian Service, and Dr. J.K. Kennedy, the Agency physician who had temporarily replaced Dr.

Griffin who had succumbed earlier to typhus. The USPHS physicians, Drs. Waller and Tappan who had diagnosed the outbreak, remained to act in an advisory capacity. Prior to Armstrong's arrival Dr. Newberne had begun improvising delousing operations. The initial equipment consisted of a few tubs, 300 gallons of a distillate consisting of 50% coal oil (kerosene) and 50% gasoline, a barrel of vinegar and one tent. The delousing process consisted of stripping and painting the individuals with distillate, and, either dipping the clothing in the distillate or boiling it. The vinegar mixed with the distillate was used on the heads to assist in loosening nits.

The process was crude and unpleasant for many of the Navajo since headaches and dizziness frequently followed the distillate baths. Skin irritation in the form of blisters occurred commonly if the subjects dressed before the distillate evaporated from the clothing. This method deloused about 700 to 1,000 Navajo before more humane methods were adapted with the availability of suitable equipment.

While waiting for the construction of more efficient and more humane delousing equipment and methods, the team directed its attention to educating the Navajos about the nature of the disease, and the isolation and treatment of cases. Through the reservation police and trading posts, the team summoned, at regular times, inhabitants of the infected areas to gather for instruction regarding the "new sickness." The inhabitants gathered together willingly in well attended meetings. Inasmuch as the reservation residents did not grasp the scientific basis of the infection, the team appealed to their prejudices by telling them that the lice imported from hated Mexico caused the disease. At the meetings the team instructed the residents about the benefits of bathing, the frequent use of boiling water for killing lice on clothing and the use of coal oil (kerosene). The team also

instructed them to place dirty pelts, skins and bedding out in the intense daytime sunshine of the elevated reservation plateau (about 6,000 feet) in hopes that this might have a destructive effect on the infested objects. The team explained the dangers of spreading the disease through the medium of the “sings.” Since the Navajo dreaded being deprived of their local healers, the team allowed the “sings” to continue but only under the following conditions: the medicine man had to go singly; he could not permit friends and neighbors to collect; the singer had to be free of vermin and could go only after the patient, clothing and bedding had been deloused; the singer also had to be deloused before leaving the premises or mingling with other households. The medicine men cooperated fully with this approach, and none of them developed typhus following implementation of the plan. Additionally, the adoption of this approach resulted in cessation of new typhus cases that could be attributed to the “sings.”

Prior to the availability of improvised general delousing equipment (since the team found it impossible to purchase suitable equipment in the available markets), the team commenced delousing individual cases at once as soon as a diagnosis was made. The patient was bathed in a nicotine sulfate 1:1,000 solution. Clothing and bedding were either boiled or treated with nicotine sulfate or distillate. The team also deloused other members of the family as well as inhabitants of any nearby neighboring hogans. The team repeated delousing at intervals of not more than six days. In the absence of sufficient time and official personnel, the team entrusted local attendants to perform repeat delousing following the first. The team did not have the means to delouse the hogans. The clean Army tents, that the team made attempts to request, did not arrive until well after the epidemic emergency had passed.

The team improvised isolation of cases. Only three patients were isolated in an emergency hospital opened in Shipwreck, New Mexico. The team abandoned case isolation because of the difficulty of transporting patients to the facility and because the patients and families objected to the procedure. The team isolated subsequent cases in their own hogans with only a single attendant to look after them; other family members sought temporary shelter elsewhere until the danger of contagion had diminished. General delousing of the reservation population began after the team decided on specifications for the construction and purchase of improvised equipment mounted on a small truck. The components of the assembled apparatus included the truck, a 3-horsepower boiler, a 400-gallon tank for bathing water, and 2 steam tanks for sterilizing the clothes, pumps, spray baths and three tents. The general delousing operations began July 9, 1921.

The delousing occurred by districts – 5 in number. Prior to going into a district, local mounted police rode out to notify the people that delousing would begin on a certain day at a specified location. They instructed the people that they should come and bring their bedding, quilts, blankets, clothing and other personal possessions. One visit by guards usually sufficed, but if any intended candidates for delousing failed to appear, the guards had instructions to pay a second visit and to bring in the laggards. When the Indians arrived, the attendants instructed them to deliver their blankets, and other articles that would not be injured by steaming, to the steam sterilizers. There, these articles were subjected to live steam for from 25 to 30 minutes. While this steaming was occurring, the women took their pelts to the tubs where they washed them in a solution of nicotine sulfate (40% black leaf used in dipping sheep) 1:1,000 dilution in alkaline water kept at



temperature 100F or above, following which the articles were allowed to dry. The applicants' heads were next thoroughly washed with a mixture of equal parts of kerosene and dilute acetic acid. The males, who would submit, had their hair cut. About 15% permitted it. There were two bathing tents, one for men and the other for women and children. Another tent was reserved as a dressing tent for women. These tents were in charge of male and female attendants who were immune to typhus. In the tents, the clothes were removed completely, placed individually in separate sacks, which were then thrown out of the tents and taken by another attendant to the steam sterilizers. Shoes, belts, hats and other articles damageable by heat were sprayed with a 1:500 nicotine sulfate solution.

The unclothed Indians next proceeded to the shower bath where, under the supervision of an attendant, their heads and bodies were thoroughly washed with soap and water. Initially, a special soap, prepared by boiling 1 part of soap chips in 4 parts of water with the addition of 2 parts of kerosene, was the detergent. This mixture, used in the preliminary bathing, was diluted 1:4 with water. After this preliminary bath, they bathed in an ordinary bath of soap and water. They then received rough towels to dry themselves off followed by a sheet for cover until their own sterilized clothes became available.

The sanitation team conducted delousing stands at 5 places accessible to the entire reservation district except for a portion of the reservation in Utah that apparently had remained free of infection. The team deloused each of the infected areas two or three times at intervals of approximately 20 days. The team terminated the delousing campaign

on September 3, 1921. No cases were reported from the involved areas after January 1922 (the date of the report). The last case occurred on June 13, 1921.

The sanitation team deloused 6,205 men, women and children during the general campaign, exclusive of about 1,000 who they deloused individually prior to the organized or general campaign. The total figures did not take into account the considerable number of “repeaters” who voluntarily underwent repeated delousing, some even following from one delousing station to another.

The team also strove to protect the locals employed in the delousing operations. Three of the attendants were immune to typhus. The team issued to all attendants one-piece uniforms of louse-tight material and instructed the attendants about personal bathing procedures, and the steaming of uniforms and clothing. No cases of typhus developed among any of the employees.

According to Armstrong, the eradication campaign had a number of salutary effects among the involved population. In addition to the eradication of the disease from the reservation, a benefit of scarcely less importance was the educational value of the campaign among the inhabitants. Culturally, they viewed bathing initially with suspicion and fear, but later they came to enjoy it. They willingly brought their families and household belongings distances of from 10 to 50 miles in order that they might be cleaned. Traders were selling large quantities of soap on the reservation at the close of the campaign, whereas previously its use among the Navajo was extremely limited.

Another salutary effect was learning about the nature of the typhus and how to actively control the disease. The Navajo, who had passively accepted their body vermin as a natural and necessary evil – since they believed that lice came from inside the body and

passed outside through the skin -, learned methods by which they could at least get temporary relief from these pests. In fact, many individuals were voluntarily applying the lessons learned when the campaign came to an end. The terminal effect of the general delousing of the districts upon vermin was most marked in the case of body lice which were found rarely; however, head lice were still prevalent quite widely in the deloused areas at the close of the campaign owing to the hatching of new crops of nits from survivors that had not been killed (this situation is exemplified in modern times by the difficulty in eradicating head lice in affected nursery-age groups and school children). Armstrong listed some of the knowledge gained from the epidemic that was relevant to the early 1920s:

“(1) The Navajo Indian Reservation must be considered a potential focus of typhus fever and will remain such as long as the native inhabitants are permitted to live in their present vermin-infested condition.

(2) Indians enjoy being clean and free of vermin. If bathing and laundry facilities should be instituted at a few points where water is available, it is believed the Indians would avail themselves of the advantages. They requested repeatedly that this arrangement be made. Dr. Newberne, Chief Medical Supervisor, Office of Indian Affairs, made recommendations covering this point to the Department of the Interior.

(3) Medical men and government employees upon the reservations should keep typhus fever constantly in mind as a possibility in every case of illness (with fever and rash).

(4) Although it was necessary to make a number of concessions regarding isolation and quarantine of cases and exposure in order to gain the cooperation of the natives, vigorous delousing measures brought the epidemic quickly under control.”

In this fashion, Armstrong, representing the United States Public Health Service, and in association with Indian Affairs physicians, was able, by utilizing crude and improvised methods, to arrest the progress of a typhus epidemic before it assumed catastrophic proportions. He showed sensitivity and respect for Navajo traditions in modifying conventional epidemiological standards for quarantine and isolation of cases. In later years when the author was present in the NIH Building 7 small conference and luncheon room, he heard Armstrong on several occasions describe, in starker terms than in the published report, the unsanitary and primitive living conditions on the Navajo Reservation in the 1920s. Prevention still remains important in the avoidance of body lice secondary to crowding, unsanitary living conditions, wars, famines and natural disasters. At the present time, the infection responds readily to many broad-spectrum antibiotics. Fortunately, living conditions, although still not ideal, have improved markedly for the Navajo whose economic status has benefited from a variety of profitable income producing activities. The Navajo also has the advantage of improved access to better educational facilities (6).

#### Dengue Fever.

The Hygienic Laboratory, from time to time, assigned its Commissioned Officers to write reviews and informative reports on illnesses of public health importance in order to disseminate current knowledge to the practicing medical profession. Dr. Armstrong wrote an extensive review in August 1923 providing updated information about dengue fever (7). Armstrong gained much of his knowledge of this disease from personal experience. The Laboratory sent him to Monroe, Louisiana to study an outbreak of

dengue in September 1922 (1). While there he became ill with the disease. In the review that he wrote (7), he did not describe his illness, but his publication included a typical temperature chart of a patient with dengue fever identified with the initials “C. A.” On returning to his laboratory, Armstrong was unable to pass dengue fever from the blood of patients to experimental animals including guinea pigs, rabbits, white rats or Rhesus monkeys. After the conclusion of the epidemic, the State Health Officer of Louisiana, and the President of the Munroe Board of Health thanked the Hygienic Laboratory (1) for assigning Armstrong to “investigate dengue fever.”

Dengue (3, 8) is an acute arbovirus infection—a term used to describe any virus transmitted by an insect (arthropod) to vertebrates—that presents chiefly with fever, malaise, enlarged lymph glands and rash. Epidemics occur worldwide over large areas of the tropics and subtropics including the Pacific Basin, Southeast Asia and Africa. Outbreaks recurred in the Caribbean region including Puerto Rico and the United States Virgin Islands in 1969. Indigenous infections were recognized in the Continental United States in 1980 but they have not recurred recently.

Dengue viruses are members of the Flaviviridae (Flavi virus family). Genetically, they are single stranded non-segmented RNA viruses. They occur in 4 distinct serogroups, types 1 through 4. The Flavi viruses include yellow fever and Saint Louis encephalitis. Dengue virus is transmitted from person to person primarily through *Aedes aegypti* mosquitoes, although other species of *Aedes* are involved in Asia and the Pacific areas.

Dr. Benjamin Rush (8) wrote the first clinical report of dengue based on personal observations in 1789. He termed the illness “break bone fever” to describe the prominent

musculo-skeletal pain characteristic of the infection. The viral etiology and mosquito transmission were established in the first two decades of the 20<sup>th</sup> century. During World War II, Albert Sabin (8) described the multiple serological types. The severe form called “dengue hemorrhagic fever” was described in the early 1950s; it is an important epidemic disease in Southeast Asia.

In his short autobiographical summary (9), Armstrong lists dengue as one of the infectious diseases that he contracted during his professional career, but he did not specify the occasion or the time of his possible exposure in his review. His manuscript (7) was a comprehensive and up-to-date review of knowledge about dengue in 1923. The manuscript covered definition of the disease, its importance, geographic distribution and previously reported epidemics. He described the etiology as a filterable organism in the blood stream, shown to be transmitted by mosquitoes as demonstrated in volunteers. He described how the epidemiology of the disease was influenced by climate, age, sex, diffusion in susceptible populations, economic status, crowding, epidemic case chronology (epidemic curve) and incubation period.

Armstrong provided a detailed account of symptoms and physical signs including the onset, primary rash, body pains, fever, secondary rash, gastro-intestinal and genito-urinary features, pulse, lymph gland involvement, joint manifestations and nervous system involvement; he listed the characteristic laboratory changes in the counts of red and white blood cells. He also enumerated associated complications involving the eye, hemorrhagic tendencies, cardiovascular system complications, relapses and delayed recovery. He discussed factors in the prognosis for recovery, the approach to diagnosis and differential diagnosis, and symptomatic treatment to relieve discomfort.

In additional discussion, he indicated that immunity was generally long lasting among individuals infected during an epidemic; he did call attention, however, to apparent repeat infections after several years. The information that dengue exists in multiple serological types, that do not confer reciprocal immunity against one another, appeared many years later (8).

Armstrong described the spread of infection by mosquitoes and the biologic habits of *Aedes aegypti*, the species primarily responsible for the carriage and transmission of dengue virus. He also discussed the various *Culex* varieties implicated in the transmission of dengue and the mutual interrelationships of the periods of human and mosquito infectivity for each other.

The manuscript contained a major portion devoted to a discussion of dengue prevention. This section had several components. The first dealt with control of the infected patient by isolation and the protection of the susceptible population by adequate screening to prevent mosquito access. The second component was an outline of methods then in use for control of mosquito proliferation. These were basically the control methods previously used to retard the spread of yellow fever in Cuba during the Spanish-American War and in Panama during the construction of the Canal earlier in the 20<sup>th</sup> century.

Except for less detailed information about the biologic properties and nature of the virus itself, Armstrong's review was an up-to-date source of information in 1923 for the medical practitioners and scientists who needed precise reference data about dengue fever.

The “Devil’s Grip” in Virginia. (10, 11)

In mid-July 1923, requests arrived at the Hygienic Laboratory from health officers of several communities in Virginia, including Danville and Waterview, for help with outbreaks suspicious of botulism. Dr. George McCoy, Chief of the Laboratory, assigned Armstrong to the investigation. The outbreaks were caused by an entity completely unfamiliar to the generation of the physicians practicing in the area at that time. On July 23, 1923, Charles Armstrong (10), at the request of State Health Commissioner, Dr. E.G. Williams of Virginia, accompanied State Epidemiologist, Dr. George E. Payne, to Bowling Green and vicinity for the purpose of investigating an outbreak of disease of unknown etiology. The symptoms described by physicians, patients and parents bore a striking resemblance to an outbreak of illness in June 1888 first described by Professor W.C. Dabney of the University of Virginia in and about Charlottesville among university students and townspeople. One of the victims of the 1888 outbreak, suffering from the characteristic severe, spasmodic discomfort around the rib cage and upper abdomen, bestowed upon the affliction the colorful sobriquet “The Devil’s Grip.” The report by Payne and Armstrong (11) described in greater detail the epidemic of 1923 (10) that was prevalent in counties in northeastern Virginia. For this illness they used the more descriptive name of “Epidemic Transient Diaphragmatic Spasm.”

The disease was characterized by acute onset with epigastric (mid upper abdomen) pain, difficulty in breathing, fever, tenderness along the lower ribs and a duration of one day to three weeks. The disease was often intermittent with periods of recurrent chest pain and fever alternating with symptom-free intervals. The disease spread within families and among persons in close contact with one another. In the 1923



epidemic the disease affected rural areas more than urban areas and involved children more than adults. It caused no deaths but it seemed to lead to occasional serious sequelae (which in light of subsequent knowledge about the disease's etiology seem to be unlikely consequences). Payne and Armstrong echoed the contemporary belief that this disease was infectious but the etiology was unknown. This epidemic resembled others reported and described by various European authors and identified by numerous designations, usually for the areas in which the epidemics occurred. In more recent years this entity has been a well-recognized illness and has been labeled "epidemic pleurodynia." It is diagnosed readily when occurring in epidemics; diagnosis can be confused with various acute chest and abdominal painful illnesses when occurring in isolated, non-epidemic cases.

Discovery of the viral etiology of this illness occurred with the advent and common use of the suckling mouse as a laboratory host for the cultivation of Coxsackie viruses. Dr. Gilbert Dalldorf (12) first isolated Coxsackie viruses around 1947-1948 from the feces of patients with paralytic disease, presumably poliomyelitis, in the town of Coxsackie in upstate New York. Dalldorf isolated many strains in suckling mice and classified the strains into Groups A and B according to the pathologic changes caused in the tissues of the mice by the viruses. In 1949 and 1950, investigators at Yale Medical School (12) noted laboratory infections in some of the personnel working with the viruses; some of these illnesses suggested epidemic pleurodynia, and the investigators showed later that a Coxsackie Group B type 1 strain probably caused the illnesses. In 1947, Finn and associates (12) reported a large outbreak of epidemic pleurodynia in Boston, Massachusetts. Despite a diligent laboratory search, the investigators found no

infectious cause for the outbreak. However, in 1949, Weller, Enders, and others, including Finn (12), retrieved frozen material from the outbreak and isolated again a Coxsackie Group B type 1 strain from the specimens. In 1950 and 1951, Dr. Robert J. Huebner and associates (12) of the Laboratory of Infectious Diseases, NIH were called to investigate an outbreak of epidemic pleurodynia in northeast Texas. They were able to isolate a Coxsackie Group B type 3 strain from 16 of 22 cases contemporarily with the occurrence of the epidemic. Dr. Huebner was a young investigator, with an already distinguished research reputation, whom Dr. Armstrong recruited for the Laboratory in 1944 when Armstrong was the Chief. The etiology of epidemic pleurodynia thus appears to be one or more strains of Group B Coxsackie viruses. Studies in the later 1950s showed previously undisclosed potential virulence. They also have been found to cause fatal meningoencephalitis (brain infections) in newborns (13), and they are recognized as causes of infant and adult myocarditis (inflammation of the heart muscle).

### Miscellaneous Assignments

#### Pasteurization of Milk.

One of the Laboratory's functions was oversight on the integrity of the nation's milk supply (14A, B, C). In November 1922 the Laboratory apparently detailed Armstrong to cooperate in developing a program for a meeting of the World's Dairy Congress. The President of the Congress Association thanked the Laboratory for Armstrong's participation (1). On March 26, 1923, the Laboratory ordered Armstrong to go to Endicott, New York to observe a series of tests of commercial pasteurizing machines in connection with experimental work on the pasteurization of milk (1). On

May 30, 1923 he sent back to the Laboratory a report of the work done on experiments in milk pasteurization, performed April 17, 18, 19, 1923, in cooperation with North Public Health Bureau in Endicott, New York (1). In 1927, Armstrong and Thomas Parran, Jr., the future Surgeon General of the USPHS, wrote a manuscript about further studies on the importance of milk and milk products in the causation of outbreaks of disease in the United States (14B).

#### Ragweed Pollen Standardization.

In 1924-1925, Armstrong studied methods (15A, B, C) to standardize the potency of ragweed pollen extracts used in the treatment of patients with hypersensitivity (allergy, “hay fever”) to ragweed pollen. He collaborated with his colleague at the Hygienic Laboratory, Dr. W. T. Harrison. These studies were part of the Laboratory’s mission to safeguard vaccines used in the treatment of human medical illnesses. Dr. Harrison later became head of a section that became the Division of Biologic Standards. Dr. Harry S. Bernton, a civilian employee and later a special expert consultant in bacteriology and epidemiology (1), aided Armstrong and Harrison in their ragweed studies. Dr. Bernton collected ragweed pollen and suggested composition of solutions to maintain the potency of ragweed extracts. Dr. Bernton later entered private medical practice as one of the first allergists in the Washington, DC area, and he continued a longtime collaboration with the Hygienic Laboratory/NIH.

#### Continuing Education.

For many years the USPHS has had the tradition of providing opportunities for continuing education and maintaining the professional skills of its commissioned officers. The disruptions caused by World War I, followed by the national upheaval precipitated by the 1918 influenza pandemic, necessitated the discontinuation of formal teaching programs for PHS officers. Fortunately, this situation proved to be temporary. In 1922, the PHS resumed classes for instruction of its officers (16). Simultaneously, the great research institutions and teaching centers in Western Europe were experiencing a resurgence of academic activity and scientific discovery. In 1924, Charles Armstrong (16) was one of two officers stationed at the Hygienic Laboratory who had the opportunity to spend four months of study in Europe's centers of learning where he had the opportunity to acquire new knowledge and observe laboratory techniques.

In these initial studies at the Hygienic Laboratory, Armstrong discharged his obligations well. He helped stem an epidemic of typhus on the Navajo Indian Reservation using methods not much different today used in separating the vectors from their human hosts. He was about 25 years too early in not having effective antibiotics to treat the patients at risk for severe morbidity or mortality. He authored a comprehensive review of dengue fever for his professional colleagues without the subsequent refined knowledge of the biology of the virus. He investigated an outbreak of epidemic pleurodynia, carefully noting the clinical features of illness and the epidemiological character of the outbreak which he compared to previously reported outbreaks. Lack of knowledge about the infecting organism was a handicap. With the satisfactory accomplishments of these

projects and the other studies mentioned, Armstrong was off to a respectable and promising career in the laboratory and in the field of epidemiology.

#### Notes – Typhus, Dengue, Devil’s Grip

- 1) Williams, R. C., *loc. cit.*; The National Archives (USA) at College Park, Maryland kept records of Armstrong’s first few years at the Hygienic Laboratory. The information was written in hand, in ink on 3 by 5 inch cards and stored in the RG (Record Group)-90 files. These files filled in an important gap on information about Armstrong’s early career; Harden, *loc. cit.*; *NIAID Intramural Contributions, 1887-1987*, viewable at [http://www.history.nih.gov/articles/NIAID\\_Intramural\\_Contributions.pdf](http://www.history.nih.gov/articles/NIAID_Intramural_Contributions.pdf).
- 2) Armstrong, C. Typhus on San Juan Indian Reservation, 1920 and 1921. *Public Health Reports* 37: 685-693, March 24, 1924.
- 3) Cecil-Textbook of Medicine, Goldman, L. Bennett, J. C., et al Editors. 2000 21<sup>st</sup> Edition, W. B. Saunders, Philadelphia, London. Hornick, R. B. author of chapter on *Typhus* p. 1767. Hereafter referred to as “Cecil”.
- 4) Zinsser, Hans, 1935 *Rats, Lice, and History*, Little, Brown and Co., Boston
- 5) Carson, Rachel, 1962 *Silent Spring*, Houghton, Mifflin Co. Boston.
- 6) The Web site of “Navajo Nation” in 2006 discloses a healthy prosperous community with a vibrant economy, educational opportunities, natural resources in oil, gas and uranium, pride in its heritage and proud of its World War II Veteran heroes, “The Navajo Code Talkers” who contributed to victory in the South Pacific.

- 7) Armstrong, C., Dengue Fever, *Public Health Reports* 38: 1750-1784, August 23, 1923.
- 8) Mandell, Gerald, et al. editors, 2005, *Principles and Practices of Infectious Diseases*, 6<sup>th</sup> Edition, Elsevier-Churchill, Livingston Inc. London. Earlier editions also utilized. Henceforth referred to as “Mandell.”
- 9) Armstrong autobiographical notes, *loc. cit.*
- 10) Armstrong, C., “Devil’s Grip” in Virginia. *Public Health Reports* 38:1964-1965, August 24, 1923.
- 11) Payne, C. C., and Armstrong, C., Epidemic Transient Diaphragmatic Spasm, Disease of Unknown Etiology, Epidemic in Virginia. *Journal of the American Medical Association* 81: 746-748, 1923.
- 12) Review Article. Huebner, R. J., Beeman, E. A., Cole, R. M., Beigelman, P. M., and Bell, J. A., The Importance of Coxsackie Viruses in Human Disease, particularly Herpangina and Epidemic Pleurodynia. *New England Journal of Medicine* 247: 249-256, 285-289, 1952.
- 13) Kibrick S. and Benirschke, K., Acute Aseptic Meningitis and Meningo-encephalitis in Newborn Children Infected with Coxsackie Virus Group B Type 3. *New England Journal of Medicine* 255:1883-1889, 1956.
- 14) A) Armstrong, C., et al., Commercial Pasteurization. *Public Health Bulletin. No. 147*, 1925. B) Armstrong, C., and Parran, T., Jr., Further Studies on the Importance of Milk and Milk Products as a Factor in the Causation of Disease in the United States. Supplement No. 62 to the *Public Health Reports*, 1927. C) Armstrong, C., Federal Government Aids States in Insuring Pure Supplies of

- Milk for Ultimate Consumers. *The United States Daily*, Saturday, November 27, 1926. Topic I – Public Health Milk-Borne Diseases.
- 15) A) Harrison, W. T., and Armstrong, C., Some Experiments on the Antigenic Principles of Ragweed Pollen Extract. *Public Health Reports* 39: 1261-1266, May 30, 1924. B) Armstrong, C., and Harrison, W. T., A Study of Ragweed Pollen Extracts for the Use of Ragweed Pollen Hypersensitiveness. *Public Health Reports* 39: 2422-2428, September 19, 1924.
- C) Armstrong, C., and Harrison, W. T., Standardization of Pollen Extracts by the Complement-fixation Test. *Public Health Reports* 40: 1466-1472, July 10, 1925.
- 16) *Annual Reports of the Surgeon General*, 1922, 1924.

## Smallpox Vaccination and Tetanus; Postvaccination Encephalitis

In the mid to late 1920s Charles Armstrong became involved in investigations (1-6) that resulted in measures designed to eliminate tetanus as a potential complication following vaccination against smallpox. He considered this achievement as one of the significant contributions of his scientific career (7).

Smallpox, until it was declared eliminated worldwide by the United Nations World Health Organization (WHO) in 1980 (8), was one of the pestilential scourges known to antiquity. It would revisit communities at variable intervals causing widespread epidemics with mortality of up to 30 per cent among its victims. Smallpox (scientific name – variola), whose only known hosts are humans, spreads from person to person by respiratory droplets and fomites. It produces a severe febrile illness with development of a widespread pustular pox-like rash in which all the skin lesions are simultaneously in the same stage of development. There is general organ involvement of the liver, kidney and heart. Severe scarring from the healing rash occurs frequently. Some societies attempted to prevent smallpox in susceptible populations by immunizing with live smallpox virus. This procedure, known as “variolation”, was the administration of material from a smallpox pustule into the skin of the recipient. Variolation usually resulted in a smallpox illness that left the recipient immune to subsequent infection when re-exposed later to patients with smallpox. Variolation also resulted in death and severe morbidity in a variable number of vaccinees.

David McCullough (9), in his Pulitzer Prize-winning biography of John Adams, described Abigail Adams’ taking the Adams children, household servants, and family



relatives from Braintree, Massachusetts, the family's hometown, to Boston, Massachusetts about 20 miles away, where a smallpox epidemic was raging in June-July 1776. Abigail undertook this migration for the purpose of getting everyone inoculated against smallpox. Variolation was a familiar, well-established method in Boston of immunizing people against smallpox upon subsequent exposure. About 100 years previously one of the town pastors had learned of this method from a household slave who described its use in Africa for many years. The procedure consisted of the injection of a small amount of pus from a smallpox vesicle into the skin of a susceptible vaccinee. Abigail Adams and her entourage crowded into the Boston home of her uncle Isaac Smith. The entire household received inoculations of smallpox. The Adams family acquired smallpox successively and remained ill for two months. Fortunately, all recovered. Abigail's husband, John, during this period, was at the Continental Congress in Philadelphia helping to draft the Declaration of Independence; he was unable to leave the Congress to assist with the family crisis. John Adams, himself, received variolation during a previous smallpox outbreak in Boston in 1764 by Dr. Joseph Warren. Dr. Warren, who was an active pro-independence patriot, became an American Revolutionary War hero. He died on June 17, 1775 during the Battle of Bunker (Breed's) Hill. The American Revolutionary Armies also were immunized by variolation at various times.

The modern era of vaccination against smallpox began with Dr. Edward Jenner in 1798 (10). Jenner exploited the observation noted in the rural area where he practiced in England, that persons, who had contracted cowpox, appeared to be immune when later exposed to smallpox. Jenner was born in Berkeley, Gloucestershire, England, on May 17,

1748. At age 19, after receiving a general education, he served an apprenticeship with a country physician at Sodbury near Bristol. In 1768 a young, countrywoman sought his medical advice. When he asked her about smallpox, she replied: “I cannot take that disease for I have had the cowpox”. Though this concept was accepted commonly among the rural inhabitants, the practicing physicians placed no credence in this concept. Jenner in 1768, for the first time, considered the scientific possibilities of this theory that he did not fully realize until many years later after skillful observations and experiments. In 1770, after his apprenticeship, he went to London to complete his medical studies at St. George’s Hospital. He lived in the house of the famed anatomist and naturalist, Dr. John Hunter, who encouraged his scientific interest and pursuit of the cowpox question. Jenner maintained the friendship until Hunter’s death during “an attack of angina pectoris”. Through his association with Hunter, he had entered into the study of anatomy and “natural history”, and, in consequence of his proficiency in these studies, was offered the position of naturalist on one of the expeditions of the famed explorer and navigator Captain James Cook. Despite this tempting offer, Jenner in 1773 chose to return to his native village in Gloucestershire to resume his career as a country practitioner. It is not known how much this career choice was influenced by his interest in the relationship between cowpox infection and subsequent immunity to smallpox. Jenner immediately began to observe systematically and to record cases of cowpox as represented by the hands of milkers and whether or not the patients were attacked or were immune to smallpox. He discussed his interests and presented his views to the county medical society on a variety of subjects, some of which the society accepted politely; however,

the society told him he would have to resign if he kept presenting his views on smallpox with which his fellow practitioners disagreed vehemently.

Jenner continued his observations. By 1796, he felt that he had sufficient evidence to test his theory. On May 14, 1796 he performed his first vaccination (from vacca = Latin, for cow). Lymph taken from the hand of Sarah Nelmes (case XVI) (10), a dairymaid affected with cowpox, was inoculated into healthy 8-year old James Phipps (case XVII) (10). Phipps went through a typical case of cowpox. Six weeks later, July 1, 1796, Jenner injected material from a smallpox pustule into Phipps' arm. Phipps remained completely well.

For the next several years, Jenner continued the process of vaccination among patients in his practice. Finally, in 1798, he applied to the Royal Society in London for permission to present his conclusions before that "august body". The president of the Society replied that Jenner "should be cautious and prudent, that he had already gained some credit by his communication to the Royal Society, and ought not risk his reputation by presenting to the learned body anything which appeared so much at variance with established knowledge and withal so incredible" (10).

Jenner did not present his conclusions to the Royal Society but he did visit London from April to July 1798. He did try to present his findings to professional friends. In June 1798, while still in London, his classical monograph (self-published) on vaccination appeared. He returned to Gloucestershire in July without arousing any interest in vaccination among London physicians. He left, however, a supply of cowpox virus with Mr. Cline, an orthopedist at St. Thomas Hospital. Mr. Cline used this material for unrelated reasons on one of his patients who developed cowpox. Mr. Cline was

persuaded to try giving smallpox to the same patient, and the patient remained well. As a result of these events, Mr. Cline became an enthusiastic advocate of vaccination, and he urged Jenner to move to London to join him in a lucrative practice.

Jenner preferred to stay in the country environment. Friends, who believed in Jenner's incredible discovery and contribution urged him to apply to Parliament for compensation for the lost remuneration from practice and the extra expense entailed by extensive travel associated with his investigations. Parliament appointed a committee that examined carefully Jenner's files and records, agreed with the conclusions and awarded him the sum of L10, 000. It is amazing that a political, non-scientific body was the one to recognize Jenner's accomplishments rather than the established medical "authorities". However, in 1813 the University of Oxford conferred upon him the degree of Doctor of Physic. On the other hand, the College of Physicians of London refused to admit him to its ranks without the usual examination. Finally, vaccination became accepted widely in England after appreciation of Jenner's studies.

In contrast to the early abuse heaped upon Jenner, the introduction of the innovative concept of vaccination into the United States was greeted with enthusiasm. Dr. Benjamin Waterhouse (1754 – 1846), Professor of Physic at Harvard Medical School, (11) performed the first vaccinations in America using his own children as subjects. His "History of the Kinepox, Commonly called the Cowpox" (1800) is one of the great American medical classics. This was from "A Prospect of Exterminating the Smallpox – Being the History of Variolae Vaccinae or Kine-pox commonly called the Cowpox as it appeared in England: With an account of a series of inoculations performed for the Kinepox in Massachusetts Boston 1800)".

Dr. Waterhouse described the genesis of his own efforts in vaccination in the following manner: “At the beginning of the year 1799 I received from my friend, Dr. Lettsom of London, a copy of Dr. Edward Jenner’s ‘Inquiry into the causes and effects of the variolae vaccinae, or Cow-pox’: a disease totally unknown in this quarter of the world. On perusing this work I was struck with the unspeakable advantages that might accrue to this, and indeed to the human race at large, from the discovery of a mild distemper that would ever after secure the constitution from that terrible scourge, the smallpox. “As the ordinary mode of communicating even medical discoveries in this country is by newspapers, I drew up the following account of the Cow-pox which was printed in the *Columbian Centinel* March 12, 1799” (11).

Dr. Waterhouse sent to England for the vaccine material. He inoculated his 5-year old and 3-year old sons, the first with the vaccine from England, and the second, with infectious material from the arm of the first. He also inoculated a 12-year old servant boy with the vaccine from England. He had to be away for a few days but he invited his colleagues, Drs. Warren and Danforth, to visit and observe the children as they went through the stages of a primary “vaccination”. From the pustule of his 3-year old son, Dr. Waterhouse inoculated his infant daughter and her nursery maid, both of whom went through the development of primary vaccinations. Dr. Waterhouse vaccinated a total of seven household members.

In the interest of providing full disclosure and to prove the protective effect of vaccination, Dr. Waterhouse enlisted the aid of Dr. William Aspinwall, physician to the smallpox hospital in Boston, in a letter as follows (11): --- “I have procured some of the vaccine matter and therewith inoculated seven of my family. The inoculation has

proceeded exactly as described by Woodville and Jenner; but my desire is to confirm the doctrine by having some of them inoculated by you.

“I can obtain variolous (smallpox) matter and inoculate them privately, but I wish to do it in the most open and public way possible. As I have imported a new distemper, I conceive that the public have a right to know exactly every step I have taken in it. I write this, then, to enquire whether you will on philanthropic principles try the experiment of inoculating some of my children who have already undergone the cowpox. If you accede to my proposal, I shall consider it as an experiment in which we have co-operated for the good of our fellow citizens, and relate it as such in the pamphlet I mean to publish on the subject. I am etc. B.W.”.

Dr. Aspinwall agreed readily to test the efficacy of vaccination. Dr. Waterhouse offered 3 of his children he had vaccinated. Using fresh, dependable smallpox matter, Dr. Aspinwall chose to inoculate the 12-year old boy in the presence of Dr. Waterhouse. Dr. Aspinwall also hospitalized the boy in proximity to a patient ill with smallpox. On the fourth day post-inoculation, the boy developed a slight swelling of his arm but in a day or two, the swelling subsided, the arm became well, and the boy did not develop smallpox. Waterhouse proclaimed (11), “One fact, in such cases, is worth a thousand arguments”, a refreshing attitude in light of Jenner’s experience with the English medical establishment.

Following the successful demonstration of the protective effect of vaccination against smallpox, the practice of vaccination became accepted and gradually found its way prominently into the practice of medicine in the United States during the 19<sup>th</sup> century. It became part of the standard immunization schedules of most of the 20<sup>th</sup> century in pediatric practice and in the Armed Forces. Various pharmaceutical companies

and state boards of health developed methods for the commercial production of vaccine virus by harvesting cowpox lesions from the bare abdomens of young calves. The regulatory functions of the Hygienic Laboratory and its successor organizations (Division of Biologics of LID, FDA) oversaw the standardization for potency and sterility of smallpox vaccine.

Charles Armstrong first announced his interest in the problem of tetanus as a complication of vaccination in a manuscript in 1925 describing tetanus in the United States following the use of bunion pads as a vaccination dressing (1). Tetanus (12), colloquially termed “lockjaw”, is a disease manifested by generalized, uncontrolled involuntary tonic muscle spasms caused by the action of a potent central nervous system toxin produced by the bacillus *Clostridium tetani*. This organism is a motile, gram positive, anaerobic, non-encapsulated rod; it forms spores located at one end of the rod under adverse conditions. Heat, disinfectants and various antibiotics inactivate the vegetative forms of tetanus. The spores are highly resistant to heat, disinfectants and desiccation. The spores are widely distributed in nature; they can be found in human and animal feces and can survive in dry soil for several years. Tetanus occurs when spores gain access into damaged or devitalized tissue where, along with foreign objects, conditions develop to provide favorable anaerobic environments for germination of the vegetative forms of the bacteria from the spores. The vegetative forms produce the central nervous system toxin responsible for clinical tetanus. The toxin enters through the terminal peripheral nerve endings close to the wound and travels along the peripheral nerves to the central nervous system, primarily spinal cord and brainstem, at the rate of approximately 250 millimeters per day (about 10 inches). Once it reaches the cell body of

the motor nerve, the toxin passes to an electrically sensitive area (pre-synaptic terminal) where it blocks the release of a neurotransmitter that inhibits impulses going to the nerve controlling muscle function. Loss of the inhibitory influence results in unrestrained central firing with sustained muscular contraction. The shorter the peripheral nerve pathways, the shorter the incubation period, and the sooner the affected muscles become involved to produce the muscle spasms and contractions. Spasm of the of the facial and jaw muscles give rise to the “lockjaw” and the familiar frozen smile or “risus sardonicus”. The prognosis for recovery depends on the amount of nerve toxin produced and fixed in the central nervous system, regeneration of nerve tissue, the extent of total body muscle involved, and the intensity of the treatment employed to reduce excess spasms, support respiration and maintain nutrition. Mortality is high. Tetanus is a preventable disease. Tetanus toxoid administration is part of a regular schedule combined with other primary childhood immunizations including pertussis and diphtheria. During adulthood, tetanus and diphtheria toxoids are combined for periodic booster doses. The incidence of tetanus is diminishing gradually in the United States.

In the initial manuscript (1) Armstrong reported 11 cases of post vaccination tetanus, most of whom died, following the use of bunion pads as a vaccination dressing. His colleagues, Dr. Ida A. Bengston and Mr. Conrad H. Kinyoun, demonstrated tetanus organisms in approximately 25 per cent of 200 bunion pads of the same make as those used on cases developing tetanus. The organisms were usually incorporated into the glue of the pads. The criterion of infection of the pads was the development, on appropriate bacteriologic growth media, of an organism morphologically like tetanus that developed a toxin lethal for mice and neutralizable with tetanus antitoxin. In 9 of the 11 cases the



vaccinations were definitely primary or initial vaccinations. The inoculation method used was the outmoded scarification method which was locally traumatic. This consisted of multiple cross-hatching scratches of a wide area (about ½ to 1 square centimeter) of skin of the left upper deltoid or mid-thigh region. Following vaccination this often left a visible scar euphemistically labeled “a sanitary dimple”. In the cases described, Armstrong reported local, severe, foul smelling tissue damage that undoubtedly provided the necessary anaerobic conditions for the emergence of toxin producing vegetative bacilli from the contaminating tetanus spores. In this initial paper, Armstrong concluded and strongly advised that bunion pads should not be used as vaccination dressings.

In a later paper in 1929 (6, 2) Armstrong stressed the expanding role of the vaccination dressing as conducive to the production of post-vaccinal tetanus. Among 116 collected and investigated cases following vaccination, Armstrong found that all had developed following primary “takes” that had been covered for all or part of their active course by some type of dressing strapped to the vaccination site. The types of dressings used on these 116 cases were as follows: celluloid shields, 53; gauze, 40; bunion pads, 17; gauze and shields, 5; adhesive bandage; 1. The source of the tetanus organisms was unknown except in a small proportion of cases. In 1917 McCoy and Bengston (13) traced an outbreak of postvaccinal tetanus to the use of ivory bone point scarifiers. By the time of the 1929 manuscript, Armstrong had collected additional cases related to the use of infected bunion pads (1) for a total of 17 cases. Prolonged search by members of the Hygienic Laboratory among commercial vaccine virus disclosed no contamination with tetanus organisms. The source of the tetanus organisms in areas of vaccination was thus still unknown. The entrance of tetanus into the vaccination area would have to be

considered entirely fortuitous given the widespread distribution of the organism in nature. In view of this, the investigators at the Hygienic Laboratory, including Armstrong (2, 6), sought to examine the role of the vaccination dressing in promoting conditions at the vaccination site conducive to the development of tetanus. They determined that fastening the dressing firmly to the vaccination by means of straps or tapes prevented the drainage of lymph and capillary blood when the area swelled from the primary take. The accumulated fluid softened the vaccinal vesicle producing an exudation of serum and pus. The resulting tissue damage promoted the development of putrid, anaerobic conditions suitable for the germination of ingested tetanus spores to the toxin-producing vegetative bacillary forms. Armstrong also demonstrated that a mixture of intentionally tetanus-contaminated vaccine virus rubbed vigorously on the abraded skin of rabbits and monkeys did not result in tetanus unless the lesions were covered subsequently. Additional experiments involving deep subcutaneous injection of vaccine virus followed by intravenous injection of tetanus spores also resulted in tetanus among the laboratory animals.

As a preliminary conclusion Armstrong stated (6) that while physicians might be unable to prevent such accidental contamination, he felt that the evidence was practically complete that, by observing a proper vaccination technique, the development of tetanus as a vaccination complication could be eliminated. Furthermore, he defined a proper vaccination as one in which the insertion area was not over one-eighth inch in its greatest diameter, made by some method that did not remove or destroy the epidermis (top layer of the skin) and which gave a superficial implantation of the virus. The multiple pressure method as advocated by Dr. James P. Leake, (Surgeon, USPHS), admirably met these

requirements and was recommended. Dressings fixed to the vaccination site were to be avoided. Armstrong indicated that should a dressing be deemed necessary for any reason, a large square of gauze pinned to the inside of a loose-fitting sleeve might be employed.

In this 1929 study Armstrong concluded formally as follows: 1) tetanus as a complication of smallpox vaccination was confined, as far as he was aware, to primary “takes” in which some type of dressing was strapped to the vaccination site. 2) He produced evidence which indicated that in post-vaccinal tetanus the specific organism gained entrance to the vaccination through an accidental infection from extraneous sources. 3) Laboratory evidence showed that a deep implantation of *C. tetani* in the devitalized components of a “take” is necessary before post-vaccinal tetanus will develop. 4) A dressing strapped to a cutaneous (skin) vaccination permitted this deep implantation of organisms by producing severe “takes” and by retaining exudate there from at the vaccination site. 5) Injection methods of vaccination such as the intra- or subcutaneous techniques were suitable methods for the experimental production of post-vaccinal tetanus and would seem to be, from the standpoint of this complication, potentially dangerous methods for human use. 6) He explained the freedom of openly treated cutaneous vaccination from the complication by the continual wiping and ventilating action occasioned when the arm was moved within the sleeve or under the bedclothes. The light friction kept the vaccine vesicle dry and firm, and, thus, either prevented or promptly wiped away any exudate that might appear. 7) A small, superficial implantation of the virus, as recommended in the multiple pressure technique advocated by Dr. James P. Leake, and the abandonment of dressings fixed to the vaccination site would eliminate tetanus as a complication of vaccination. If a dressing was deemed

advisable for any reason, the objectionable feature of the fixed covering could be avoided by pinning a few layers of gauze to the inside of a loose fitting sleeve.

During the period of this report (6) Armstrong presented these views vigorously to a wide medical audience (3, 4, 5). Armstrong (4) addressed a strongly worded critique rebutting several investigators who, in a totally uncontrolled study, advocated “intra-dermal vaccination” as the sole method of vaccine administration to the exclusion of all other well-established safe methods of vaccination. The gentle, multiple pressure method advocated by Armstrong and Leake gained wide acceptance; the only modification was the later introduction of the bifurcated (two-pronged) needle that continued in use until the United States discontinued routine vaccination in 1972.

Armstrong’s investigations and recommendations helped remove one of the possible hazards associated with smallpox vaccination. The incidence of post-vaccinal tetanus gradually diminished and disappeared. The widespread practice of vaccination resulted in the elimination of smallpox from the United States and from those countries where standard medical practice included vaccination. The last case of smallpox in the United States occurred by importation into New York City in 1949. Despite the success of vaccination in eliminating smallpox, there was general recognition, since the time of its original use, that a variable number of mild and life-threatening reactions accompanied vaccinations. Most people experienced minor reactions including sore arm, fever and body aches representing an actual attack of cowpox. In the past about one out of every thousand persons vaccinated for the first time experienced serious but not life-threatening illnesses. These included toxic or allergic reactions at the vaccination site (erythema multiforme), spread in persons with atopic (allergic) dermatitis (eczema

vaccinatum), generalized vaccinia in persons with healthy skin, progressive vaccinia infection to other body organs (liver, kidneys, heart) and the dread complication of brain (and spinal cord) involvement (post-vaccinal encephalitis) in about 1: 1,000,000 cases. Also inadvertent escape from the vaccination site and exposure of susceptible persons, such as infants, pregnant women and various immuno-compromised patients, represented additional complications. With the realization that the risk of vaccination was greater than the exposure to smallpox, the United States Public Health Service (8), in 1971, recommended the discontinuation of routine vaccination. Routine smallpox vaccination among the American public stopped in 1972 after the disease was declared eradicated in the United States. Due to the success of vaccination against smallpox, the World Health Organization (WHO) had undertaken the worldwide elimination of smallpox by means of vaccination. The last case occurred in Somalia, Africa in 1977, and the WHO declared that the world was officially smallpox free in 1980.

The hope that the world would continue to be free of smallpox disappeared September 11, 2001 with the terrorist attacks on the World Trade Center in New York City and the United States Department of Defense Headquarters, the Pentagon, in Arlington, Virginia. These catastrophic events raised the specter of the potential use of bioterrorism weapons of mass destruction among which smallpox was a prime candidate in a new generation of unprotected potential victims. Following the eradication of smallpox in 1980, samples of the virus were stored in two official locations, the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia and a repository near Novosibirsk in Russia (14). These stores are not a problem; however, the existence of samples of other biologic agents, possibly salvaged when the Soviet Union reportedly

destroyed all their stocks of biological warfare weapons, remains a frightening possibility if they might have fallen into the wrong hands. Shortly after September 11, 2001 CDC updated its smallpox-response plan to address the possibility of a bioterrorist attack involving smallpox. In view of the shortage of available stocks of the standard vaccine stored since 1982, several groups of investigators (15, 16) studied the immunogenicity and clinical responses to undiluted and diluted smallpox vaccine in 680 volunteers. Vaccine diluted 1:5 and 1:10 still produced primary takes in more than 95 per cent of 18-32-year old volunteers. The usual number of adverse reactions occurred. Of interest though, especially in view of Charles Armstrong's previously described observations, the investigators applied a covering to the vaccination. A few layers of gauze were placed over the insertion site, and the area was covered with a transparent, semi-permeable adhesive membrane. The investigators changed the covering every 3-5 days to observe the development of the vaccination vesicle. The technique of covering the vaccination was different than the ones among the patients described by Armstrong. The chance of the volunteers getting tetanus was unlikely for several reasons. The coverings among the volunteers were not strapped down and the coverings were changed at frequent intervals. The young volunteers probably had all received childhood tetanus immunizations and boosters, and the coverings were of a semi-permeable, transparent, self-adhesive material not available to Armstrong's contemporaries. The investigators adopted the use of protective coverings to prevent autoinoculation of the eyes and genitalia of the volunteers and to avoid inadvertent inoculation of unvaccinated persons.

The whole smallpox vaccination program has become the subject of recent criticism (17) since there has been no credible evidence that Iraq in the 1990s ever

possessed or converted smallpox virus as well as other biological agents into weapons of mass destruction. By mid-June 2004 627,000 military employees and 40,000 civilian first responders and health care workers had been vaccinated. The civilian program reported 900 “adverse events” occurring within days of the inoculation, including one confirmed death from the vaccine. The military reported one death and 75 cases of heart “inflammation” caused by the vaccine. These events should not have come as surprises to the Army and civilian medical authorities since the complication rate from vaccination was greater than the risk of exposure to smallpox virus in the 21st century. The fate of the vaccination program is undetermined at this writing. Efforts are underway (18) to find an effective but safer vaccine than the one in current use. Stored vaccines from European pharmaceutical companies were also being acquired by the United States until the country had manufactured sufficient supplies to vaccinate the entire population.

The current vaccine, the one retrieved from storage (8), is “Dryvax-R”. The vaccinia currently licensed in the United States is a lyophilized, live virus preparation of infectious vaccinia virus (Wyeth Laboratories, Marietta, Pennsylvania). Vaccinia vaccine does not contain smallpox (variola) virus. Previously the vaccine had been prepared from calf lymph seed virus derived from the New York City Board of Health (NYCBOH) strain of vaccinia virus and has a minimum concentration of 10 to the 8<sup>th</sup> pock-forming units (PFU/ml). Vaccine is administered by using the multiple puncture technique with a bifurcated needle. A reformulated vaccine, produced by cell culture technique, is now being developed.

#### Postvaccinal (Postvaccination) Encephalitis

Charles Armstrong developed an interest in this potentially serious or life-threatening complication following vaccination against smallpox. He outlined the nervous system manifestations that might follow acute infections such as smallpox, chickenpox, measles, mumps, and vaccination against smallpox. He indicated that the central nervous manifestations of these illnesses constitute a group strikingly similar in their epidemiology, symptomatology and pathology.

The apparently increasing incidence and reports of postvaccinal encephalitis (19) in various European countries, in England, Netherlands, Germany, Portugal, France, Switzerland, Poland and others focused Armstrong's attention on this apparent complication of vaccination. In the 1920s the incidence of "encaphites" of 1:4,000 in the Netherlands led to the temporary suspension of compulsory vaccination.

Armstrong reviewed the reported symptoms and diagnosis of this complication. The symptoms usually occurred suddenly and had their onset in 70 per cent of the cases from the 10<sup>th</sup> to 13<sup>th</sup> day following vaccination, that is, when the vaccination, usually primary, was at its height. The symptoms for different cases varied somewhat but Armstrong recorded these as occurring most frequently: 1) Fever, (104F or higher in severe cases). 2) Vomiting. 3) Headache. 4) Stupor or coma. The stupor might develop within a few hours after the onset of the symptoms and was always present in fatal cases). Symptoms of meningeal irritation (related to the meninges, the three layers of membranes covering the brain and the spinal cord: resistance of the neck to movement and the legs to elevation) were usually present in conscious patients and absent in others. Convulsions were common in young children; also cramps and spasms. Trismus (severe tonic contraction of the jaw muscles) had been observed occasionally and was important to



note since it could lead to confusion with tetanus. Varying degrees of limb paralysis was noted occasionally in some cases. The eye muscles were usually not involved. The Babinski (up-going great toe sign) was usually positive indicating brain or spinal cord involvement (upper motor nerve cell involvement). The cerebrospinal fluid usually showed little or no change to chemical, microscopic or bacteriological studies, The cerebrospinal fluid pressure might be slightly increased, and cell counts, predominantly lymphocytes (white blood cells), as high as 200-300 per cubic millimeter had been observed. Armstrong stated that these clinical features were non-specific and could occur with many acute inflammatory and viral infections of the central nervous system. Death, which might follow in 30 to 40 percent of the cases, usually occurred from the third to the tenth day following onset of symptoms. Recovery, when it took place, was usually rapid and complete; however, some intellectual impairment and localized limb weakness might occur as residual manifestations in some cases.

Microscopic examination of the central nervous system in fatal cases disclosed areas of loss of myelin (a fatty substance in the brain and within the sheath of nerve fibers) around blood vessels (perivascular demyelination) and inflammatory cellular infiltration scattered throughout the white matter of the brain, usually including the spinal cord as well. Armstrong described these findings as non-specific, similar to and indistinguishable from the lesions encountered in the encephalitis that occurred after smallpox, measles, chickenpox and mumps.

Armstrong described no distinguishing or predictive epidemiological features or factors predisposing to this complication after vaccination. Some cases tended to occur in rural or urban clusters, among some families, at various ages from several months to 22

years; however cases below one year or over 8 years seemed to be rare. Encephalitis appeared more commonly among girls, and seemed to occur most frequently with primary vaccination. The type and source of virus seemed to have no relationship to the occurrence of encephalitis.

The cause of the complication was unknown but most authors at that time suggested the activation of a latent agent in the vaccine or the recipient as a possible factor in the production of encephalitis. Others postulated that the complication was due to the vaccine itself or to the induction of a local “hyperallergic state” in the central nervous system by the vaccine.

Prevention of encephalitis, as advocated by the health authorities at the time, was basically the avoidance of routine vaccination in the absence in the community of smallpox, poliomyelitis or other transmittable infections of the central nervous system. Practically all the authorities outside the United States, at the time, stressed the importance of performing primary vaccinations during the first year of life, since at this period postvaccinal encephalitis appeared to be relatively less common.

Armstrong indicated that the usual ages for performing primary vaccinations in the United States were in the sixth or seventh year. He remarked that this would seem to predispose the United States population to the postvaccinal complication. He also stated that such cases had been reported from various areas of the country. He concluded his report (19) as follows: “It seems therefore that this complication is occasionally found in the United States, and, as health officers, we should all be on the lookout for the occurrence of symptoms pointing to the central nervous system in persons recently vaccinated. Should such cases come to your attention, they should be considered worthy

of the most careful investigation. The Public Health Service is anxious to learn of such cases should they occur and would be glad to render any assistance possible in the study of them”.

In response to this request Armstrong was able to report (20) after several years on 72 cases occurring in the United States. This information, published in the Public Health Reports, was based on the “Cutter Lecture” delivered in Boston, Massachusetts March 31, 1932. Armstrong also suggested changing the terminology of this entity from “postvaccinal” to “postvaccination encephalitis” since vaccine was isolated in only rare instances from the central nervous system, and the complication usually occurred temporally with the height of the vaccination reaction. Armstrong also offered a possible explanation for the etiology and pathogenesis of the encephalitis based on epidemiological and experimental observations. He also offered and suggested a therapeutic strategy designed hopefully to prevent the occurrence of this tragic event that resulted in 37 to 42 per cent mortality.

The etiology of postvaccination encephalitis is still indeterminate (21). During the period of discontinuation of routine vaccinations in the United States after 1972 opportunities for additional studies on this problem have been minimal to non-existent. According to Armstrong (21), “In the absence of definite information as to the etiology of postvaccination encephalitis, attempts at its prevention are more or less empirical. However, it is an established fact that primary infant vaccinations and likewise secondary vaccinations performed at any age tend to be relatively quite unlikely to be followed by this complication. Now, in both of these relatively insusceptible groups, the vaccination reactions tend to be milder than is the rule among primary reactions performed after the

first year of life and in which the susceptibility to postvaccination encephalitis is highest. Without committing ourselves as to the etiology, it seems logical, therefore, that any procedure which would influence the vaccinated individual toward a more effective immunity response to vaccine might be of advantage in an attempt to prevent this complication”.

Armstrong then described his observations that plump, healthy animals reacted most severely to vaccine virus whereas scrawny, skinny animals reacted poorly or not at all to the same virus. Another observer quoted by Armstrong stated that spare and thin individuals tended to stand vaccination better than “plump, full-bloodied ones”. Of interest in this regard is the observation noted by Dr. Tom Rivers in an earlier chapter (22) where he noted the relative resistance of scrawny, urban youths to influenza virus compared to the apparent susceptibility of healthy, vigorous, sturdy rural farm boys. Armstrong also mentioned other laboratory studies where a previous infection tended to ameliorate the course of a subsequent infection. He also drew on epidemiological observations (23) related to factors influencing possible susceptibility to paralytic poliomyelitis. He stated that the incidence of poliomyelitis, a less “virulent” disease, seemed to be correlated positively with immunity to diphtheria as determined by a negative Schick test (in a controlled population study) (23). He also showed that susceptibility to scarlet fever, a more “virulent” disease, was also correlated, but to a lesser extent, with immunity to diphtheria.

To test the implications of these observations, Armstrong reasoned as follows: “Proceeding upon the homely fact that judicious exercise is essential for the functional well-being of familiar tissues – even to bones and teeth – it may be assumed that the

same is true of those tissues which constitute the defense mechanism, wherever and whatever they may be. It was therefore decided to determine whether a preliminary immunization by the injection of a non-specific antigen might increase temporarily the animal's efficiency in its reaction against a subsequent inoculation with vaccine". To test this hypothesis, Armstrong planned to immunize mice against various antigens and subsequently compare the number of deaths among previously immunized and non-immunized groups following intra-cerebral inoculations with a virulent vaccine virus, developed at the National Institute of Health, capable of producing a fatal encephalitis. A dose of virus was selected that was slightly less than sufficient to kill all of a group of normal mice. Diphtheria toxoid, broth and typhoid vaccine were used to make the preliminary inoculations, and normal saline was used as the control material. Diphtheria toxoid was used, however, in most of the tests for several reasons. Armstrong felt that it was known to be an efficient exerciser of the "immune mechanism". Also, if efficiency could be demonstrated experimentally, it could be utilized in children by the simple procedure of administering diphtheria immunization first, followed by vaccination against smallpox, rather than in the reverse order, as was the custom in many United States localities.

The mice were divided into groups and given two subcutaneous inoculations of the test antigens. After appropriate intervals, the mice received various dilutions of the vaccinia virus intra-cerebrally, and they were observed for 25 days. At the end of that period the diphtheria toxoid immunized mice had a 27 per cent survival rate compared to a 12 per cent survival rate for the control group. There were more survivals in the diphtheria toxoid immunized groups than in the other groups and the toxoid treated mice

tended to die later than the controls. These experimental results suggested a possible protective effect of prior diphtheria toxoid immunization against the lethal action of intracerebral vaccinia administration.

Despite this protection of a few mice from a cerebral virus infection by means of a previous non-specific stimulation of the defense mechanism, Armstrong stated that the protection did not necessarily lead to the conclusion that children could be similarly protected from postvaccinal encephalitis. He also stated that the final test in man must, of course (for obvious reasons), be sought in epidemiological investigation. It was in the hope of stimulating such investigations that Armstrong reported these experimental results. He also referred again (23) to the 1916 New York City Poliomyelitis Commission Report which noted that among 954 poliomyelitis patients one to four years of age that the attack rate among the Schick positive (diphtheria susceptible) was 6 to 7 times as high as among the Schick negative (diphtheria immune) patients. He quoted the Commission's observation as follows: "A susceptibility to one of the less contagious diseases indicates that the child is more apt to be susceptible to other contagious and infectious diseases". Armstrong, drawing on other studies from the Hygienic Laboratory, compared the susceptibility of other groups of patients to the "highly infectious" diseases such as measles and scarlet fever according to whether they were positive or negative by skin test to diphtheria and scarlet fever.

In discussing the available experimental results and epidemiological studies, Armstrong speculated that the various post infectious encephalitides, which were apparently on the increase, might be due to a common faulty response to infections on the part of a functionally inadequate defense mechanism. He stated that it was probable that

infections differed in their ability to exercise the immune system; as an example, he noted that many of the common respiratory diseases apparently gave little specific immunity and could hardly be expected, therefore, to call forth non-specific protection. In making this statement, however, Armstrong was handicapped by lack of information developed 20 to 30 years later by his protégé, Robert J. Huebner, his associates and many other investigators who discovered new groups of respiratory disease viruses with their multiple, variable immunological and antigenic specificities.

In closing his discussion Armstrong indicated that where primary school vaccination was practiced, it was probable, that for many children vaccinia was a notable experience, constituting their first exposure to a disease that gives a solid immunity. He felt that the evidence he submitted in his presentation suggested the advisability of giving the child, especially if more than one year old, the benefit of experience with the nonviable diphtheria toxoid, which, as far as he knew, had not caused encephalitis, before the child received inoculation with vaccine virus, a living antigen capable of infinite multiplication. He stated further, that even if no immunity to central nervous system involvement occurred, the fact that in the 20<sup>th</sup> century diphtheria had maintained a death rate seventy times as high as smallpox, would seem to dictate such a change.

Armstrong summarized his recommendations as follows: 1) the only practicable means so far suggested for the encephalitis occasionally noted following smallpox vaccination had to do with the vaccination procedure. 2) A suitable vaccination technique was defined as one using small, multiple, superficial insertions never over one-eighth inch in greatest diameter and which employed no routine dressing. 3) Infancy was the best time for performing primary vaccinations insofar as the prevention of

postvaccination encephalitis was concerned. 4) Evidence was presented which suggested that inoculation with diphtheria toxoid tended to render mice somewhat more resistant to vaccine virus administered intra-cerebrally. 5) It was suggested that primary vaccinations, especially after the first year of life, be deferred until contemplated immunizations against diphtheria or other diseases by means of inanimate antigens had been accomplished. 6) The hope was expressed that a recent preliminary exercise or mobilization of the immunity or defense forces might lead to a more efficient anti-vaccine-virus response, with the result that the ensuing reaction might tend to simulate primary infant or secondary vaccinations in their comparative mildness and freedom from postvaccination encephalitis. In support of this hope, Armstrong quoted again the epidemiological observation that possibly the high percentage of poliomyelitis cases recorded among diphtheria-susceptible children in New York City in 1916 might be due in part to an increased resistance to poliomyelitis among children immune to diphtheria.

It is apparent that the major accomplishments of Armstrong in vaccination research, along with the contributions of other members of the Hygienic Laboratory, influenced the practice of safe pediatric immunization procedures. The American Committee for Immunization Practices (ACIP) adopted the schedules for administration of vaccines in infancy, early childhood and adolescence based on these early recommendations and also the introduction of new vaccines as they became available for use. Smallpox vaccination is not recommended currently for administration in the first year of life. It is preceded by other immunizations in early infancy according to the ACIP schedule of immunizations. The usual standard medical texts, though comprehensive and updated with new editions every few years, unfortunately, leave in the dust the



accomplishments of the original investigators and do not record the historical antecedents of many “routine” day-to-day medical practices and procedures.

Notes – Smallpox Vaccination and Tetanus; Post-vaccination Encephalitis

- 1) Armstrong, C.: Tetanus in the United States following the use of bunion pads as vaccination dressings. *Public Health Reports* 40: 1351-1357, June 26, 1925.
- 2) Armstrong, C.: Tetanus following vaccination against smallpox and its prevention with special reference to the use of vaccination shields and dressings. *Public Health Reports* 42: 3061-3071, December 16, 1927.
- 3) Armstrong, C.: Postvaccination tetanus and its prevention. *Journal of the American Medical Association* 90: 738-740, March 10, 1928.
- 4) Armstrong, C.: Intradermal (injection) vaccination. *Journal of the American Medical Association* 91: 1530-1531, November 17, 1928.
- 5) Armstrong, C.: Vaccination. *Hospital Social Service* XIX: 390-398, 1928
- 6) Armstrong, C.: The role of the vaccination dressing in the production of postvaccinal tetanus. *Public Health Reports* 44: 1871-1884, August 2, 1929.
- 7) Armstrong autobiographical notes.
- 8) Centers for Disease Control (CDC), Smallpox Vaccine Overview, April 24, 2004.  
[http:// www.bt.cdc.gov/agent/smallpox/vaccination/facts.asp](http://www.bt.cdc.gov/agent/smallpox/vaccination/facts.asp).
- 9) McCullough, D. *John Adams*, Simon and Schuster, New York, May 22, 2001.  
David McCullough won the Pulitzer Prize in 2002 for this biography.
- 10) *Classics of Medicine and Surgery* collected by Camac, C. N. B., Dover Publications, Inc., New York, Henry Schuman, New York, 1909.Pp: 206-296.

- Series of essays by Edward Jenner (1749-1823) describing the discovery and introduction of vaccination into the practice of medicine.
- 11) *Source Book of Medical History* Compiled with Notes by Logan Clendening. Waterhouse, B.: "On the smallpox." Dover Publications, Inc. New York, Henry Schuman, New York, 1942. Chapter XXVII: The history of the kine-pox, commonly called the cowpox. Pp. 301-306. Part of a collection of essays on smallpox. Dr. Benjamin Waterhouse described the introduction of smallpox vaccination into the United States.
  - 12) Mandell, Ibid 3<sup>rd</sup> Edition. Chapter on anaerobic bacteria, Bartlett, J. G. p.1842; Chapter on tetanus (following), Cate, T.
  - 13) Quoted by Armstrong in note 1 this chapter.
  - 14) Fauci, A. S., Editorial: Smallpox vaccination policy. The need for dialogue. *New England Journal of Medicine* 346: 1319-1320, April 25, 2002.
  - 15) Frey, S. E, et al: Clinical responses to undiluted and diluted smallpox vaccine. *New England Journal of Medicine* 346; 1265-1274, April 25, 2002.
  - 16) Frey, S. E. et al: Dose-related effects of smallpox vaccine. *New England Journal of Medicine* 346: 1275-1280 April 25, 2002.
  - 17) Calabresi, M. and August, M.: Was smallpox overhyped? *Time Magazine* p. 16, July 26, 2004. New York.
  - 18) Witte, G.: Government considers new smallpox vaccine. *The Washington Post* Section E, p. 1, April 15, 2004, Washington, DC.
  - 19) Armstrong, C. : Postvaccinal encephalitis. *Public Health Reports* 44: 2041-2044, August 23, 1929.

- 20) Armstrong, C.: Postvaccination encephalitis with special emphasis reference to prevention. *Public Health Reports* 47: 1553-1568, July 22, 1932.
- 21) There was little available in the medical literature about the pathogenesis of the encephalitis following smallpox vaccination at the time this manuscript was written. Other authors have speculated about an “immunologic” mechanism as the cause of this complication.
- 22) Rivers, *Ibid.* Pp.52-53.
- 23) Frost, W. H. quoted by Armstrong with respect to the 1916 poliomyelitis epidemic in New York City.

## Psittacosis (“Parrot Fever”)

Charles Armstrong’s next major investigative challenge, which also became potentially life threatening for him, occurred in the winter of 1929-1930. He was still engaged in the experimental study of the effects of vaccinia virus pneumonia and the pathology of generalized vaccinia in rabbits with his colleague, pathologist Ralph D. Lillie (1, 2). He also continued to formulate his hypothesis about the etiology of post-vaccinal encephalitis (3). Dr. George W. McCoy, Director of the Hygienic Laboratory, called upon Armstrong to study the new public health problem caused by infected parrots and other psitticine birds (parakeets, cockateels, love birds and others). Armstrong was able to identify initially that the agent did not grow on ordinary media for culturing bacteria, that it was not filtered by the various size bacteriologic filters, that the tissues and excreta from infected parrots were highly infectious for other healthy parrots, laboratory animals and humans. On the basis of these observations he was able to recommend highly effective quarantine provisions to prevent the importation of sick and infectious parrots.

Ritter, a Swiss scientist, first described psittacosis in 1879 (4). Ritter reported the disease after a Swiss family who kept parrots and finches experienced severe illness in 5 family members and 2 visitors 3 weeks after one of the birds died. Three of the family/visitors died of their illnesses. Isolated reports of the disease occurred in the world’s medical literature after Ritter’s report. In 1892 E. Nocard isolated an organism from the wings of parrots during an outbreak in Paris. Nocard identified the organism as a

salmonella bacterium, and taxonomists labeled the organism *B. psittacosis* *Nocard*.

Scientists recognized this organism as the cause for psittacosis for many years.

In August 1929 a large outbreak of psittacosis occurred in Argentina. Toward the end of 1929, around November, an outbreak of psittacosis with increasing intensity occurred almost simultaneously on three continents – Europe, North America, and South America (5, 6). A shipment of diseased parrots for the Christmas trade from a South American port was most likely the cause of the widespread outbreak. In the United States cases began occurring in November and December 1929. Doctors in the United States had no previous experience with the disease. The investigators at the Hygienic Laboratory, whose activities exposed them to a variety of serious communicable diseases, had never seen any cases. However, the previous reports from Argentina earlier in 1929, describing patients with high fever, lung congestion, slow pulse and early delirium in association with sick or dying parrots, enabled physicians to make diagnoses quickly when the epidemic began to appear in the United States. The fatality rates were high. Of 169 cases reported from November 1929 to May 1930, 33 were fatal (5, 6, 16). An initial case in close proximity to the Hygienic Laboratory in Bethesda, Maryland occurred in Annapolis, Maryland. Shortly thereafter additional cases were reported from Baltimore and Philadelphia (probable ports of entry) and later Washington, DC. Then other areas began reporting cases.

There is some conflict in the time sequence of the next series of events (5, 6). In the account by Furman (6), she reported “that early in January 1930 thirty-six cases of psittacosis were reported to Surgeon General Hugh S. Cumming, with three deaths in nearby Baltimore alone. Telegrams from State health officers and others, asking for

advice on psittacosis, deluged the desk of the Surgeon General. He turned the problem over to Dr. McCoy, Director of the Hygienic Laboratory, who put Charles Armstrong in charge of psittacosis research. On January 6, 1930 Dr. Armstrong headed a group of physicians sent to Annapolis to see a case or cases of psittacosis.” Armstrong brought back no suspect parrots on this trip, but soon he was bringing back suspect parrots from Washington, DC, Baltimore and the Eastern Shore of Maryland. Others were shipped in from Maine and Ohio.

Experimental work on psittacosis commenced at the Hygienic Laboratory on January 16, 1930. Readers interested in a colorful and life threatening account of Charles Armstrong’s duel with psittacosis are referred to Chapter 6 titled “McCoy” in Paul DeKruif’s book *Men Against Death*. (7). (The investigators at the Hygienic Laboratory were favorite subjects about whom he wrote lovingly, sincere tributes in his flamboyant “microbe hunter” style. Among the people he portrayed were Joseph Goldberger [pellagra], Edward Francis [tularemia], Alice Evans [undulant fever = brucellosis] and others. DeKruif received his doctorate at the University of Michigan in microbiology. He started a promising career in research at the Rockefeller Institute but he resigned or was terminated because of a professional impropriety. He embarked upon a literary career of popular medical writing becoming well known, successful and prolific in the 1930-1940s with many books and magazine articles. Later, he also became active and influential in the National Foundation for Infantile Paralysis and the March of Dimes. He was the science adviser to the author Sinclair Lewis when the latter was writing the novel *Arrowsmith*. DeKruif took this opportunity to draw viciously satiric portraits in the novel of his former senior associates at the Rockefeller Institute (8)).

Based on the initial early results of Armstrong's investigation, on January 24, 1930, President Herbert Hoover (5) issued Executive Order No. 5264 which "prohibited the immediate importation of parrots into the United States, its possessions and dependencies from any foreign port except under such conditions as might be prescribed" until the causative organism and means of transmission of psittacosis could be studied. Surgeon General Cumming, at the same time, started holding regular staff meetings to put into effect the provisions of the executive order. Over time and into the present era, regulations for the importation of parrots and other exotic birds have been established and administered by various United States government agencies (5, 9).

Armstrong and his trusted laboratory technician, Henry "Shorty" Anderson, (5, 6, 7) delved immediately into efforts involving irritable, aggressive birds that demonstrated extremely unhygienic habits. The birds projected their fecal and oral droppings out of their cages onto the floor surrounding their cages and scattered their food in similar fashion. The cages were improvised arrangements consisting of a few conventional open cages but primarily of metal garbage cans with wire mesh covers on top. Armstrong was aware that the ill birds were highly contagious. He tried to confine potential infection from the rest of the building by working with his assistant in two small dark basement rooms. For other primitive sanitary precautions, they kept the birds behind moist curtains soaked in disinfectant, and they placed troughs containing cresol in the doorways. They also scrubbed down the walls and floors with disinfectant. They did try to take some minimal isolation precautions themselves; they worked with heavy rubber gloves and wore either laboratory aprons or smocks. The modern extensive bio-safety protective measures were not in common use in microbiology research institutions in the 1920-

1930s except for a few centers such as the Rockefeller Institute (10). There seemed to be a cultural disdain among most early microbiologists for safety measures that they felt would impede their professional manual proficiency in the laboratory.

Within a few short days, Armstrong was able to produce a transmissible illness from sick to healthy birds either with cage droppings from infected birds or the ground up tissue of a parrot that had died. Some of the sick birds died but others apparently survived the infected material and many of these became asymptomatic carriers of psittacosis. Armstrong submitted many infectious specimens for examination to Dr. Sara Branham (11), a skilled Hygienic Laboratory bacteriologist, who hunted in vain for evidence of the salmonella organism described by Nocard earlier in France. She was unable to find this organism or any other bacteriologic organism in the material submitted to her by Armstrong. Bacteriologic filters (12) did not hold back the agent that was producing clinical and laboratory signs of infection with psittacosis in the healthy birds. Armstrong had thus isolated a filterable agent that did not grow on the usual bacteriologic media and that produced infection in birds.

Disaster struck on the morning of January 25 only nine days after Armstrong and Shorty Anderson had begun their laboratory investigations. Armstrong, who was feeling fine, came into the “old red brick building on the hill” and found Shorty, slumped over his office desk, obviously very ill, with a high fever and complaining of a severe “throbbing, splitting” headache. It was not difficult to presume that he had probably acquired infection with psittacosis. This precipitated his admission to the old United States Naval Hospital that was then adjacent to the Laboratory in downtown Washington, DC Shorty’s illness worsened progressively. His hospitalization at this particular juncture



presented an unforeseen dilemma inasmuch as the experimental work started by Armstrong was still far from completion. In a rare display of leadership, courage and responsibility and over the objections of other Laboratory staff members and family, Dr. George McCoy, the Director, joined Armstrong down in the dank basement rooms and assisted him in the duties normally performed by the ailing Shorty Anderson.

Anderson's condition continued to deteriorate with the massive involvement of his left lung by psittacosis, persistent high fever, and "toxicity" from uncontrolled infection. Armstrong would visit Shorty as often as he could in the hospital. During the latter stages of his illness punctuated by fluctuating periods of delirium and mental clarity, Shorty, who scrupulously and compulsively was in the habit of personally paying his bills each month, asked Armstrong, as a dying request, to make sure that all his bills were paid. Shorty died on February 8, 1930, was autopsied, and buried with full military honors (He had been in the Navy.) in Arlington National Cemetery. Almost the entire staff of the Hygienic Laboratory attended the funeral with one notable exception. On February 8, the day Shorty died, Charles Armstrong was admitted to the Naval Hospital with a temperature of 104F and a diagnosis of psittacosis. Dr. McCoy was the person who had to carry out Shorty's wish to have all his debts paid.

On February 6 Armstrong noted a little chill and skin tenderness shortly after coming into the Laboratory. The next day he lost his appetite completely. He stole away to a remote area, took his temperature surreptitiously and noted a fever of 102F. The next day he was in the hospital. A chest x-ray showed a white shadow enveloping the lower half of his left lung, and serial x-rays showed progression of the pneumonia gradually filling up the lung. When Dr. McCoy saw the rapid spread of the disease in Armstrong,

he decided to try a desperate attempt to slow or reverse the process by using a method of unknown, unproven or questionable value: namely, the administration of convalescent blood serum to Armstrong from a patient recently recovered from psittacosis. In the 1930s there was no knowledge of the hazards of blood borne pathogens or methods for the testing of the still undiscovered hazards of hepatitis A – E, human immunodeficiency virus or other viral agents. Blood could still be cultured to ensure sterility against the usual bacteria. There was also no guarantee that the administration of convalescent serum would be effective in ameliorating the disease. Despite these reservations, McCoy called upon Dr. Roscoe R. Spencer of the Rocky Mountain Laboratory to come east and to help search for potential blood donors among patients recently recovered from psittacosis. (Dr. Spencer was to be honored later that year for the development of a tick-based vaccine to prevent Rocky Mountain spotted fever.) (13) Dr. Spencer traveled extensively around the State of Maryland. Accounts differ about the source of the convalescent blood finally given to Armstrong (6, 7). DeKruif reported that the blood came from an elderly lady who graciously refused payment if the blood were to be used to try to save a life. Furman reported that Spencer procured blood from the Johns Hopkins Hospital in Baltimore, Maryland through Dr. Harold L. Amoss. The blood was given to Armstrong who improved immediately and recovered over a period of several weeks.

When Armstrong became ill, McCoy carried on with the investigative work himself, confirming and rechecking the experimental findings. He forbade any of the other Laboratory scientists to come to the basement rooms or to try to help with the work. McCoy, himself, never became ill. Then unexpected happenings occurred. Laboratory personnel, who had no contact with the basement area or worked in proximity to the

rooms where the work was in progress, gradually became ill with psittacosis and required hospitalization. Including Armstrong and Shorty Anderson, McCoy (14) reported a total of 11 cases developing among Hygienic Laboratory personnel between January 25 and March 15, 1930. The reason for the spread of psittacosis to other personnel not in direct contact with infected birds was not apparent. Rivers (15), in his oral autobiography, stated that the only thing hygienic about the Hygienic Laboratory was its name. He described the facility as unbelievably filthy, and he speculated that the psittacosis organism was possibly disseminated around the Laboratory by the large cockroach infestation. In any event, McCoy realized that the building was massively contaminated with psittacosis and that drastic action had to be taken to contain the epidemic within the Laboratory. McCoy (14) observed that there was a rather long and fairly uniform interval between cases down to and including the fourth case, while the remaining seven cases formed a group with dates of onset varying to only such an extent as to lead to the suspicion that all were infected from a common source, but the source was unknown. McCoy, considering the incubation period of psittacosis to be 9 to 10 days, suspected that the group of seven cases probably was infected in the early part of March.

McCoy decided to shut the Laboratory down for the first time in its history on March 15, 1930. The remaining healthy personnel carried out the experimental animals not involved in psittacosis research to temporary quarters. McCoy, himself, went down to the basement rooms, exterminated with chloroform all the animals used in the psittacosis studies, including sick and healthy parrots, all the guinea pigs, mice, rats, pigeons and monkeys and burned all the dead bodies in the Laboratory incinerator. He then disinfected all the animal cages with cresol. The windows of the Laboratory had been

sealed shut for what was to come next. McCoy had sent for the fumigation squad from the Quarantine Station at Baltimore, Maryland. When all the people were out of the North and South Buildings by 2:00PM, McCoy turned the fumigation squad loose to begin fumigating the tightly sealed empty building with heavy applications of cyanide gas designed to exterminate any residual creeping or crawling creatures in the building. The legend goes that so much cyanide was used, sparrows flying 50 feet over the building, stopped in mid-flight and plummeted to earth.

The laboratory epidemic ran from January through March 1930. The last four patients left the hospital early in April. Since there were still unanswered questions that needed to be addressed, McCoy transferred psittacosis research to the Quarantine Station at Curtis Bay near Baltimore Harbor in April. Armstrong had recovered fully by this time. He set up a laboratory in a deserted building on the Station with the help of a new assistant, Mr. Lanham. Lanham had worked in the Hygienic Laboratory as a night watchman and had also recovered from his laboratory-acquired psittacosis. McCoy considered that both Armstrong and Lanham were immune and unlikely to become ill again from psittacosis. Armstrong realized that he would be away from his Washington, DC home for a long period, so he moved his family, his wife and daughter, to Curtis Bay for the summer. He invited his interviewer and friend, DeKruif, to visit him at Curtis Bay but the latter found “many excuses” to decline the invitation (18).

While he was at Curtis Bay, in addition to further investigative studies, Armstrong prepared an epidemiological review (16) that he presented June 18, 1930 in Washington, DC to an annual meeting of Public Health Service and State and Territorial Health Officers. He recorded that the causative organism that had been discovered almost

simultaneously by several investigators, including himself and Dr. McCoy, was a filter-passing agent present in the sputum and organs of infected persons, and in the organs and discharges of infected birds. It was not the bacillus described by Nocard in Paris. The organism that caused psittacosis appeared to be dispersed through the air easily and the parrots seemed to give off the discharges in a dry form. Spread was from bird to man. Person to person spread had not been observed. He established that the extensive series of recent psittacosis epidemics totaled 850 cases in 14 different countries. More women than men had the disease. He speculated that the women spent more time in the homes where the birds were kept as pets and that they did more caring for the birds than the men did. Of the 167 cases reported in the United States during the 1929 and 1930 epidemics, 105 were women and 62 were men. There were 33 deaths all in persons under 30 years of age. Discovery of the infectious agent early in the course of Armstrong's investigation led to the issuance of the Executive Order (noted previously) that placed limitations and established regulations on the importation of parrots and "love birds" into the United States.

The events associated with the psittacosis epidemics and the Hygienic Laboratory's dramatic involvement probably helped propel the final enactment of the legislation to expand the role of the Public Health Service and the Hygienic Laboratory in the overall responsibility for the Nation's health. In the latter 1920s, increasing legislative activism by members of Congress and lobbying efforts by senior Public Health Service staff finally led to the creation of the National Institute of Health to succeed and assume the duties and mission of the Hygienic Laboratory. For details of the creation of the National Institute of Health, consult the excellent exposition by Dr. Victoria A. Harden

(17). The law of May 26, 1930, written by Senator Joseph E. Ransdell, Democrat, Louisiana, greatly widened the scope of the Hygienic Laboratory and changed its name to the National Institute of Health (17). Initially the major changes were in the stationery headings and the new name for the Hygienic Laboratory Bulletin. The impending economic depression retarded significant growth until the move to the current campus in Bethesda, Maryland in 1938 and after World War II.

A postscript to the Hygienic Laboratory's experience with psittacosis in 1930 began on September 22, 1932 when Senator William E. Borah wired the National Institute of Health for convalescent serum for Mrs. Borah who was seriously ill with psittacosis in Boise, Iowa. Mrs. Borah had her own collection of "love birds" for a long period. Senator Borah had known of the psittacosis outbreak at the Hygienic Laboratory and that all the patients, except Shorty Anderson who succumbed to the disease, had been treated with convalescent serum obtained through the strenuous efforts of Dr. Roscoe R. Spencer. Unfortunately, no stored serum was on hand when Senator Borah's request reached the National Institute of Health. When Armstrong learned of the need for the serum, he offered his own blood for Mrs. Borah's treatment. Due to the emergency of the situation, Dr. W. T. Harrison, Armstrong's associate of many years, withdrew the blood from Armstrong and processed it immediately to separate out the serum. The government made special arrangements to ship the blood immediately by air. The Associated Press, national and local newspapers printed almost hourly logs of the serum's progress from Washington, DC to Boise, Idaho (19). When the serum arrived, the attending doctors had a professional disagreement. The older physician in charge declared that it was no use giving the patient the serum since she was dying. The younger, more enterprising and

optimistic associate, advised giving her the entire amount (12 ounces = 350ml) at once by vein. Senator Borah concurred with the younger physician, and Mrs. Borah received the serum. She improved and recovered.



Mrs. William E. Borah, the Senator's wife, visiting the National Institute of Health on February 9, 1933. Hosting her visit were Surgeon General Hugh S. Cumming on the left and Dr. Charles Armstrong on the right. Courtesy of Mary Emma Armstrong.

When Mrs. Borah was well, she returned to Washington, DC. On February 9, 1933, Mrs. Borah visited the “Hygienic Laboratory” (now the National Institute of Health) accompanied by Surgeon General Hugh S. Cumming, and she met Dr. Armstrong (19). The newspaper accounts (19) described Armstrong at that time as “stocky, red-haired with a ruddy complexion.” Mrs. Borah’s first words to him were, “I came to thank you for saving my life.” He blushed, further reddening his facial coloration. She flustered him further by remarking, “I have some of your blood flowing through my veins. Now,

what relation are we?” The modest Armstrong was embarrassed, and disclaimed any credit for her recovery. After these initial pleasantries, Surgeon General Cumming and Armstrong escorted her through the laboratory about which she had read in Paul DeKruif’s book “Men Against Death” (7). She wanted to see all aspects of the laboratory operations. Mrs. Borah said that all through her convalescence from psittacosis she had been reading about the “health heroes” who inhabited the rambling red brick building on the Potomac. She wanted to meet most of them and to see them working with microscopes, test tubes, rabbits and rats making discoveries that would save lives – as miraculously as hers had been saved. So, with Armstrong and the Surgeon General as guides, she met her “heroes” and she explored rooms filled with cultures and cages, queer odors and queerer experiments (20).

Senator Borah felt strongly about Armstrong’s contribution to his wife’s recovery. Although government employees are not allowed to accept favors for their work, the Borahs, in gratitude presented to Mrs. Armstrong an exquisite, imported ceramic Chinese bowl that is still in the family’s possession (21).

During the epidemic at the Laboratory, the investigators used convalescent serum empirically since no other reasonable therapy was available. They had no controlled experience to determine its efficacy since many patients recovered from psittacosis without the use of serum. When Armstrong wrote later about psittacosis in 1948 (22), he did not mention serum as a treatment. Psittacosis is treated currently with a variety of antibiotics.

The following is an excerpt from the oral interview conducted by Wyndom Miles in October 1966 reflecting Armstrong’s recollection of events: “ I was one of the first



men who came into the Service who began to specialize. They realized knowledge to be learned was growing much faster than the ability to learn it, and you couldn't be an expert in everything. Dr. McCoy was instrumental in that.

“Some of the things that worked to the advantage of the service was in regard to psittacosis. There had been an outbreak of psittacosis in South America. A bunch of playwrights had gone there, and all came down with psittacosis. It was in the newspapers. We were on the alert for it. There was a case in Annapolis where a doctor had a woman patient who had received a parrot for Christmas, and she was taken sick. The doctor didn't know what she had. His wife was reading the paper and read about psittacosis in South America. The wife knew the patient had received the parrot, which had died, so she showed the article to the doctor. He contacted the Public Health Service to see if this was a case of psittacosis. I had never seen a case of it, but it was suggested I go to the library to see what I could find and then go to Annapolis to see what I could find out. I found a brochure but it was full of misinformation. I went to Annapolis and asked the woman if she still had the cage. She did, and I took it to the Laboratory. I also went to see the State Health Officer to let him know what I'm doing. Dr. McCoy always insisted we see the State Health Officer first. Dr. Riley wasn't in but the old laboratory man wanted to know if I would let him have some of the cage cleanings. I gave him some. We were taught that this was due to salmonella and bacillus psittacosis. This was proven wrong of course. It was quite different than this thing we had. I told him not to be sure this was a bacteria, it might be a virus. He said he'd be careful. He developed psittacosis and died. We got some parrots and inoculated them and soon they came down. My helper was taken sick one weekend, and instead of reporting in sick, he stayed home. When he came in on

Monday morning, he told me how sick he was and how he had been up all night near a radiator with a blanket around him and couldn't keep warm; we suspected psittacosis right away. Dr. McCoy made arrangements to put him in the Navy Hospital. He also died. On the day he died, I was taken sick. I had a temperature of 102F and went home. Arrangements were made to put me in the hospital. I had psittacosis. There were 9 or 11 cases (in the Laboratory including guest investigator Dr. Ludvig Hektoen). Shorty Anderson died, the rest of us lived. There was no treatment. Dr. Stenson (? Spencer) suggested we get some serum from the people who recovered. If they could give it to us, we might have some antibodies that we could passively transfer to an individual. I was the first one to get serum. When Mrs. Borah took sick, he (Senator Borah) wired the laboratory for serum immediately. Our little supply had been exhausted. I suggested we take some of my blood and send it out. It wouldn't do any harm. They decided to do this. They bled me, and Dr. (W. T.) Harrison stayed up all night preparing it. It had to be prepared carefully because there was no chance to study it for sterility. He got it ready and took it down to the waiting airplane and away it went to Boise, Idaho. When it arrived they (the attending physicians) were having a consultation. The old doctor had called in a younger doctor. The old doctor said there was no use giving the serum to Mrs. Borah as she was dying. The young doctor disagreed with that. It was very valuable serum and lots of money was spent to get it. The young doctor said he would give it to her, but wouldn't give it in small doses, rather, give it to her all at once in the vein; if it had any virtues it would have full chance to work; if it hadn't any, it wouldn't do any harm. The old Senator was for that, and it was decided to give it before the old doctor changed his mind. She was given the serum, put back to bed and her temperature began

to fall. By morning she was feeling much better. We were never sure it was the serum that cured her; we couldn't protect mice with the serum at all. However, Senator Borah was convinced that it saved her life. He was a very influential man at that time and very helpful to the service." These homely musings were recollection of events many years after their occurrence, events in which Armstrong played a major, pioneering, discovery role.

Initially the Hygienic Laboratory performed the early experimental studies with the psittacosis agent but gradually other prominent scientists became involved investigating the nature of the organism. Almost simultaneously in the early 1930s, Drs. Ralph D. Lillie of the Hygienic Laboratory, A. C. Coles of the Lister Institute in London and Walther Levinthal of the Robert Koch Institute at Dahlem, Germany reported the presence of distinctive clusters of inclusion bodies in the cytoplasm of patients who had died of psittacosis (23). These became known as "Lillie-Coles-Levinthal" or "L-C-L" bodies and are present in diseased tissues caused by other members of the group of organisms with which the psittacosis agent has been identified. Dr. Thomas Rivers (23) studied the agent in other laboratory hosts finding the white mouse especially susceptible to infection. The agent can grow in embryonated chicken eggs and in tissue culture cell lines. Dr. Karl F. Meyer of the Hooper Institute, University of California San Francisco School of Medicine was also a prominent, early investigator of psittacosis. He coined the term *ornithosis* because the agent can be carried by many species of birds besides parrots (psitticine birds). Over the course of the ensuing years up to the present, the group of agents, of which psittacosis is one member, has been studied extensively in the laboratory and in the clinic. These agents have been classified as *Chlamydiae*.

“ The Chlamydias (24) are obligate, intracellular bacteria whose extreme biosynthetic defects in intermediate metabolism and energy generation cause them to be absolutely dependant on a host cell to grow and replicate. They are among the most common of all human infectious agents and produce much disability although little mortality.” Although they contain many complex biochemical metabolic systems, their lack of certain essential enzymes and amino acids render them incapable of independent existence outside a living cell.

The chlamydia are classified into three major human disease divisions:

- 1) *C. trachomatis*: a) The classical eye infection, trachoma, seen primarily in underprivileged children in developing countries, spread by fomites and flies. b) Sexually transmitted diseases spread by direct contact among sexually active teenagers and adults including urethritis/cervicitis, epidymitis/salpingitis, and lymphogranuloma venereum. In this cluster are also inclusion conjunctivitis from infected pregnant mothers and infant pneumonia.
- 2) *C. psittaci*: The psittacosis agent spread as an aerosol from infected birds and causing atypical (non-bacterial) pneumonia of various degrees of morbidity and mortality. A more recent clinical finding has been recognition of occasional cases of blood culture-negative endocarditis (infection of heart valves).
- 3) *C. pneumoniae*: A recently recognized member of the group, originally labeled the TWAR agent, that causes a febrile respiratory disease associated with sore throat, cough and mild atypical pneumonia. Originally confused with psittacosis, it shares less than 10 per cent homology with the other three chlamydial species.

- 4) *C. pecorum*: A non-human species found primarily among ruminant animals (cattle and others).

Fortunately, chlamydial infections respond to several groups of antibiotics including tetracyclines and macrolides (erythromycin and similar) but not to sulfonamides. For this reason, although they are debilitating, uncomfortable and inconvenient, they present lesser dangers than when Armstrong and colleagues were employed on their initial groundbreaking efforts to elucidate the nature of these threatening pathogens. For current information about psittacosis and chlamydia, the reader may consult the most recent editions of Cecil's *Textbook of Medicine* and Mandell, et al., *Principles and Practice of Infectious Diseases*.

#### Notes – Psittacosis

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- 13) A) Furman, Ibid., p. 371
- B) Harden, V. A.: *Rocky Mountain Spotted Fever, History of a Twentieth-Century Disease*, The Johns Hopkins University Press, Baltimore and London. 1990. p. 144.
- 14) McCoy, G. W.: Accidental psittacosis infection among the personnel of the Hygienic Laboratory. *Public Health Reports* 45:843-845, April 18, 1930.
- 15) Rivers, Ibid. p. 157.
- 16) Armstrong, C.: Psittacosis. Epidemiological considerations with reference to the 1929-1930 outbreak in the United States. *Public Health Reports* 45: 2013-2023, August 29, 1930.
- 17) Harden, V. A., Ibid. *Inventing the NIH*.
- 18) DeKruif, Ibid. *Men Against Death*, pp. 202, 203.
- 19) The nationwide outbreak of psittacosis, including the cases at the Hygienic Laboratory, provided abundant material for publication by the national and local news media. Articles appeared in *The New York Sun*, January 11, 1930, *The Washington Herald*, January 9, 1930, *The New Orleans Times-Picayune* May 29, 1930 and many others. A summary article appeared a few years later in *The Washington Post*, July 25, 1937. Armstrong also received a letter from President W.H. McMaster of Mount Union College on February 13, 1930 inquiring about his health. In the aftermath episode involving Mrs. Borah's illness in 1932 there was a similar explosion of news media coverage. Of interest, on January 24, 1934 Armstrong received a note of thanks from Ms. Marie Dressler, the motion picture actress for autographing DeKruif's book *Men Against Death*.

- 20) Armstrong oral interview with Wyndom Miles.
- 21) Conversation with Miss Mary Emma Armstrong.
- 22) Armstrong, C. and Davis, D. J.: *Psittacosis*. Chapter XVIII-A Oxford University Press, 1948, (Revision) 488 (15) – 488 (25).
- 23) Rivers, *Ibid.*, p. 158.
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## Domesticity, Career Recapitulation, Philosophical Musings

At this juncture of Charles Armstrong's biography in science, it is probably appropriate to pause and consider the more personal aspects of his life after his joining the United States Public Health Service; these have been alluded to previously only briefly. In contrast to Armstrong's materialistic and pragmatic reasons for choosing his wife in 1916 while he was in internship and contemplating a career in the private practice of medicine, old fashioned romance and true love directed his choice when he finally married his college classmate (1910) Elizabeth Alberta Rich. They were married June 21, 1920 and the union lasted until 1965 when Mrs. Armstrong passed away. The marriage occurred in the interval between Dr. Armstrong's completion of the influenza epidemic study on Kelleys Island, his arrival at the Hygienic Laboratory and his involvement with the typhus epidemic at the San Juan Navajo Indian reservation. Their only child, Mary Emma, was born August 15, 1924. Dr. and Mrs. Armstrong with Mary Emma was a close-knit, strong family unit who remained mutually supportive during their lifetimes. Mary Emma still maintains ties to family members in Ohio.

Mrs. Armstrong and Mary Emma also had critical pressures and anxieties during those episodes when Dr. Armstrong became seriously ill from the infections acquired from the organisms to which he was exposed in the laboratory. During at least one of these episodes, when he had tularemia pneumonia in Hamilton, Montana, his physicians alerted them on several occasions to be prepared to make a final visit away from Washington, DC in expectation of his impending death. Fortunately, he survived. Despite

the inherent dangers of his occupation, the family never suggested that that he should abandon his career, and they were always proud of his scientific accomplishments.

Dr. Armstrong shared with his wife and daughter some of his experiences at work and observations about his colleagues. Recollections about the same event, however, differ among participants in the event. As an example, Dr. Robert J. Huebner (1) described in laudatory terms his affection for Armstrong and the beneficial manner with which he was introduced to his work experience at the Division of Infectious Diseases in 1944. By contrast, Armstrong at the time, according to his daughter (2), said at the dinner table, “We have just brought on a cocky, new young fellow into the laboratory. We will have to teach him a thing or two.” Gradually, though, the relationship between Huebner and Armstrong blossomed into one of deep affection, admiration and professional intimacy as each grew to recognize their mutual intellectual and research talents.

Armstrong always remained a supportive alumnus of his college, Mount Union College of Alliance, Ohio. The college also maintained a keen interest in his increasingly impressive career. On March 20, 1933, W. H. McMaster, President of Mount Union College and a personal friend, sent Armstrong a letter (3) addressed to “Dear Dr. Charles” stating that the faculty would like the privilege of recommending him to the trustees for the awarding of an honorary degree at the next Commencement which was to be held on Tuesday June 6, 1933. President McMaster also asked Armstrong for his preference of the type of degree to be conferred: Doctor of Science (D. Sc.), Doctor of Philosophy (Ph. D.), or Doctor of Public Health (D. P. H.). Armstrong preferred the Doctor of Science Degree. In a reply on March 28 (4) President McMaster stated that the degree would be Doctor of Science and that the trustees would endorse it unanimously at

their next meeting on April 4, 1933. President McMaster also wrote, “Plan to be here Commencement June 6<sup>th</sup>, when the degree will be conferred and be sure to bring your wife who also has a warm spot in all our hearts.”

The May 1933 Mount Union College Bulletin (5), announcing Armstrong’s address to the Annual Alumni Banquet, included a brief curriculum vitae and the chronology to date of his scientific activities and achievements that were the basis of awarding the honorary degree. To recapitulate: When he was an Epidemiologic Aide to the Ohio State health Officer in 1919, initial public notice of his work came in connection with his investigation of the botulinum toxin outbreak in Alliance and Canton, Ohio. His was the first demonstration that spoiled ripe olives were capable of transmitting botulinum poisoning. This investigation resulted in the revamping in the industry of the canning procedure for ripe olives (especially in California). His next major study was the investigation of the spread of influenza in an isolated (Kelleys Island) community. These two investigations, impressive in their thoroughness, resulted in his assignment to the Hygienic Laboratory in Washington, DC. His first major accomplishment in this assignment was the demonstration that tetanus following smallpox vaccination was caused by bunion pads contaminated by tetanus spores or by the presence of any type of occlusive dressing over the vaccination site. He became interested in the complication of postvaccinal encephalitis. On the basis of experimental data, he postulated concepts and developed possible strategies for avoiding this complication. In his various duties with the Hygienic Laboratory he carried out investigations of many diseases, accompanied by the appropriate reports, including control of typhus fever among the Navajo Indians, plague in Puerto Rico, milk-borne diseases, dengue fever, hay fever and poliomyelitis.

Most recently, he had isolated the causative agent of psittacosis (parrot fever) and showed that it was a filterable organism that did not grow on the usual bacteriologic media.

In 1924, the United States Public Health Service sent Armstrong abroad under a grant from the Rockefeller Foundation to make a study of laboratory methods and procedures in European institutions. In March 1932 he delivered the DeLamor Lecture at Johns Hopkins University and in May 1932 the Cutter Lecture at Harvard, honors awarded for outstanding contributions in public health both in the United States and abroad.

In recognition of his epidemiological studies, the American Society of Epidemiologists elected him as its president for 1933 succeeding Professor Milton J. Rosenau of Harvard.

During this period, he was also a member of the Division of Medical Sciences of the National Research Council.



Dr. Charles Armstrong in the old Hygienic Laboratory-NIH Building in Washington, DC, undated, performs an autopsy on a monkey. Courtesy of the National Library of Medicine.

On June 6, 1933, Dr. Armstrong received his honorary degree at the Commencement Exercise. At 6:00 PM he attended the Mount Union College Alumni

Association Annual Banquet and Reunion (5) held at the Alliance Women's Club where he was to give the evening's main address. The banquet menu included fried chicken, creamed new potatoes, asparagus with Hollandaise sauce, hot rolls, jam, pineapple mango salad, strawberry pie and ice cream, and coffee. Fortified by this substantial meal, Armstrong launched into his talk entitled "Education and Research" (5). Despite the suggestion that he describe his adventures investigating psittacosis and its personal peripheral aspects, he said he preferred to begin his talk about more current customs and general social trends in the United States of the 1930s. He started by particularly deploring students' early search for specialization in education. This trend, he felt, resulted from the students' desire to achieve vocational security in the face of the rapid increase in the sum total of knowledge that was inhumanly impossible to assimilate. He was an advocate of a broad, general, academic curriculum of the liberal arts and sciences. "Certainly, the student who considers his college courses as so many hurdles to overcome before he reaches the main contest will profit little from them. On the other hand, if the student's interest can be so aroused that he desires to know all there is to know about any particular subject and its related fields (intellectual curiosity), the beautiful interrelation of natural facts will lead him to a truly liberal education."

Armstrong further said that fine buildings, elaborate equipment and facilities or even books did not or might not ignite the spark of interest. Rather, it was the friction and interaction between interested and dedicated teachers and receptive students that provided the impetus for ignition of the spark. In this regard, he referred to memorable members of the Mount Union College science faculty with whom he shared common interests, and whose teaching styles he found stimulating. He said that these teachers by their quiet

enthusiasm demonstrated how to “coax nature into revealing her secrets with a minimum of equipment” and the “influence of their inspiration has persisted.”

He continued that hand-in-hand with the teaching of known facts, combined or dependant upon preliminary training, goes research or the acquisition of new truths. The twin sisters of education and research, he observed, had brought tremendous material advantages. Within the previous five or six decades, truly extraordinary inventions had appeared. These included man’s heavier than air flight, the airplane, the internal combustion engine automobile, the motorcycle, the electric light, the telephone, the elevator, the typewriter, x-ray machines, radiation treatments, anaesthetics, vaccines, and public health sanitary measures to control epidemics.

Through these and other discoveries that had gone far to alleviate the burdens of toil and suffering in the world, the inventors and discoverers had won honor, respect and often substantial monetary rewards for their achievements. Scientists and inventors had often not fared well in previous eras when they challenged accepted dogma. Examples in astronomy include Copernicus and Galileo. In medicine, Vesalius, the father of anatomy, became disgraced and vilified during the 16<sup>th</sup> century when he questioned the archaic concepts of the Greek physician, Galen, whose teachings had kept medical knowledge in bondage for 1300 years. Vesalius challenged the accepted knowledge of human anatomy. He felt that truth could only be obtained by going to nature itself in order to elucidate anatomical relationships by direct observation from human dissection. Civil authorities and the church, represented by the Inquisition, persecuted Vesalius because of his anatomical investigations. He died alone disgraced and unbefriended but his contributions to medicine were accepted posthumously with profound appreciation.

(Other examples not quoted by Armstrong included Semmelweis' concept about the contagion of post-partum sepsis spread by the dirty hands of obstetricians and medical students that was rejected totally by the contemporary medical profession, and Pasteur's experimental demonstration of the germ nature of infection accepted only eventually in the latter half of the 19<sup>th</sup> century. Peyton Rous in the 20<sup>th</sup> century had to wait more than 50 years before receiving the Nobel Prize for his discovery that viruses could cause cancer.)

Armstrong continued, "Knowledge has been likened to a sphere; the more it grows the larger its surface becomes, and, therefore, the more it comes in contact with the unknown. Consequently, the very acquisition of new truth engenders new problems to be solved. The search for truth must go on. Just as primitive man in the ice age learned to protect himself with artificial covering or by seeking refuge in caves, so too, must man look to education and research if we are to adapt ourselves to the changing condition of our times."

He also illustrated by example new advances giving rise to problems with which science has to contend. As examples, he pointed out the destructive forces of modern war and the annual slaughter on the highways by automobiles that exceeded the total loss in actual combat in any comparable period in the recent World War (I). He also suggested that the abundance, ready availability of food and the decreased demand on physical energy because of various labor saving mechanical machines were contributing to diabetes, lack of physical fitness, and "other ailments of obscure etiology." In conformity with his previous theories of the pathogenesis of postvaccinal encephalitis, he proposed that decreased exposure to hardships and common communicable infectious diseases was

contributing to weakness of the immunological system and the resurgence of highly virulent, but previously infrequent infections, such as poliomyelitis. He felt that man had contributed to “biological imbalance throughout the world” adding new dangers to man’s existence.

Armstrong also had major concerns about the world’s subjective social and ethical ills as well as the factors that were affecting “mere” physical factors. He felt that the tendency toward specialization was influencing the country’s whole economic and national life. He stated that representative government in the United States was becoming more and more a government by organized specialized groups having common aims and ambitions. He worried that these ambitions unless accompanied by ideals were apt to be, and often were, selfish and not to the best interest of society as a whole.

Armstrong indicated that medicine had traditionally been a calling in which recent graduates had, as part of the graduation ceremony, the reading and the recitation of the “Hippocratic Oath” that outlined the ethical relationships and duties of the physician to his patient, the public and to other members of the profession. He did not infer that the medical profession was free from the human traits of greed and jealousy, but it was a matter of pride that medicine’s countless discoveries had usually been donated to the world for the benefit of mankind without the thought of compensation. He speculated on how different things might have been at the present time if politicians, bankers, business men, and other groups and professions had kept a similar code of ethics constantly before them for the past few centuries; he proposed further that in the field of social relationships, as in geology, apparently insignificant forces when acting for long periods of time might produce significant effects.



Armstrong also wondered what effect hurry, bustle, clangor and the mere physical noise of the machine were having on the nation's mental processes, spiritual calm, efficiency and happiness. The telephone, gramophone, radio, bridge, jig-saw and cross-word puzzles had invaded the home (television and electronic computer games were still in the future); sports and commercial entertainments, the crooning of the latest song hits (Bing Crosby was in his early career then.), and many other distractions were usurping additional time from thought until an individual should begin to wonder whether, in the whirl of modern times (even in June 1933), man in a mass sense is not losing his capacity for meditation – the power of which Armstrong's Quaker ancestors so well understood. Armstrong stated these thoughts, he apologized, notwithstanding the commonly held belief that he lived in proximity to the greatest source of deliberative confusion, the Congress of the United States.

He also decried the uncritical acceptance of new ideas just because they were unique, superficially attractive and frequently at odds with established customs and morality that were firmly based on long established moral and religious principles. He especially warned against the blandishments of political false prophets and being led astray by movements or ideas that did not stand up to highly critical scrutiny.

Armstrong concluded his address: "Again the concept that everyone has a right to live his own life without discrimination (life, liberty and the pursuit of happiness) may lead to such an impulsive way of living as to engender a wave of physical experiences that may sweep away all but the most sturdy. True, if we would be scientific, we must be ready to follow truth wherever she leads and to break with the past whenever she so decrees. However, truth is often elusive and most coy, and, in many instances, we may

have to depend on making decisions upon nothing more than innate common sense. In such instances a little time spent in meditation and in turning new concepts over in one's mind and in comparing them with man's experience, as revealed in history, is perhaps the best safeguard against bizarre ideas. Science is bringing us increased leisure, and leisure may bring culture provided we obey that old maxim of 'nothing in excess' and provided we preserve a proper balance between thinking and doing, between meditation and mere motion." In appreciation of his school, Armstrong continued, "It seems to me that Mount Union College has a fine natural educational asset in her beautiful, quiet, tree-covered campus surmounted by historic buildings, where those who are privileged to study may learn, and develop that spirit of repose so necessary to the whirl and change of twentieth century civilization. Or, where they as Osler (6) put it, develop 'the calm life necessary to continuous work for a high purpose.' For what will the mere solution of the practical problems of life avail unless we reach a wise conclusion as to how human beings as members of a world society do and should behave?"

When Charles Armstrong presented these thoughts in June 1933, he was in the early mid-term of his professional career. It is interesting that society is still dealing with many of the same "problems" and issues that Armstrong described presciently more than 70 eventful years ago. The ideas he expressed represented the guideposts that directed his philosophical approach to science, knowledge, society, moral and ethical values as well as methods of seeking answers posed by problems arising from uncharted areas disclosed by his investigative quests. His inquisitive mind combined with sustained work energy in the laboratory enabled him to conceive and find solutions to the nature of many unfamiliar observations that he encountered in the laboratory. Armstrong always

presented a cheerful demeanor, and he had a healthy sense of humor, but he was a keen judge of character and did not suffer fools, slackers or deception gladly. He found great pleasure and satisfaction in his work. In 1941, when the American Public Health Association recognized his accomplishments in research by the awarding of its prestigious Sedgwick Gold Medal, he summarized succinctly a personal attitude toward his career by the remark, “I have only been doing my day’s work.”

In October 1952 the Editors of *Science* (7) asked Armstrong to write a eulogy for Dr. George W. McCoy, 1876 – 1952, former Director of the Hygienic Laboratory and first Director of the newly created National Institute of Health. In the eulogy, Armstrong, describing attributes that he admired in Dr. McCoy, and which he shared himself, wrote as follows, “In scientific matters, Dr. McCoy was an austere critic yet always kind, fair, self-effacing and loyal. As Director of the Laboratory he considered himself to be a servant rather than the master of the bench workers. In the atmosphere of his laboratories it was easier for the investigator to become absorbed in his problems; and when he was once interested, he was allowed free rein to follow his own ideas, leads, or hunches without restraint or questioning. The Director never pressed an investigator for early publication; in fact he was likely to advise ‘more study before going on record.’ Yet, he considered the investigators’ time as almost sacred and was resentful whenever administrative or other matters distracted them from their problems.

“Perhaps the personal quality that best characterized Dr. McCoy was his downright honesty. He was ever ready to acknowledge when he did not know, or to admit an error, or to change his opinion in the face of evidence; but otherwise he could not be coaxed or cajoled to do so. It was quite natural for him in a research institution to place research

above all else – he cared little for a fine ‘mill,’ but he cared everything for the ‘grist.’ He would readily approve expenditures for research necessities, but he would permit no luxuries such as rugs, fine desks, fancy furniture, or paintings in his own or other offices. Some smiled at these “peculiarities” but they were a natural and necessary result of his stern sense of propriety.”

Armstrong demonstrated these same qualities during his tenure as Chief of the Division (Laboratory) of Infectious Diseases from 1942 to 1948. He earned the respect of his subordinates, with one possible exception (8), through his fair, impartial and skillful management of the laboratory. The investigators had the personnel and whatever equipment they required for their approved research projects. Notwithstanding this, Armstrong acquired the reputation of running a frugal, efficient operation with the Laboratory presenting an annual fiscal budgetary surplus. These usually became conundrums for the bewildered financial administrators who did not know what to do with the surplus funds.

Armstrong was also steadfast in his loyalty to the Public Health Service and in his determination to continue his research efforts in his NIH laboratory on behalf of his original intension to benefit the greater good in working for the people’s health. He received a letter from Dr. W. H. McMaster (9), President of Mount Union College on October 23, 1936 offering him the attractive and lucrative position as Director of Scientific Research of the College. The offer came following Armstrong’s isolation of the viruses of Saint Louis encephalitis and the newly discovered lymphocytic choriomeningitis (see next chapter). Despite the description of potentially interesting projects for study, Armstrong, in reply, declined the offer, thanked Dr. McMaster

sincerely and stated that he did not feel that he would function well as an administrator of projects; moreover, Armstrong felt he was more attuned to functioning as a single laboratory investigator fighting disease.

Armstrong's philosophy of professional, social and moral principles provided a continuing compass guiding him through a successful scientific and personal life.

#### Notes – Domesticity, Career Recapitulation, Philosophy

- 1) Condolence letter sent by Dr. Robert J. Huebner on the occasion of Armstrong's death. Among the Armstrong personal papers.
- 2) Conversation with Miss Mary Emma Armstrong.
- 3) Letter from Dr. W. M. McMaster among Armstrong's personal papers related to bestowing an honorary doctorate.
- 4) Series of letters outlining details for awarding of the Doctor of Science degree. Among Armstrong's personal papers.
- 5) Mount Union College Bulletin, Volume 33, May, No. 4; June No. 5.
- 6) Osler, W. (Sir William Osler, Bt., M. D., F. R. S.): *Aequanimitas, With other Addresses to Medical Students, Nurses and Practitioners of Medicine*. Third Edition, The Blakiston Company, Philadelphia, 1932. Chapter III: Teacher and student. p. 39.
- 7) Armstrong, C.: George Walter McCoy, 1876-1952. *Science* 116:468, October 31, 1952.
- 8) Topping, N. (with Gordon Cohn): *Recollections* University of Southern California, Los Angeles, 1990. pp. 51, 81.

- 9) Letter from Dr. W. H. McMaster October 23, 1936 among Armstrong's personal papers. In an answering letter Armstrong expressed much reluctance in refusing the offer since he would have enjoyed returning to the tranquility of the school campus; he felt a greater duty to his commitment to personal research in the laboratory studying infectious diseases.

“Green Thumb Virologist”: Saint Louis Encephalitis; Lymphocytic Choriomeningitis

Throughout much of recorded human history mysterious epidemics ravaged widespread areas involving large numbers of individuals with serious illness and with a high percentage of deaths. Examples include the Plague of Athens during the Peloponnesian War described by the Greek historian, Thucydides (1), the infamous “Black Death” during the 14<sup>th</sup> century in Europe and Asia Minor (2), and the world wide 1918-1919 Influenza Pandemic. The advent in the 19<sup>th</sup> and 20<sup>th</sup> century of the microbiological sciences, including bacteriology, parasitology and virology, helped to pinpoint the etiologies of some of the common bacterial and parasitic causes of illness. A group of illnesses, however, involving the brain and central nervous system, producing the syndromes of fever, lethargy, coma, neurological involvement and death, and described by popular medical science writers as the “Sleepy Death” were giving up their secrets with great reluctance.

During World War I in 1916-1917 and prior to the influenza outbreak, von Economo (3) reported on a pandemic in Vienna, Austria and carefully described the clinical and pathologic features of a disease that he labeled “lethargic encephalitis”, also variously labeled “encephalitis lethargica” or von Economo’s disease. Thereafter it appeared in epidemic form in many parts of the world including the United States in 1918. After 1926, no further epidemics occurred. Pathologic features included inflammatory, destructive and degenerative changes in the gray areas of the brain and involved predominantly the basal ganglia, midbrain and pons. The clinical features were often fulminant but occasionally went through stepwise phases to a chronic stage with

peculiar motor, vegetative and psychic symptoms. Motor symptoms resembled those of Parkinsonism. Excessive salivation, tears and oily skin were often present. Mental impairment was prominent. Some patients exhibited a strange psychomotor phenomenon called an “oculogyric crisis.” This was an attack of involuntary deviation and fixation of the eyeballs, usually upwards. The crisis might last for several minutes or hours. Many patients required prolonged custodial care. During the author’s clinical years in medical school in the 1940s, the class had field trips to various chronic care hospitals where the faculty presented patients with this disease as examples manifesting signs and symptoms of Parkinson’s disease. Despite many attempts, investigators were unable to identify or isolate infectious agents from the tissues of these patients; the etiology remains unknown. Current medical texts have largely ceased including clinical descriptions of this disease. Several other illnesses characterized by “brain fever” had also produced consternation in the past in the general population. In 1909 Landsteiner and Popper (4) demonstrated that poliomyelitis virus could be transmitted to monkeys. However the appearance of widespread epidemics and the random individualized attacks of paralytic disease in the early 20<sup>th</sup> century immobilized entire communities during the late summer and early fall months. Knowledge was lacking about the reservoirs, mode of spread, and effective public health measures to prevent or limit outbreaks. Help, fortunately, appeared when President Franklin D. Roosevelt, himself a paralytic victim of poliomyelitis, through enthusiastic encouragement, mobilized private, governmental, and financial resources to promote intensive research activities leading to the unraveling of the mysteries of poliomyelitis resulting in the development of effective vaccines. Another major fear among the general population was the random appearance of central nervous system



changes following vaccination against smallpox. Fortunately, in the early 1930s, on the basis of experimental observations as described in an earlier chapter, Charles Armstrong was able to suggest a strategy to help eliminate the tragic consequences of postvaccinal encephalitis. It is with the above background that the appearance of encephalitis in the St. Louis area presented such urgency.

During five weeks from August 7 to September 10, 1933, an “encephalitis” epidemic of explosive proportions struck the vicinity of St. Louis, Missouri and the adjacent St. Louis County (5). In this time period physicians reported 656 cases to the local health departments. The severity of this outbreak invited the attention of the national, local and Washington, DC, news media (5). One month later (6), at a special session of the American Public Health Association on Epidemic Encephalitis (under the auspices of the Health Officers Section) the reported case number had increased to 522 in the County and 533 in the city. The suddenness of the epidemic course and the magnitude of the number of patients involved presented to the municipal health personnel a problem of emergent priorities. During the early part of the epidemic the local health officers of the St. Louis area formed a Metropolitan Health Council, and the Council appointed committees on administrative control, including epidemiological records and on research. The groups involved in the Council included the Health Department of the City of St. Louis, the Missouri State Health Department, St. Louis University, Washington University as well as the practicing medical professionals and the communities concerned. Among the first actions of this organization was an appeal to the newly constituted National Institute of Health (from the old Hygienic Laboratory) for epidemiological and investigative expertise.

The first NIH officer at the epidemic locale was Dr. James P. Leake, the Institute's principle epidemiologist who later became Chief of the Epidemiology Section of the Division (later Laboratory) of Infectious Diseases. Dr. Leake, a kindly, gentle person, was, nevertheless, a stickler for detail and for precise information. He worshiped at the altar of statistical sanctity and the inviolability of hard earned numbers acquired by first hand careful observation. Dr. Robert J. Huebner (7), in a conversation with the author, described Dr. Leake's statistical approach to automobile driving strategy. According to the statistical information available to him, most automobile accidents occurred at traffic intersections; therefore, Dr. Leake went through intersections as fast as he could in order to avoid an accident. Dr. Leake was also a good friend and fellow collaborator on previous investigations with Armstrong. He had tremendous respect for Armstrong's professional accomplishments and the unique imaginative way with which Armstrong approached new problems. After his initial assessment of the epidemic situation in St. Louis, Leake requested that Armstrong join him in order to supervise the laboratory aspects of the investigation. At the time (a few months after receiving his honorary D. Sc. from his alma mater, Mt. Union College in June 1933) Armstrong and family were vacationing and visiting with his in-laws (wife's parents), the Reverend and Mrs. John Rich, of Senecaville, Guernsey County, Ohio. The Division contacted him by telegram instructing him to report for duty with Leake in St. Louis to help with the investigation. Armstrong interrupted his leave, left family behind and proceeded to St. Louis to help unravel the cause of the epidemic.

The newly created Metropolitan Health Council of St. Louis appointed Dr. Ralph S. Muckenfuss, Assistant Professor of Medicine at Washington University School of

Medicine, Chairman of the Council's research committee that had the task of finding the cause of the epidemic (Dr. Muckenfuss later became Director of Laboratories for the New York City Health Department). The committee also consisted of other representatives of Washington University, St. Louis University and the various hospitals in which there were cases of the disease. Dr. H. A. McCordock, Associate Professor of Pathology, Washington University School of Medicine, was to provide support for pathological tissue examination. Armstrong joined this group to set up a laboratory for the isolation of a possible infectious agent. The group, led by Armstrong, set up a special isolation facility within the Washington University campus, and under Armstrong's direction, and his personal involvement, they began inoculating brain and other tissues from the victims of the fatal disease into a variety of laboratory animals. On September 8, 1933, at a meeting of the Metropolitan Health Council (6), Armstrong, Muckenfuss and McCordock presented a preliminary report describing the possible isolation of an agent in monkeys whose brains at autopsy showed changes similar to the brains of patients who had died of encephalitis. A definitive report published shortly thereafter (8) described the serial transmission of an agent in *Macacus rhesus* monkeys from the brains of 7 of 15 fatal human cases. As opposed to isolation attempts in previous encephalitis investigations, the probable reasons for the successful isolation and transfers of the agent were the heavy doses of the brain inoculations, additional inoculation into the abdomen, and repeated inoculations. Armstrong used heavy inoculations (1.5-2.0 ml.) of a thick brain emulsion intracerebrally (into the brain), combined with 5-10 ml. into the abdomen (intraperitoneally). He repeated the inoculations after an interval of 4-5 days.

Armstrong, observing the signs and clinical illnesses in monkeys noted that, although these features varied in degree, they were uniform in character and suggested similarities to the illnesses seen in the human encephalitis patients. As described by Armstrong (8), “The first significant symptoms appeared in from 8 to 14 days following the first inoculation and began with an elevation in temperature that tended to rise on successive days to a height of from 40.6 to 41.6 on the fourth or fifth day of the fever. When undisturbed the animals usually sat hunched up with their eyes closed as if asleep with their heads bent forward. When disturbed, however, the ill animals seemed alert and often markedly excitable. Intention tremors, most notable in the forelegs and the head, usually appeared about the second or third day and were often pronounced. Muscular weakness of one or more extremities and occasionally definite paralyses made their appearance during the febrile stage. Involvement of the eye muscles was not observed. The appetite usually continued good, and the animals often would eat greedily throughout the febrile period. Constipation was often present. Spinal fluid at the height of the fever was usually under increased pressure, clear and commonly showed cell counts of from 150 to 350 cells.

“The animals were usually sacrificed on from the second to fifth day of fever, but in a few instances the disease was allowed to run its course. In these instances the monkeys recovered completely. There were no spontaneous deaths, although some of the animals were very ill when sacrificed, and it seemed probable that some of them might have succumbed had they not been killed.”

Armstrong carried three strains of virus through five passages and thought that the illnesses were becoming more virulent in monkeys during the 4<sup>th</sup> and 5<sup>th</sup> passages. He

failed to convey the disease to monkeys by means of nasopharyngeal washings, spinal fluid and blood; however, he thought this was not surprising, suggesting not the absence of virus from these fluids, but that the susceptibility of monkeys to the infectious agent was low.

Armstrong's group tried to transmit the disease to other laboratory animals but was able to accomplish this only in white mice. Dr. Leslie T. Webster (9) of the Rockefeller Institute for Medical Research had spent many years breeding special strains of mice to use for virus isolation and transmission of neurotropic viruses. Using autopsy tissue from the St. Louis encephalitis epidemic sent to him by Armstrong and colleagues, Webster was able to establish infection by intracerebral inoculation in a strain of his laboratory-bred mice. When he informed Armstrong and colleagues, they were able to establish infection from second monkey passage brain emulsion regularly in stock white mice by intracerebral inoculation. The two strains of virus isolated in the separate laboratories were identical. The use of mice reduced the need for large numbers of expensive and irascible monkeys, and it expedited the further investigation of the infectious agent. Attempt to pass the agent to rabbits were unsuccessful.

The pathology of infection was similar in human cases, monkeys and mice. At autopsy the brains were usually markedly congested ("blood shot"). Accumulation of round cells around the blood vessels (perivascular cuffing), destruction of nerve cells in the brain and upper spinal cord, and focal collection of inflammatory cells in the brain characterized the histological features.

Since mice were more easily infected and susceptible to infection than monkeys, subsequent studies made use of mice to investigate the characteristics of the virus (9, 10).

Intracranial inoculation of mouse brain in a dilution of 1:1,000,000 could transmit infection to mice. A larger dose was necessary following intranasal inoculation for the disease to develop regularly. Armstrong used this latter route regularly for later studies of the virus (10, 11). Webster and Fite (9) reported that the virus was readily filterable. They (9) filtered the virus through graded collodion membranes and estimated the diameter of the virus particle to be somewhere between 22 and 33 millimicrons. They found that the virus was neutralized by the serum of individuals convalescent from encephalitis in the 1933 outbreak and was not neutralized by the serum of normal individuals from uninfected areas (11). The serum of recovered monkeys and mice also neutralized the virus.

The ready availability of the mouse as a laboratory host enabled Webster and associates (9) to compare the agent of the 1933 St. Louis outbreak with other viruses. They reported the absence of cross immunization with the viruses of herpes (simplex), vesicular stomatitis and equine encephalomyelitis. They also reported that serum collected from individuals recovered from epidemic (lethargic) encephalitis (von Economo's Disease) from one to ten years after the acute attack, from poliomyelitis, Japanese encephalitis and Australian-X disease did not neutralize the virus.

Armstrong and associates (9) summarized their conclusions as follows: A number of strains of a virus that seemed to be the etiologic agent of the 1933 epidemic of encephalitis in St. Louis were isolated in two different laboratories. The virus acted on monkeys and white mice and was distinct from other previously known viruses. The number of strains of similar characteristics isolated, and the neutralization of the virus by serum of individuals convalescent from encephalitis in the epidemic, but not the serum of

individuals recovered from other diseases, justified the conclusion that it was the etiologic agent of the recent epidemic.

At the height of the epidemic many observers on the scene described the varied presentations, the manifestations, and the clinical course of encephalitis as they occurred in St. Louis in 1933. Dr. James P. Leake provided a brief clinical overview of the illness in his early report of the outbreak. Dr. Theodore C. Hempelman of the Department of Pediatrics, Washington University School of Medicine and the St. Louis Children's Hospital presented a detailed account of his experience with the illness (12). A major observation from epidemiological and laboratory studies (13) indicated that, similar to the situation with poliomyelitis infection, protective antibodies occurred in many people in the St. Louis who gave no history of prior illness. This observation suggested previous infections with the virus that produced either mild, non-specific illnesses or completely inapparent infections. Armstrong (10) devised a method for producing asymptomatic, non-lethal specific immunity in white mice by infecting them intranasally with St. Louis encephalitis. He stated that the interest in these findings resided in their possible relationship to the natural mechanism whereby immunity developed without recognizable symptoms of the diseases. In order to test the hypothesis of inapparent infections further, Dr. J. G. Wooley (of the NIH), with mentoring by Armstrong (11), described the distribution of immunity against St. Louis encephalitis in the United States as determined by the serum protection (intracerebral) test in white mice. They summarized their conclusions as follows: 1) Serum protection tests carried out on 524 human sera collected from 49 cities located in 26 states and the District of Columbia gave definite protection in 158 or 30.1 per cent, questionable protection in 56 or 10.7 per cent and no protection in

310 or 50.1 per cent. 2) Sera giving definite protection were collected from 32 cities located in 21 states and the District of Columbia. 3) Of sera from 39 clinically definite encephalitis cases from the St. Louis epidemic (1933), collected 4 to 10 months following the attack, 37 or 94.8 per cent showed protection. Among 113 normal controls having no known exposure to encephalitis cases, there were 11, or 9.4 per cent, whose sera gave protection, while among 56 normal controls who had been in contact with cases, there were 20, or 35.7 per cent whose sera showed definite protection. 5) A positive serum protection test was believed to be evidence that the serum donor had been in contact with the virus of encephalitis and had suffered either a clinical or sub-clinical type of infection. 6) They also stated that the serum-protection test they reported indicated that the St. Louis type of encephalitis was immunologically distinct from encephalitis lethargica (von Economo's Disease), poliomyelitis and the post-infectious encephalitides. A particularly vexing problem was trying to determine how the virus spread. The early epidemiological data exonerated the water and milk supply. Despite a superficial epidemiological resemblance to poliomyelitis because of its similar seasonal incidence in late summer and early fall, St. Louis encephalitis differed from poliomyelitis in its predominant clinical presentation and its major incidence in the elderly. The epidemic occurred in a drought-like period that had been preceded by a heavy rainy season. The result was scattered pools of stagnant water that were ideal areas for the luxuriant proliferation of mosquito larvae. Suspicion then focused on mosquitoes as possible vectors from an unknown host or reservoir. In 1930 Dr. K. F. Meyer et al. (14) isolated Western equine encephalomyelitis (WEE) from horses in California and in 1933 Kelser (15) showed that *Aedes aegypti* mosquitoes could transmit WEE experimentally. Based



on the WEE studies, Dr. L. L. Lumsden, a member of the Public Health Service team in St. Louis, postulated a mosquito vector, likely one of the *Culex* varieties, either *C. pipiens* or possibly *C. quinquefasciatus* both of which were indigenous and prevalent in the St. Louis area. The mosquito as a vector, however, was not proven at the time of the ongoing 1933 investigation. Later, in 1941 Hammon et al. (16) isolated from *Culex tarsalis* both WEE and St. Louis encephalitis, Hess and Holden in 1958 and Brody and Browning in 1960 both isolated St. Louis encephalitis from *C. pipiens* and *C. quinquefasciatus* establishing them as vectors for the virus (16). Thus, by 1958 Lumsden's accuracy of observation and conclusions about the mosquito as vector were proven (17).

In 1933, however, as part of the epidemiological studies (3B, 13), the Public Health service under the direction of Surgeon L. L. Williams was carrying out insect transmission studies, particularly with mosquitoes. Also participating with Williams were Drs. James P. Leake and Bruce Mayne all of whom offered themselves as experimental volunteers in the manner of Walter Reed's yellow fever investigations in Cuba during the Spanish-American War. In 1933 Major James S. Simmons, Director of Laboratories, Army Medical School and Major V. H. Cornell, Curator of the Army Medical Museum at Washington, DC were also directing mosquito studies simultaneously. Major Kelser of the United States Army (see above) proved that the "sleepy death" of horses in the San Joachin Valley could go from guinea pig to guinea pig via the bites of *stegomaia* (species of *Aedes aegypti*) mosquitoes; however, these were not present in the San Joachin Valley. Thousands of these special mosquitoes were shipped from Memphis, Tennessee, where Major Kelser was stationed, allowed to feed on patients in St. Louis, and then investigators fed them initially on monkeys. When the monkeys did not become ill, Drs.

Leake, Williams and Mayne volunteered to allow the mosquitoes to feed on them despite the possibility of a serious or fatal outcome. However, and fortunately, nothing happened so the 1933 investigators could not at that time prove that mosquitoes were the vectors for transmitting St. Louis encephalitis.

After cessation of the epidemic in St. Louis, Armstrong returned to the laboratory in Washington, DC, where he continued additional investigative studies of the virus in monkeys but gradually shifted primarily to white mice. The study in monkey nervous tissue provided an unexpected surprise to be described. He probed more deeply into the pathologic changes brought about by the virus in mice under conditions of partial immunity and seasonal variation (18, 19).

The passage of 70 years has been witness to the major accumulation of knowledge about the nature of St. Louis encephalitis and its status among the group of viruses of which it is a member (20). It has been classified as a Flavivirus. Other viruses in this group producing virulent disease are Yellow Fever, Dengue, Dengue Hemorrhagic Fever, Japanese Encephalitis and Tick-Borne Encephalitis. There are approximately 60 arthropod-borne or transmitted diseases, including Flaviviruses, of which 30 are known to cause human disease. The Flaviviruses are spherical, 40-60 nm in diameter and consist of a lipid envelope covered densely with surface projections comprising 180 copies of the M (membrane) and 180 copies of the E (envelope) glycoproteins. The viruses are unstable in the environment and are sensitive to heat, ultraviolet irradiation, disinfectants (alcohol, iodine) and acid pH. The molecular RNA structure of the viruses has been described.

Epidemiologically, the viruses are maintained in nature by birds as natural hosts and reservoirs, mosquitoes as vectors, and humans as incidental or accidental hosts. With reference to St. Louis encephalitis, the virus is transmitted to birds in the United States by *Culex* mosquitoes, *C. pipiens* and *C. quinquefasciatus* in Midwestern and Eastern States, by *C. nigripalpus* in Florida and by *C. tarsalis* in the Great Plains and further west. Clinical diagnosis still depends on recognition of constitutional signs and symptoms including fever, and various neurological abnormalities, especially severe febrile headache, aseptic meningitis, mental clouding, movement disorders, and coma with or without worsening course to eventual death. Virus isolation, antibody development and newer molecular immunologic techniques for early diagnosis help identify the specific pathogen accurately.

#### Lymphocytic Choriomeningitis

The maxim that “Chance favors the prepared mind” is attributed to Louis Pasteur. Charles Armstrong’s discovery of the virus of lymphocytic choriomeningitis (21) demonstrated the veracity of this maxim exquisitely. The discovery occurred while Armstrong continued to pass serially infected monkey brain tissue to other monkeys. In the transmission from monkey to monkey of infectious materials from a fatal case of the 1933 epidemic of St. Louis encephalitis, Armstrong encountered a virus apparently quite distinct from the strains previously isolated by himself, Muckenfuss, and McCordock (8), and subsequently in white mice by Webster and Fite (9). This virus, differing from any virus with which Armstrong was familiar, he designated as the virus of “experimental lymphocytic choriomeningitis”, based on the pathological changes in brains produced by

the intracerebral inoculations of monkeys and mice. His colleague, Dr. Ralph D. Lillie, assisted with the pathology studies.

Armstrong encountered the virus during serial passage of infectious monkey brain derived from patient C. G., a fatality during the 1933 St. Louis epidemic. Her physicians made a diagnosis of encephalitis of the type prevalent during the epidemic on the basis of symptoms and signs pointing to central nervous system involvement. The patient, C. G., was a 42-year old African-American housewife with a past medical history of chronic poor health for 12 years accompanied by “chronic constipation,” remote abdominal surgery and underlying diabetes mellitus. Her final illness began August 13, 1933 with general malaise, progressing to fever, severe headache, vomiting and drowsiness. Her illness worsened, escalating to delirium and terminating rapidly in coma and death. The detailed clinical, hospital and autopsy records could not be located at the County Hospital where she died. The central nervous tissue including brain and spinal cord were sent for initial investigative processing to the local research laboratory at Washington University and were then transported to the NIH laboratory for further study.

Armstrong carried the virus strain from C. G. through 5 monkeys (rhesus no. 5, no. 18, no. 37, no. 787, and no. 800). He considered the illnesses produced by these passages similar to the six other strains isolated by himself and his colleagues. In a retrospective examination, reinvestigation of the symptomatology and pathology of these early transfers by Armstrong tended to confirm this opinion.

Armstrong described the initial isolation of the new virus as follows: “On November 2, 1933, rhesus no. 37 was inoculated with brain material from monkey 800 (6<sup>th</sup> transfer). Monkey 37 had been inoculated twice previously (September 28 and

October 2) with the Freeman strain of St. Louis encephalitis but had failed to react with recognizable symptoms. The eighth day following the inoculation from monkey 800, however, monkey 37 showed a fever of 40.5C, was slightly tremulous and slow of movement and refused food. The following day (November 11) the temperature was 40.2C. The spinal fluid was under increased pressure, clear and showed 439 cells per cu. mm., almost entirely lymphocytes. The animal was etherized for passage. The brain was markedly congested and edematous, but in no way distinguishable grossly from the brains of monkeys infected with the usual St. Louis encephalitis strains.

“The microscopic pathology as reported by Surgeon R. D. Lillie, however, presented peculiarities which reappeared with successive transfers. Likewise, transfers to white mice revealed features quite distinct from those observed with other encephalitis strains, and a comparative study soon compelled the conclusion that we were dealing with a second distinct type of experimental infection.”

With the recognition that he was probably dealing with a previously unknown infectious agent, Armstrong embarked on a detailed study to define the characteristics and nature of the agent. He established that experimental choriomeningitis was caused by a virus as indicated by the following considerations: 1) Transfer occurred repeatedly with inoculums sterile to culture on ordinary media. Contaminating bacteria occurred rarely and played no role in producing disease in experimental animals. 2) Filtrates of brain, as well as spinal fluids and sections of nervous tissue demonstrated the harboring of the infectious agent, and contained no visible or stainable organisms. 3) The infectious agent suspended in either saline or broth readily passed a Berkefeld N (ceramic) filter which held back ordinary bacteria (at conditions of room temperature, pH 7.6, pressure 40 mm.

Hg.). 4) Centrifugation at high speed for 15 minutes (designed to precipitate ordinary bacteria) failed to remove the infectious agent from spinal fluid and brain suspensions, although there was evidence of diminution of the amount of virus. 5) Monkey and mouse strains were found to retain their infectivity for at least 206 days when stored at 4-10C in 50 per cent glycerine in 0.85 per cent saline. 6) A temperature of 55-60C for 20 minutes destroyed the infectivity of brain suspensions for mice. 7) He did not find cell inclusions, found in some viral diseases, in histological sections. The above criteria, standard for the time, thus indicated to Armstrong that he was dealing with a virus.

Further studies showed that rhesus and cebus monkeys, white mice, wild mice, and guinea pigs were susceptible to infection by intracerebral inoculation. White rats and rabbits were not found susceptible by this route.

He also described in detail the physical signs of illness in monkeys and white mice. Monkeys, unless sacrificed, usually survived the infection; the mice invariably died in convulsions. Standard features of the spinal fluid in monkeys were increased pressure, clear fluid and cell counts varying from 150 to 1,260 cells per cu. mm., almost entirely lymphocytes. White blood cell counts, while the monkeys were ill, varied from 10,000 to 19,400 cells per cu. mm. without constant differential counts.

Armstrong, in studying the distribution of virus in the tissues of monkeys during the febrile attack by mouse transfer, regularly found the agent in the brain, spinal fluid, blood and in a single demonstration in urine collected at autopsy. He also demonstrated the virus in the blood and brain of mice.

In addition to intracerebral inoculation, Armstrong demonstrated other experimental routes of infection in monkeys. He was able to infect monkeys with the

virus by injection into the spinal canal (intrathecal route), into the veins (intravenous), into the abdomen (intraperitoneal) and into the windpipe (intratracheal). When inoculated by each of these routes, monkeys became ill, recovered, then failed to react when challenged by intracerebral injection with live virus indicating the acquisition of immunity to the virus.

The major feature that distinguished this new virus from St. Louis encephalitis was the microscopic pathologic anatomy described in detail by Dr. Ralph D. Lillie (21). As described: In the majority of the monkeys there was more or less diffuse and irregular cellular infiltration of the meninges (membrane coverings of the brain). Usually the exudate was composed chiefly of small lymphocytes. In most animals there was a more or less pronounced swelling, edema and lymphocytic infiltration of the choroid plexi (the cellular membrane lining the intracerebral ventricles). Often the two layers of the plexal epithelium were separated by dense masses of lymphocytes of such magnitude as to enlarge the plexal villi four to six times. Scattered areas of lymphoid infiltration and focal areas of intracerebral pathology occurred elsewhere, but the major foci of lymphocyte infiltration in the brain meninges and choroids plexus determined the descriptive naming of this infection as *lymphocytic choriomeningitis*.

The mystery surrounding the discovery of this new virus was its origin. Armstrong speculated as follows: "It is not obvious whether this virus came from Case C. G. or from one of the monkeys used in the transfer of virus from the case. In either event the virus was apparently present in a latent state and was activated during successive transfers.

“In view of the shorter incubation period of this virus in monkeys as compared to that of encephalitis strains, it would seem logical to expect that in the transfer of a mixed infection the choriomeningitis might ultimately displace the encephalitis strains. This result has actually been observed during the transfers from monkeys synchronously inoculated with the two strains. In mice, however, the opposite was observed for the encephalitis, with its shorter incubation period, after a few transfers supplanted the choriomeningitis strain.

“It is to be remembered, however, that monkey 37 was apparently immune to encephalitis (Freeman strain) but not to the choriomeningitis, a condition calculated to suppress the encephalitis virus to the advantage of the latter (choriomeningitis) should both have been present”.

Armstrong further discussed the fact that lymphocytic choriomeningitis (henceforth referred to as LCM) was not a commonly occurring spontaneous disease in monkeys since he had encountered no naturally immune monkeys. He also wondered whether this virus might be present in the human population since the clinical disease in monkeys closely resembled recently described (22) cases of so-called “lymphocytic or aseptic meningitis” for which no infectious agent had been isolated. He also indicated the initiation of future studies utilizing neutralization tests of human sera against the viruses of St. Louis encephalitis and LCM to determine the prevalence of human exposure against these agents.

In order to demonstrate that LCM was a previously undescribed virus and distinct from St. Louis encephalitis strains and other agents, Armstrong showed that: 1) Cebus monkeys and guinea pigs refractory to encephalitis strains succumbed to LCM strains. 2)



The incubation period for St. Louis encephalitis and LCM was different in monkeys and mice. 3) The clinical illness produced by the two viruses was different in monkeys and mice. 4) LCM was almost constantly found in the blood and spinal fluid of monkeys during the febrile phase of LCM infection while encephalitis virus had not been demonstrated in these fluids during this period. 5) LCM failed to produce detectable symptoms in mice when introduced into the nose (intranasally) while encephalitis virus “took” readily by this route. 6) The pathology produced by the two viruses in mice and monkeys was usually readily distinguishable. 7) Cross neutralization tests between St. Louis encephalitis and LCM showed them to be immunologically distinct; LCM, likewise, was dissimilar to the recent encephalitis strains isolated in Japan. These Japanese strains were epidemiologically and clinically similar to the St. Louis encephalitis strains but again quite distinct from them. 8) Armstrong said that the LCM agent did not possess the characteristics of a herpes virus since it had no effect on rabbits. Furthermore, it did not correspond with any described virus then known to the microbiology community. For all of these reasons Armstrong considered LCM to be a hitherto undescribed infectious agent of which the significance in nature was unknown at that time.

In a brief summary of this virology classic: 1) Armstrong isolated a previously undescribed neurotropic virus encountered during the experimental transmission of encephalitis virus from the 1933 St. Louis epidemic from which it was readily differentiated. 2) He outlined the symptoms of the experimental infection in monkeys and mice. 3) He demonstrated the virus in the central nervous system, spinal fluid, blood and urine of monkeys and in the brain and blood of mice during the experimental disease. 4)

He considered the virus, possibly either of human or monkey origin, to be of unknown significance as a cause of disease in nature.

Armstrong maintained a continuing interest in the new virus. Over the next several years he and collaborating physicians from the United States Naval Medical Service (23, 24,) and physicians practicing in the local vicinity (22, 25) were able to establish the virus as the etiology of a specific medical entity including its various clinical presentations. In April 1935 (26) he recovered LCM from the central nervous system of a patient from Maine who died with an illness characterized by meningeal signs. He also demonstrated spontaneous infection among some of the laboratory's stock monkeys by isolation of virus and detection of antibody development. During this same period he also noted a "grippe-like" illness without central nervous system involvement in a laboratory attendant who developed potent neutralizing antibodies during convalescence. This latter case led Armstrong to suggest that immunity might develop in the absence of recognizable central nervous system involvement. He also indicated that laboratory observations in experimental animals showed that the virus was distributed widely throughout the various organs, that there was no marked neurotropism, and he speculated that it was conceivable that immunity might result from systemic infection without central nervous system involvement (27). This was indeed shown to be the case with observation of future additional cases.

In June 1935 Armstrong and Paul F. Dickens, United States Navy Medical Corps collaborated on several almost simultaneous reports (23, 24) entitled "Benign Lymphocytic Choriomeningitis (Acute Aseptic Meningitis) – A New Disease Entity". They included 4 detailed case reports, including one seen and reported by Dr. Walter

Bloedorn (25), all of which had similar clinical histories, physical examinations and laboratory findings, and all the sera of which showed immunologic protection in animals against infection with the virus. They also reported the isolation of the virus by Eric Traub (28) of the National Naval Research Center in March 1935 from white mice and by T. M. Rivers and T. F. Scott (28) of the Rockefeller Institute in May 1935. Subsequent studies of the viruses of Armstrong, Traub, Rivers, and Scott by cross neutralization experiments showed that these three viruses were immunologically identical.

The two manuscripts (23, 24), utilizing almost identical language, provided the following summary: 1) A symptom complex of headache, fever, signs of meningeal irritation, cerebrospinal fluid under increased pressure, with an increase in cells predominantly lymphocytes, coupled with normal chemical values (chloride, sugar, urea) and a negative spinal fluid Wasserman test (for syphilis) was a clinical entity, usually running a benign course, that had previously been designated in man as acute aseptic meningitis. 2) The virus of Armstrong (LCM) produced a symptom complex in monkeys similar to the above. 3) The blood serum of patients recovered from the disease protected animals from the virus of Armstrong (National Institute of Health). Serum taken early in the disease showed no protection and usually demonstrated protective antibodies only after the second week of illness. 4) This disease occurred sporadically in man and had been transferred experimentally to animals. 5) The strains isolated by Armstrong at the National Institute of Health, Traub at the National Naval Research Laboratory, and Rivers and Scott at the Rockefeller Institute were identical by serological studies. 6) The cases reported in these manuscripts by Armstrong and Dickens covered scattered

geographic areas, having their origin in California, Maryland, District of Columbia, Illinois, Ohio and Virginia.

After this summary they concluded: 1) the symptom complex was a distinct disease entity. 2) This condition, by priority, should be called “acute aseptic meningitis”, but, in view of the recent advance in the knowledge of its etiology, this designation was a misnomer and they suggested the term “acute lymphocytic choriomeningitis” as a more accurate designation. 3) The etiological agent was a filterable virus first described by Armstrong and Lillie. 4) The blood serum of patients recovered from acute aseptic meningitis protected animals from the virus. This might be used to confirm the diagnosis. 5) Monkeys, mice and guinea pigs were susceptible to the virus, and it was conceivable that a reservoir of the disease might exist in animals.

Over the course of the next several years, Armstrong and colleagues expanded their knowledge and concepts of LCM through surveys of various population groups for the presence of serum neutralizing antibodies (29, 30, 31). The groups included random samples, outbreaks of febrile central nervous system infections, prison populations, United States Marine Hospitals and others. They found that white laboratory rats were susceptible to the virus and provided another experimental host with which to conduct investigations. Armstrong, in collaboration with Wooley and Onstott (30), using the practical and reliable serum virus-neutralization test in mice, demonstrated antibodies in 138 of 1,248 sera tested (11 per cent), questionable protection in 131 (10.4 per cent), while 979 (78.6 per cent) sera provided no protection. Sera from Federal penal institutions and the beneficiaries of the United States Marine Hospitals gave a higher incidence of protection than did those from people of comparable ages from other groups

and were probably not representative of the general population. Armstrong could only speculate about reasons for this observation. He and his associates demonstrated antibodies in protection tests in 90 sera from 481 adults (more than 17-years) or 18.3 per cent, while only 5 sera from 396 persons under 17-years, or 1.2 per cent, showed protection. They could not establish the reason for this difference in seroincidence by age differential. They did show, however, protective antibodies in 17 of 52 sera (32.1 per cent) from individuals in whom a diagnosis of “aseptic meningitis “ had been made. Armstrong again reiterated that a positive protection test most likely indicated that the serum donor had been in contact with the virus of LCM. The occurrence of demonstrable antibodies in 117 sera from 997 individuals without history of central nervous system or meningeal involvement suggested to Armstrong that immunity might result not only from a frank symptomatic attack, but also from either a subclinical infection or a clinical condition, possibly an upper respiratory symptom complex, unrecognized as due to LCM virus. The answer came later. Armstrong continued serological testing for the next few years (31) with basically the same results.

The next major breakthroughs in knowledge about the virus were Armstrong’s discovery of the host, the common house mouse (*Mus musculus*) and the presence of endemicity in the mice (32, 33). Also, in the scientific literature from France, LCM was becoming known as “La Maladie d’Armstrong” (34). The initial breakthrough occurred as the result of local environmental investigations related to two patients hospitalized in the medical service of Dr. Lewis K. Sweet, Chief Medical Officer in Pediatrics at the old Gallinger Municipal Hospital in Washington, DC. (Later renamed DC General Hospital and for the past few years operationally defunct). The first patient, who became ill

November 1938, was a 23-year old African-American housewife who presented with the classical clinical and laboratory findings of LCM. Armstrong isolated the virus in white mice and guinea pigs from spinal fluid, blood and urine. The patient developed convalescent antibodies. The second patient, who also became ill November 1938, was a 17-year old African-American adolescent, a general cleaner in a well-kept apartment house. He developed a febrile illness with meningeal signs. He was admitted to Gallinger Hospital after a spinal needle broke off in his back following an attempted lumbar puncture to obtain fluid. His initial clinical course and laboratory results were consistent with LCM. Specimens for virus isolation were collected late (eleventh day of illness), and virus was not isolated. He did, however, develop protective antibodies in late convalescence. After the acute illness he returned to his home in West Virginia where he was hospitalized for low-grade fever and non-specific neurological symptoms. He recovered fully.

The occurrence of these local cases presented Armstrong with the opportunity to study some of the family contacts and home conditions in order to possibly help increase his knowledge of how the disease might be spreading. He began his study by obtaining sera from some family members. Sera from the husband and brother-in-law of Patient 1 possessed no antibodies. Serum from a second brother-in-law, who had lived in the affected home for several years was, however, strongly protective. Patient 2 roomed with a married couple whose sera were also examined for LCM antibodies. Blood from his landlady contained potent antibodies, while the serum of the husband was only moderately potent.

Armstrong next checked the home conditions of the two patients. Patient 1 became ill in a home located on the outskirts of the District of Columbia (now probably part of the suburbs). It consisted of a flimsy, slovenly kept shed, attached to which was a toilet in poor sanitary condition. The inhabitants hauled water from the city supply and stored it in a container. The house was unscreened. Patient 2 roomed with a couple on the third floor of a brick house in a well-maintained residential section of the city. The home was clean, orderly and was equipped with sanitary indoor plumbing that was in good condition. The patient took his meals at various restaurants and stated that he never brought food into his room.

Armstrong then inquired about rodent infestation in the environments of the two patients. Inquiry at the home of Patient 1 elicited the information that many mice had been noted in September and October 1938 but the occupants had eliminated them by trapping, poisoning and the burning of sulfur. No recent infestation was noted, but in December 1938 3 mice were captured, two in the house (kitchen) and one in the grass 75 feet from the patient's house. One of the house mice, a large female was the only animal that demonstrated virus. One kidney and one-half the spleen of this mouse passed infection to laboratory white mice through successive transfers. The virus was identical to the original strain isolated by Armstrong.

At the rooming house of Patient 2, Armstrong learned that mice had been especially prevalent during the early summer, but that the inhabitants destroyed many by trapping. Box traps were set in the home. An adult male was captured in the patient's bedroom on January 23, 1939. Pooled organs failed to grow virus when passed successively into susceptible laboratory mice. A large female, No. 945, and a less than

half-grown female, No. 947, were trapped on January 25 in the kitchen. Pooled tissues from each of these mice produced transmissible infections in susceptible laboratory mice.



Dr. Charles Armstrong examining small rodents for signs of paralysis, in the old Hygienic Laboratory-NIH Building, probably around 1939. Courtesy of Mary Emma Armstrong.

On the basis of the serological studies related to the two cases and their family contacts, the isolation of virus from mice from the patients' homes and the failure to find infection in 21 mice trapped in 8 houses wherein human LCM cases did not occur, Armstrong felt secure that the association between the human cases and the mice was more than a coincidence. He believed that the mice constituted the source of the infection for the following reasons: 1) In each instance the human case was ill in the home for only 4 days before being removed to the hospital; it would appear rather remarkable for both cases to have infected the mice of their respective abodes. On the other hand if the



disease was primary in the mice, the occurrence of the infected rodents in association with the cases was explained. 2) The housewife in both households apparently suffered infection while one mate escaped, and the only evidence in the other household members was a moderate degree of immunity as judged by the results of the serum virus-neutralization tests. These findings suggested an exposure to infection in the home rather than a human contact infection. 3) The capture of a less than half-grown infected mouse in the home 87 days after the patient in Case 2 had been removed from the house indicated the existence of active infection in the mice independent of the presence of a recognized human case. 4) The presence in the home of Patient 1 of a person who possessed strongly developed antibodies, at a time when the patient's immunity was but partly developed, suggested that the patient did not constitute the initial introduction of the virus into the household. Because of these reported findings, Armstrong suggested that gray house mice, *Mus musculus*, constituted a reservoir of LCM from which humans could be infected. He also indicated at this time the pursuit of further investigations of methods by which effective exposure to infection might be accomplished

Choriomeningitis remained a subject of continued interest for Armstrong.

Additional studies (33) provided definitive proof that the mouse was the major reservoir for the spread of infection to humans. He also helped expand knowledge of the clinical spectrum of the disease. In a 1940 report (33) written in association with local internists, Drs. J. J. Wallace and Louis Ross, he described two additional cases proven by virus isolation and serological identity with the original strain, the biphasic course of the clinical illnesses and the isolation of virus from mice trapped in the homes of each case. He found further 5 of 9 mice living in the same side of the block of one of the patients to

be positive for virus. Eight mice were trapped in the row of houses directly across the street from the patient but Armstrong was not successful in recovering virus from any of them. With tongue-in-cheek, Armstrong observed, "It appears that an open street is not readily traversed by gray mice."

Armstrong expanded surveillance of the mouse population of Washington, DC. He trapped more than 400 mice, including those already mentioned, from various parts of the city. Of the 400 mice captured, 365 survived for examination. He recovered the virus from 64 of a total of 303 gray mice, or, approximately 1 out of every 5 mice examined was a carrier of the virus. The mice examined came from 76 different homes while the infected mice came from 34 dwellings. Thus, 44 per cent of the mouse-infested homes studied were harboring mice infected with LCM. From these 34 infested homes a total of 122 mice were examined of which 64, or 52.4 per cent, were active carriers of the virus. All four of the DC patients were located in association with clusters of the 34 houses that harbored infected mice.

Armstrong staved off criticism (33) of the use of white laboratory mice to isolate LCM in view of several reports that indicated some stocks of white mice had been spontaneously infected with the virus. He showed that he used the same stock of white mice with other viruses and did not encounter LCM. He also used numerous random controls. As a further check on the reliability of using white mice to isolate LCM, Armstrong did immunity studies in gray mice trapped in infected and non-infected homes. He injected 62 mice from infected homes intracerebrally using stock laboratory virus (LCM). In this group 41 of 62 survived, indicating 66 per cent immunity. He next injected 47 mice from non-infected homes. Only 5, or 10.6 per cent survived. Twelve

(12) white mice used as controls for this group died. In this way, Armstrong defended his methods for using white stock laboratory mice free of LCM for isolation of viruses from infected feral mice.

It also had been noted by others (35) that an infected mother mouse might convey the infection to her offspring, and that such congenitally infected mice carried the infection for months. Armstrong (unpublished data) stated that these findings had been confirmed by Victor Haas at NIH. Haas showed that such congenitally infected mice were much more effective transmitters of infection to other mice than were artificially inoculated animals. Armstrong's finding of 52 per cent of mice from homes harboring mice to be carriers of virus, in a study extending over several months, suggested to him a persistent type of infection such as results from the congenital type of spread.

By the early 1940s the various clinical syndromes associated with LCM had been described. Armstrong was finally able to isolate the virus from a laboratory investigator working with LCM who presented with a "grippe-like" illness without central nervous system or meningitis-type signs and symptoms (36). About the same time Lt. Colonel Harry Plotz of the Army Medical Corps reported to Armstrong a similar illness in a laboratory investigator who was studying the virus at the Army Medical Research Center in Washington, DC. It was also becoming obvious at this time (and subsequently in the future) that LCM presented a health hazard to laboratory personnel working with the agent (36).

The clinical presentations gradually recognized in the early 1940s included: 1) The "Grippal" or non-nervous system type, suspected almost initially on the basis of surveys of random blood sample testing for antibodies. Many patients with antibodies

could recall no symptoms compatible with a central nervous system or meningeal illness.

2) Meningeal type: Often biphasic with initial fever, headache, stiff neck, vomiting, Kernig's and Brudzinski's signs (of meningeal irritation) and appearance in the spinal fluid of many white blood cells, primarily lymphocytes. 3) Meningo-encephalitic type: Signs of meningitis plus somnolence, disturbance of deep tendon reflexes, weakness, paralysis and some loss of sensory perception. 4) Asymptomatic type: Presence of positive serum antibodies without recollection of compatible illness.

Armstrong wrote several excellent review articles in the early 1940s summarizing the knowledge acquired to date, largely by him, about the disease (37, 38, 39). These included The Harvey Lecture of The New York Academy of Medicine, October 1940 (37), a review of the same subject appearing in *The Transactions and Studies of the College of Physicians of Philadelphia*, April 1940 (38), and The Kober Lecture of 1942 at Georgetown University, May 1942 (39). The local and national press media (40) covered widely Armstrong's laboratory discoveries of LCM and the associations between virus, mice and men.

The press also covered rather extensively an illness that occurred around November 1934, about one year after Armstrong returned from St. Louis. He was hospitalized for about three weeks at the United States Naval Hospital in Washington, DC with "fever, skin eruption, and delirium." No definite diagnosis was made other than "encephalitis". On January 25, 1935, *The Washington News* reported in an Armstrong related news release that he had recently recovered from encephalitis.

In order to get another perspective, the following verbatim excerpt from the Wyndom Miles oral history interview in 1966 describes some of Armstrong's

recollections of the events associated with LCM: “We got it (St. Louis encephalitis) growing in monkeys but not in mice. We brought back a number of brains refrigerated. I got a virus, which I thought was entirely different from studying the brains. I got the history of the person from which the brain came; it was a colored woman and she had died from what was thought to be St. Louis encephalitis. Unfortunately, the history on her had been consumed in a fire in one of the annexes of George Washington University, so we could never find if her clinical could fit in or not. It was a different virus, which we called benign choriomeningitis, a horrible long name. Dr. Dickens and I, he was in the Navy helping on it, proved it was a human disease. Dr. Rivers of Rockefeller confirmed that. We said it goes from mice to men. Dr. Rivers said it was probably the other way. But we found that mice were a continuing reservoir of the virus; that is if the mother has little ones while she has had encephalitis, all the little ones will have the virus but no symptoms and will continue carrying that for the rest of their lives and their offspring will be infected. I carried through her 39 transfers down. Dr. Halls [EAB- Probably Dr. V. Haas] then took over and he went through 200, I think, and they were still infected. Down on E Street there was a black that had a trash collector, and in his big pile of trash there were a lot of mice. He had a case in his family and one of his neighbors had a case. We went down there trapping and found that well over 50 per cent of the mice there were carrying this virus. We inoculated a healthy mouse and in a week it was dying of encephalitis. We thought that was enough to indicate that it came from mice to men but we had to clinch it. We found that on one side of E Street there was a heavy infestation of choriomeningitis in mice, while on the other side of the street they were practically free. It looked like mice didn’t cross a busy street; they had more sense than we had, while

people were going across either way. That I think convinced Rivers it was from mice to man. That disease was more common than we thought. We had a case in the laboratory which was a dead ringer to influenza, and there was not a laboratory which could say it wasn't influenza. We had two cases where vaccine was manufactured; they were making an encephalitis or some vaccine using a live virus that had gotten choriomeningitis mixed in it. The two workers had died, so it wasn't such a benign disease. We had a few cases that came from dogs and they were hot too, so the benign was sloughed off the name.

[The interviewer then asked Armstrong how he discovered it was passed from mice to man] We didn't know how at first, but from man to man there were no cases of infection, and from mice to man there were a number of cases that handled mice. One patient had taken a mouse out of a trap. It seemed to be transmitted by most any route, and if you put it into a monkey, for instance, it came out in saliva, urine, etc., so when you got an animal with it he spreads it everywhere.

“I got sick when I was working with these two viruses, and then encephalitis. That was in the old days when we made out our own payrolls, and I was too sick to sign it. I got over it all right. We wanted to see what I had, and I was immune to both choriomeningitis and St. Louis encephalitis; so I had them both and never knew which one gave me the symptoms. I judge it was likely the choriomeningitis. Senator Borah came in with the most gorgeous bouquet of flowers in a bowl he had bought in China [EAB – That must be how Armstrong received the bowl mentioned in an earlier chapter].”

Among the press coverage reporting Armstrong's illness was *Time – The Weekly Newsmagazine* (41). On July 29, 1936 the Editorial Secretary, J. Pequignot, sent him the following note: “Dear Dr. Armstrong: The enclosed letter has come to us from one of

your admirers, and we think it only fair that we should pass it along to you. (The young correspondent does not know that we are doing so.)

“We have already written him that you are well again and back to work. Sincerely yours, etc.”

The enclosed letter, written in a typically boyish scrawl, reads as follows:

Time, Inc,

Durango, Colo.

Dear Editor,

June 19, 1936

I read a long time ago that Dr. Charles Armstrong was very sick. Since that I have never heard anything more about him. I cut his picture out because I thought he was very brave saving other peoples lives. A couple of months ago I went to a show about Louis Pasteur which made me think about Dr. Armstrong. My name is James Beatty Noland. I am nine years old and will be in the 5<sup>th</sup> grade when school starts again in September. The thing I wanted to know was what happened to Dr. Armstrong because I wanted to be like he was. Please write me a letter and tell me what happened to him.

Yours very truly

James Beatty Noland

Armstrong apparently replied graciously to this touching letter indicating to his admirer that he was alive and well.

Since the original discovery, description and early investigations, LCM has assumed its position in the current hierarchy of virology. It is classified as an Arenavirus (42). The Arenavirus family, which also includes Lassa fever and the South American hemorrhagic fevers, is characterized by single stranded RNA, a unique morphology and the usual employment of rodents as virus reservoirs. The viruses can be divided into two

major phylogenetic and antigenic groups corresponding to 1) LCM, Lassa and close relatives in association with Old World Rodents, (family Muridae, subfamily Murinae) and 2) the Tacaribe complex from the New World or American Rodents (family Muridae, subfamily Sigmodon tinaie). The correspondence between the phylogeny of the hosts and viruses suggest a long-associated co-evolution. The New World viruses, derived from clinical cases were isolated as follows: Jumin, 1958, Machupo, 1963, Lassa, 1969, Guarnarito, 1989, and Sabia viruses, 1990. For details of virus characterization, molecular virology, and clinical manifestations, consult recent editions of texts on virology (43) or clinical infectious diseases (44).

At present LCM is considered to be frequent as determined by the prevalence of antibodies in persons without prior history of illness. Clinical illness is infrequent. Most recognized cases occur in the autumn when rodents seek indoor shelter and are associated with rodent infestation. The usual pathway of infection is by the aerosol route. Cases have occurred in association with rodents such as mice, hamsters or guinea pigs often acquired from pet shops. Occasionally dogs may harbor the virus. There have been laboratory outbreaks as described. Recently LCM has been transmitted by tissue transplantation from asymptomatic individuals (45, 46).

In December 1996, Dr. Robert M. Chanock , Chief, Laboratory of Infectious Diseases (LID), NIH wrote as follows in his review (47) of LID for the Board of Scientific Counselors in the section Long Term Research Goals and Readjustment of Specific Approaches in Response to Technological Advances: “Despite many temptations to limit study to smaller and smaller model systems of infection, the research goals of LID have remained the same, namely 1) delineation of the etiology,



pathogenesis, and epidemiology of medically important viral diseases and 2) development of means for their control. This credo for conduct of research in LID was first articulated by Armstrong and Huebner over 50 years ago, and it still continues to serve as our compass. An important subtext of this credo is that LID scientists are allowed and encouraged to pursue an infectious disease problem from beginning to end. This means that they must master most or all of the approaches and technologies required for the successful pursuit of such a broad objective.”

Charles Armstrong’s approach to the study of LCM demonstrated adherence to the principles of the above goals that resulted in the major elaboration of knowledge about this virus. He succeeded while utilizing the uncomplicated technological tools of the 1930s. He discovered the virus, associated it with a variety of recognizable human infectious presentations, established a laboratory method for diagnostic recognition, performed studies to evaluate its epidemiologic significance, discovered the animal reservoir, proposed public health measures for control and studied the nature of the disease in its rodent host. Over the years fine, sophisticated studies have elaborated on the biology, chemistry and molecular structure of the virus, but, in comparing them to Armstrong’s investigations, they are really merely commentaries.

Notes – “Green Thumb” Virologist; Saint Louis Encephalitis; Lymphocytic Choriomeningitis

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- 17) Lumsden, L. L.: Saint Louis encephalitis in 1933: observation on epidemiologic features *Public Health Reports* 73: 340-353, 1958, quoted by Horsfall, *Ibid.*, pp. 622, 652.
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## Poliomyelitis

Charles' Armstrong's involvement in poliomyelitis research originated in the national forces generated as the result of the election of the disease's most famous victim to the Presidency of the United States. Many prominent investigators and health workers, supported by an enthusiastic and philanthropic base, over the course of a relatively few years, were able to make major advances concerning the nature of the virus causing the disease, growing it in large quantities to make immunizing vaccines and to mount effective efforts to protect and eliminate the disease from large populations in many areas of the world unless stymied by social taboos, cultural barriers, inaccessibility, political conflicts, religious preferences or just plain ignorance. In commemoration of its 20<sup>th</sup> Anniversary Founding, the Trustees of the National Foundation for Infantile Paralysis invited Armstrong and fourteen other distinguished, accomplished scientists to Warm Springs, Georgia on January 2, 1958 to be inducted into "The Polio Hall of Fame" (1).

*Poliomyelitis* (polios – Greek – "gray"; myelos – marrow, myelitis – Greek – "inflammation of the spinal cord"; nomenclature based on the prominent anatomical location of pathological involvement) is a viral disease caused by members of the *picorna* group ("pico" = small; "rna" referring to the nucleic acid core or genome). Its natural habitat is the human alimentary tract and it belongs to the family of *Enteroviruses* that also include the *Coxsackie A and B viruses*, the *Echoviruses* and the *Rhinoviruses*. The polioviruses exist in 3 distinct immunological types. Despite their widespread distribution in nature, the paralytic and crippling hallmarks of the disease were first recognized only in the relatively recent past of human history.



A brief outline follows of modern information about the acquisition of knowledge and the initiation of control measures for poliomyelitis derived from several sources (1); this provides a time frame for Armstrong's involvement in poliomyelitis investigation. The crippling aftermath and limb atrophy resulting from poliomyelitis was probably noted sporadically for many centuries. Dr. Jacob von Heine, a German orthopedist, first described the disease clearly in 1840. He wrote the first book on the disease published in Stuttgart, Germany. His writing described the acute paralytic disease among a few babies or toddlers, usually non-fatal. He saw them many years later with chronic paralytic disease and limb deformities that he occasionally tried to correct by surgery. In 1887, Dr. Oskar Medin, a Swedish physician, first recognized poliomyelitis as an acute infection during an epidemic in Stockholm; he published a report in 1890. He observed the initial clinical manifestations including fever, malaise, and body aches often followed by paralysis. Deaths occurred during this outbreak, and pathologists observed the pathology in the spinal cords and lower brains of the victims. They noted the destruction of the motor cells in the anterior horns (gray matter) of the spinal cord and in the motor nuclei of the cranial nerves in the medulla and pons. In 1905, another Swedish physician, Dr. Ivar Wickman, began the study of polio epidemics with careful epidemiological and clinical observations. He described the various manifestations and outcomes of infection; he postulated person-to-person spread and the existence of healthy carriers based on epidemiology. In 1907 he commented on the wide prevalence of non-paralytic polio from his observation of patients during the epidemics. He labeled the sicknesses he was seeing as "Heine-Medin Disease" – its original eponym.

About the beginning of the 20<sup>th</sup> century, epidemics of poliomyelitis began occurring with increasing frequency, almost on an annual basis, in Europe and North America in scattered areas with increasing intensity, morbidity and public apprehension. This new scourge was paradoxical inasmuch as other pestilential diseases and those associated with poor sanitation were diminishing gradually, but poliomyelitis was not disappearing following the improvement in public health standards and the initial introduction of immunizing vaccines for childhood illnesses. Polio remained a complete mystery to the private and public health practitioners, as well as a source of fear for the general population because of ignorance of how it was spread and of what measures could control an outbreak.

The era of the laboratory study of poliomyelitis began in 1909 when Dr. Karl Landsteiner, in Vienna, Austria, passed infection from the spinal cord tissue of a polio fatality to several non-human primates, monkeys (*Macacus rhesus*) and baboons. He also postulated that the infectious agent was a virus. He did not work further with poliomyelitis. He moved later to the Rockefeller Institute in New York City where he did his pioneering work on blood groups and immunology. Thereafter, Dr. Simon Flexner, Director of the Rockefeller Institute, and other Institute investigators dominated polio research for the next several decades. The Institute was one of the few private organizations with the facilities, financial resources, and personnel to conduct research utilizing and dependant on expensive, irritable, and irascible monkeys. Flexner found that the poliovirus passed through the finest porcelain filters that held back any microscopically visible bacteria. In looking for a portal of entry for polio in humans, Flexner found that he could infect and paralyze monkeys by instilling infectious polio

tissue high up in the nasal passages. He infected monkeys by intracerebral passage and later recovered poliovirus from the nose after the monkeys became paralyzed. He postulated that polio gained entrance to the brain by way of the exposed nasal nerve endings (olfactory nerve) and followed the nerve to the brain. Later the reverse occurred and the virus reappeared in the nose where it could be a source of infection to other persons. Later investigators in the 1930s and 1940s (see below) found that the portal of entry was through the fecal-oral route and that a viremia originating from the infected alimentary tract invaded the central nervous system to produce the neurological manifestations of poliomyelitis.

Polio epidemics appeared annually unabated. The worst epidemic in the United States on record, shortly after research efforts and accurate record keeping began, occurred in New York City in 1916 with over 9000 cases. The public health officials were at a loss to recommend control measures to prevent spread since so little was known about how polio spread. Attempts to treat patients with intraspinal injections of serum from patients who had recovered provided no definite results but were generally deemed useless.

In the summer of 1921, Franklin Delano Roosevelt, scion of an upper Hudson River Valley patrician family, educated at Harvard College and Columbia Law School, former Assistant Secretary of the Navy, Democratic Vice-Presidential Candidate in 1920, lawyer in a prestigious New York City law firm and a rising, popular, political figure, took his wife and children to the family retreat on Campobello Island to remove them from New York City in order to remove them from the current outbreak of poliomyelitis. Campobello Island, Canada is located in the Bay of Fundy close to and off the northeast

coast of Maine. While there, he pursued a vigorous physical life style that included swimming in the frigid waters of the Bay of Fundy and leading his children on races along and through the rocky coast line. After three days of this activity, he developed fever, severe limb aching and paralysis. Medical specialists from Boston invited to the Island made the diagnosis, and Roosevelt returned to New York City amidst great secrecy concerning his illness and disability. Through indomitable will and perseverance, Roosevelt determined that he would overcome his physical handicap, project an appearance of vigorous good health and resume his political career with the eventual goal of becoming President of the United States. Shortly after convalescence from his acute illness, he joined his lifelong friend, Mr. D. Basil O'Connor in a lucrative law practice. O'Connor was to play a major role in managing the complex financial and philanthropic aspects of the organizations associated with Roosevelt's poliomyelitis. Roosevelt, in 1924, discovered the decrepit sanitarium in Warm Springs, Georgia that he visited frequently for therapy. Under O'Connor's management Warm Springs was renovated, and it became the home of the Warm Springs Foundation that accepted charitable donations for polio research and treatments.

After Roosevelt's election, annual charitable balls were held nationwide from 1934 to 1937 around his birthdays on January 30 and were labeled "President's Birthday Balls." The "Birthday Balls" raised large sums of money the purpose of which was to "finance the fight against polio." O'Connor managed the collection of money but a special commission was established called the "President's Birthday Ball Commission." Eleven prominent citizens were invited to serve, none of who had experience or background in medical research except for Paul DeKruif who began his professional

career as a bacteriologist. He became prominent as a popular writer of medical science books for the lay reading public. The reputation he acquired from this activity helped establish his reputation as an advisor for medical affairs related to poliomyelitis. He exuded great enthusiasm but he was often uncritical in his judgments of the scientific merits of research proposed by others. Rivers (2) and Smith (3) had dubious assessments of his contributions during his association with the Commission and, later, the Foundation. DeKruif was acquainted with the microbiology research community and invited investigators to apply for project funding from the influx of funds now available. Unfortunately, several tragic events were associated with studies financed by the Commission. In 1935, Drs. William N. Park and Maurice Brodie carried out a vaccination program that was completely ineffective in providing immunity, and Dr. John Kolmer used a live vaccine that caused illness and fatalities. These efforts were widely condemned by the public health practitioners and the scientific community. More benign fiascos involved the attempts to use chemical blockade to prevent the entrance of poliomyelitis virus through the nasal membranes, also around 1935-1936. This procedure had some rationale from laboratory evidence but its application in an epidemic situation was impractical; the procedure was also doomed to be unsuccessful since the investigators were unaware at this time of the later establishment of the alimentary tract as the major portal of entry of the virus into the body. Unfortunately, Armstrong became involved in one of these attempts to control a polio outbreak (see below).

On September 23, 1937 President Roosevelt called for the creation of the “National Foundation for Infantile Paralysis” to lead, direct and unify the fight against polio. On November 22, 1937 Eddie Cantor, the actor-comedian, suggested the name

“March of Dimes” for the annual fund raising appeal, and the White House became inundated with avalanches of dimes coming from collection venues (churches, movie theaters, etc.) in towns, cities, and counties all over the United States. On January 3, 1938 the National Foundation for Infantile Paralysis was incorporated and Basil O’Connor was named president. He located the Foundation headquarters several floors below his law office at 120 Broadway, New York City. He directed the Foundation activities with direct supervision and superlative efficiency for many years. He established many committees dealing with relevance to administration, fund raising, patient services and research. The Virus Research Committee was composed of distinguished and accomplished scientists including Charles Armstrong. The Foundation established many local chapters that collected funds and provided help to patients.

In mid-1938, with ample funds available, the Research Committee made its first grants to the Yale University Poliomyelitis Unit. The prominent members of the group included Drs. John Paul, James Trask, Dorothy Horstmann, and later Joseph Melnick. In 1933, Paul and Trask suggested that there were strain differences among polioviruses that were shown later to exist in three immunologic types. In 1938 they, along with other investigators, found polio regularly in stools of patients, and experimentally, monkeys and chimpanzees. The Yale group, under Paul’s leadership, undertook many epidemiological studies. Horstmann and her colleagues first detected the presence of viremia in infected subjects; this helped explain the spread of infection from the gut to the central nervous system. Another prominent group of investigators who contributed to the understanding of polio infection consisted of David Bodian, Howard Howe, and Isabel Morgan working at Johns Hopkins University. In 1941, Bodian and Howe

demonstrated alimentary tract infection in the chimpanzee. They also did extensive pathology studies of infection in monkeys, and they suggested the probable pathogenesis of infection in these subjects. In the later 1940s Bodian, Morgan, and Howe were able to group 14 strains of polio into the three basic types. In 1948-1949, Morgan was able to immunize monkeys with a formalin inactivated polio vaccine. Prior to all the above events Armstrong, in 1939, was able to adapt the Lansing strain (type II) of poliovirus to cotton rats and white mice. This was a major advance in polio investigation since it opened the way to quantitative measurement of virus and neutralizing antibody on a scale that was impossible to achieve in monkeys. This provided a major quantitative epidemiological tool until 1949 when John Enders, Thomas Weller, and Frederic Robbins adapted a passage of the Lansing strain to grow in tissue culture containing non-neural tissue.

This latter Nobel Prize winning discovery strongly encouraged the possibility that an effective vaccine against poliomyelitis grown in tissue culture might be feasible. It was important, therefore, to determine the exact number of immunological types that existed. From 1948 to 1952, funded by the Foundation Virus Research Committee, several prominent research centers received the task and funds to type by immunologic methods as many of the known isolated poliovirus strains as possible. This activity resulted in establishing the three polio types: Brunhilde (type I); Lansing (type II); and Leon (type III).

Among the poliovirus typing center investigators was Dr. Jonas Salk, Director of the University of Pittsburgh Virus Unit. Dr. Salk was planning and developing simultaneously a killed polio vaccine much to the objections and criticisms of the virus

research and academic communities. Dr. Salk succeeded in developing a killed polio vaccine containing the three immunologic types. Dr. Thomas Francis, Jr. of the University of Michigan, who had been Dr. Salk's early research mentor, conducted and oversaw a successful, controlled field trial of the vaccine starting April 1954. On April 12, 1955 before an enthusiastic audience of investigators, politicians, and members of the press, Dr. Francis, representing the Polio Vaccine Evaluation Center at the University of Michigan, pronounced the Salk vaccine to be effective and safe. The United States government licensed the vaccine for use almost immediately, and the National Foundation launched a program of free vaccination for school children in the first and second grades. Shortly after initiation, the program had to be cancelled abruptly because batches of vaccine from the Cutter Laboratories were causing clinical poliomyelitis. After much consultation with the Public Health Service, polio investigators and the re-evaluation of manufacturing standards for safety, the program resumed, and a large percentage of the population received immunization with the Salk vaccine.

A different approach to polio immunization was the effort by Dr. Albert Sabin (and others) to prevent infection by immunizing the alimentary tract using attenuated polio strains that had lost their ability to grow in the central nervous system. Sabin developed his vaccine strains during the 1950s and early 1960s. In view of the success of the Salk vaccine by this time period, most of the field trials with the oral polio vaccines occurred in the Soviet Union where large susceptible populations could be immunized within short periods. By the mid-1960s the Sabin oral polio vaccines supplanted the Salk vaccine for routine immunization in the United States, and they helped eliminate polio from the Western Hemisphere and many parts of the developing world. However, a slight



but definite risk of paralytic disease (1:2,400,000 cases) occurred when some of the virus regained the ability to invade the central nervous system. In 2000 (4), the Centers for Disease Control (C.D.C.), the American Committee for Immunization Practices (A.C.I.P.), and other interested organizations recommended a return to the injected Salk-type vaccine for primary immunization, reserving oral vaccine for persons exposed to virulent strains re-introduced into the United States, and for areas in other countries where polio is endemic.

With its original fight against polio largely accomplished, the National Foundation changed its name in 1979 to the “March of Dimes” (5) to honor that effort. “The current programs include campaigns to improve the health of pregnant women, mothers and women of child-bearing age; provide education about birth defects, genetics and nutrition to health professionals; and fund research that will help save babies’ lives. In 2000, the organization provided \$36.1 million for research” (5).

The above outline of major events in the history of poliomyelitis is intended to provide a chronological frame of reference for Charles Armstrong’s research in poliomyelitis. The creation of the President’s Birthday Ball Commission, the March of Dimes and the incorporation of the National Foundation provided the financial means to support and provide generous funds for research and patient services. In 1935, the Birthday Ball Commission formed a Special Research Advisory Committee for the purpose of making grants to medical investigators. The Committee consisted of Dr. Max Peet, a neurosurgeon, Dr. Donald Armstrong, a vice-president of Metropolitan Life Insurance Company, Dr. George McCoy, former Director of the Hygienic Laboratory (now the NIH), and Paul DeKruif, the popular medical-science writer who had become

influential in poliomyelitis affairs because of his perceived knowledge of science, medicine and his widespread circle of acquaintances in medical research. The Committee began making grants to medical investigators in May 1935. Following the tragic failures and events of the Brodie-Park and Kolmer vaccines, a desperate public was ready for any new, safe, hopefully effective approach to stop the ravages of the regularly recurring, mysterious epidemics.

From a theoretical standpoint for which there were published and established experimental data, attempts to prevent poliomyelitis infection by blocking the entrance of the virus through the nose with a chemical barrier seemed to be a reasonable and safe approach. As noted previously, it was not until later that the fecal-oral route was recognized as the major portal of entry of poliovirus into the body setting up infection initially in the alimentary tract. Simon Flexner, at the Rockefeller Institute (see above) in early polio investigation, was able to infect monkeys through the nose, observe disappearance and then reappearance of infectious virus in the nose about five days later. Other investigators at the Rockefeller Institute, including Peter Olitsky, Albert Sabin and Herald Cox demonstrated chemical blockade using a different virus and laboratory host. Working with the equine encephalitis virus in the mid-1930s, they were able to infect white mice by dropping the virus into the nose. They found that they could prevent infection by first instilling tannic acid into the nose (6). At Stanford University, Dr. Edwin W. Schultz (7), generously funded by the Committee, was able to block polio from infecting monkeys by first instilling a solution of astringent alum (aluminum sulfate) into their noses. He carried the studies an additional step forward. He opened the skulls of the monkeys, and, under direct vision, he severed completely both olfactory

nerves. He then instilled live poliovirus into the noses of the monkeys, but the ones with the severed nerves did not become ill. Dr. Schultz thus showed that severing olfactory nerves of the test animals prevented the development of paralysis from poliovirus instilled nasally.

Armstrong arrived at his conception of poliovirus infection prevention by chemical blockade through a series of laboratory observations over several years. His initial observations were related to postvaccinal encephalitis (see previous chapter) when he noted that mice pre-immunized with diphtheria toxoid survived longer and in greater numbers, when subsequently injected with vaccinia virus intracerebrally, than mice not pre-immunized with diphtheria toxoid. He also demonstrated that mild irritation of a rabbit's eye with diphtheria toxin prevented the blinding effect of vaccinia virus. In his experiments with St. Louis encephalitis, he found that he could prevent infection in mice by the nasal route through the prior instillation of a dilute solution of alum (sodium aluminum sulfate), an astringent mucus-coagulating chemical (8). Aware of the studies of his contemporaries, Schultz and Gebhardt in California (7, 13) and Sabin, Olitsky and Cox at the Rockefeller Institute (6, 12), Armstrong, and his colleague W.T. Harrison (9, 10), were able to prevent infection with intranasally administered poliovirus virus in monkeys by chemical blockade. Since they felt that alum alone was too irritating, they settled on a solution of equal parts alum and picric acid (trinitrophenol) to a final concentration of 0.5 per cent of each ingredient (11). This was the mixture that was recommended for the nasal spraying in the poliomyelitis preventive field studies that were about to take place.

The field trials for this approach occurred in close approximation to the growing awareness in the mid-1930s of the experimental studies. Armstrong, in November 1936, read before the Southern Branch of the American Public Health Association at their Fifth Annual Meeting in Baltimore, Maryland, “The Experience with the Picric-Alum Spray in the Prevention of Poliomyelitis in Alabama, 1936” (14). He stated that in the absence of any established, practical method for preventing human infection with poliomyelitis, it seemed that the experimental evidence justified a trial of the method in man. With this view in mind, the appearance of poliomyelitis in Alabama in 1936 afforded an opportunity to carry out such a field trial. As per usual custom, following a conference between state and federal administrators, the latter decided to offer the method for application in the affected area.

For the purpose of orienting the practicing medical community, the State Health Department supplied each physician in Alabama with a résumé of the experimental studies carried out to that time, including instructions as to the preparation and application of the solutions.\*

According to Armstrong, the résumé emphasized and made clear that the evidence for the protective action of the proposed spray was based entirely upon animal experimentation and was not to be considered of proven value in the prevention of poliomyelitis in man. Armstrong also indicated that the Surgeon General of the United

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\* (11) Solution A. Dissolve 1 gram of sodium alum (sodium aluminum sulfate) in 100 cc of physiologic salt solution (0.85 per cent). Turbidity may be removed by filtering one or more times through some filter paper or Berkefeld filter.

Solution B. Dissolve 1 gram of picric acid (c.p.) in 100 cc of physiologic salt solution (0.85 percent). (Warming will facilitate solution.)

Mix equal amounts of Solutions A and B. This gives a 0.5 percent solution of each ingredient, which is stable, and it is this mixture which is to be dispensed.

On the appearance of cases of poliomyelitis in the community, spray the nose thoroughly once daily on alternate days for 3-4 applications, then once weekly thereafter for the duration of the poliomyelitis season. The spray should be directed upward toward the top of the head.

States Public Health Service, moreover, detailed a medical officer [C.A. or W.T.H.?], who was familiar with the details of the experimental work, to the infected area. This officer, through a series of well attended meetings with physicians, the first of which was held in Montgomery, Alabama July 15, 1936, fully acquainted the profession with the theoretical and experimental bases for the proposed method.

The health officials directing the field trials advised that the proposed remedy be administered either by a physician or under his immediate supervision for several reasons: a) The proposed spray had not been administered to any large group of individuals, and it was desirable that its application be closely observed for side and untoward effects, and, that any such effects be reported promptly. b) It was felt that a physician acquainted with the rationale for the treatment could apply it more professionally than an emotionally involved parent unacquainted with nasal anatomy. c) Record keeping was important for all treatment, and forms for that purpose were made available to physicians.

Since proper application of the solution to the nasal cavity was fundamental to the success of the method, The President's Birthday Ball Commission made a grant in March 1936 to Dr. Max Peet of the University of Michigan to determine the best method for the application of the chemical for nasal installation. Utilizing X-ray studies of opaque substances in monkeys, Dr. Peet and associates demonstrated that spraying the monkeys' nasal vaults coated the area as completely as the usual method of flooding the nose. The position of the head apparently was not critical. The preparation of the spray and the schedule of spraying were as outlined above by Armstrong and Harrison. The investigators and the State Health Department concurred that, rather than crowding

children into physicians' offices, the spraying should be carried out in the open. The local authorities, through the extensive coverage by the lay press, attempted to advise and educate the public about the aims and the hopes of the spray.

By consensus, Birmingham and the surrounding county of Jefferson, Alabama were selected as the most suitable locations in which to begin study of the effect of the spray. What Armstrong and the State Health Department hoped to be a reasonably controlled and directed field study evolved into a protocol-abandoned pandemonium. A minority of physicians preferred not to employ an experimental procedure; others felt that the parents could be taught to do the spraying – after demonstration and instruction in the procedure. They encouraged the parents to purchase the materials and to spray their own families. The newspapers printed the formulas for the solutions that the local pharmacists could mix, and the families could purchase the sprayers from the pharmacies. The overwhelming majority of the physicians were solidly aligned with the efforts of the Health Department. Armstrong wrote: “It soon became evident, largely through the activity of the people themselves, that what we had hoped would be a test by and under the profession, had become a test by the masses, largely uninstructed, upon the masses, with all the variations of methods which such a procedure implies. The same thing happened in Tennessee and Mississippi where spraying was also instituted. In a surveyed area, only 57 from 1,153 families were regularly sprayed by physicians.” This restrained statement masked Armstrong's frustration and anger at the authorities' helplessness in controlling a panicked population faced with a frightening, mysterious, perceived community danger.

The people were taking the spraying program into their own hands, and the study soon became a shambles. Paul DeKruif, by virtue of his position on the Research Committee of the President' Birthday Ball Commission was involved in the planning discussions of the study and the distribution of funds through grants. He corresponded and visited frequently with Armstrong about the program. He described the events associated with the study in his usually florid style in his book "The Fight for Life."(15) There was no way that any kind of controls could be placed on the people in the epidemic area. People overwhelmed the pharmacies with requests for the spraying solutions. Spraying technique was randomly applied and irregular. Babies and seniors were overlooked largely. Many people preferred to spray their own families rather than paying the modest fees suggested for the procedure. In the interests of economy, many families shared the same sprayers, usually hand-held nebulizers, and solutions, and they neglected any pretense of sterilization of the equipment between the spraying of family members or friends. The persons doing the spraying usually kept no records of when and with what regularity they sprayed the recipients. The program as it developed was an epidemiologist's nightmare.

Despite the irregularities and deficiencies of the program, Armstrong still attempted a survey and tried to obtain data about the persons who were sprayed and the incidence of acute flaccid paralysis as an indication of infection with poliovirus. The only control he could use was the incidence of paralysis in persons who were sprayed compared with those who did not receive the spray. There was actually a slight decrease in disease among those who received the spray but the difference was of dubious significance; also the data did not indicate the amount and regularity of the spraying.

Armstrong felt that the spraying as applied, usually to children, was inefficient due to inadequate delivery into the nasal cavity.

Armstrong presented the following conclusions about the study: 1) Chemicals capable of blocking the olfactory route of infection must be thoroughly applied to the nasal vault if maximum protection was to be secured. 2) Many children actively resisted and thus rendered spraying difficult. (When asked later why this was so, Armstrong answered: "They wiggle.") 3) Sympathetic parents, unfamiliar with the anatomy of the nose, were not, as a class, qualified to administer prophylactics properly. 4) A house-to-house survey revealed complaints from 885 among 4,631-sprayed individuals. Headache, temporary nausea, burning of nostrils, symptoms of head cold, irritated throat and irritation of eyes, in the order named, were the most usual complaints. Had the applications of the chemicals been more uniformly thorough, more unpleasant consequences might have developed. 5) Seven instances of hypersensitivity or of idiosyncrasy to the drugs were reported from the whole epidemic area. 6) The actual incidence of poliomyelitis in the group sprayed by whatever method was less than the calculated incidence based upon the rate in the unsprayed group (16:217) (Birmingham area). In the total epidemic area there were estimated 270,000 sprayed and 160,000 not sprayed individuals. 7) The occurrence of cases in persons who had sprayed for several weeks in the advised manner threw question on upon the method as employed. 8) In the face of an epidemic of poliomyelitis, the people could be relied upon to employ any simple, inexpensive prophylactic method of promise. 9) It seemed probable that the most effective method of application, as well as the most ideal solution, had not been found yet. Investigative work should therefore be continued.



Additional attempts occurred utilizing sprays to prevent poliomyelitis. With additional funding from the President's Birthday Ball Commission, Dr. Edwin Schultz (16) was able to test other solutions in monkeys. He found that he could protect animals with zinc sulfate solution. One or two applications appeared to be effective for longer periods than the alum-picric acid and did not require repetition. Test spraying in adult college graduate students indicated that this solution, in contrast to the alum-picric acid, was very irritating and not well tolerated in the nose. Children were especially difficult recipients, and Armstrong never knew when he personally administered the alum-picric acid whether he was achieving spraying the nasal vault because the children wiggled so much. He quipped facetiously that the only thing that would control the children during a nasal spraying was to encase them in total plaster body casts.

In 1937, the spray idea (17) received an extended test in Toronto, Canada where the local medical society enlisted the aid of the regional ear, nose and throat specialists to devise a method to successfully fill both the nasal cavity and vault with zinc sulfate solution. These doctors suggested that the proper method was to put the child on its back and lowering the head so that the nostrils faced straight upward. This was not a method for spraying large numbers of persons in an epidemic situation, and the proposed logistics to do a proper controlled trial were impractical. The spray was not without its dangers. Some people lost their sense of smell. As quoted by Rivers (17), Dr. Donald Fraser of the Connaught Laboratories never regained his sense of smell, and "that the only objection he had to this loss was that he couldn't enjoy his sherry any more." Much to the chagrin and frustration of Paul DeKruif, who had enthusiastically promoted the spraying program, none of the public health community, who would be involved, could come up with a plan

to carry out a well-controlled spraying program in time to avert epidemics of poliomyelitis. No further serious attempts materialized to extend the concept of spraying noses for polio prophylaxis.

In the Wyndom Myles oral history, Armstrong made the following comments (18): “I did have one experience with zinc sulfate, with alum first, and then with picric acid. I found if you put that in the nose of a monkey, you could drop poliovirus in the nose and they wouldn’t come down. It was thought that the infection was spread through respiratory methods and it looked as though it might be worthy of a trial. So, [?] DeKruif came through the lab one day and I showed him the results. He became very excited and went down to see the Surgeon General. I wasn’t quite ready to let loose of it yet, but the Surgeon General gave me orders to get ready to proceed to the South where they were having a great deal of polio and try this treatment. There were some questions that hadn’t been answered yet, just what it would do to the sense of smell, and what the dangers were, and whether it would be effective in man. I went to Michigan to see a worker [Dr. Max Peet?] there, and I said I did not know whether any (one) could reach the membranes of a human like you can a monkey. He said it would be much easier in a human than a monkey, and he said he thought it would work. So, I went down to Alabama. We asked the people to get the doctor to give this spray treatment, but that didn’t last long. The patients would be all yellow with picric acid, and if you’d go to the movie, they would be giving it to everybody when they came out of the movie; they’d get a bottle of picric acid. The results came through, and it looked as though the picric acid had not helped. I was able to withdraw the experiment, so I wasn’t blamed for to put anything over that was unreasonable.” Armstrong did not pursue this method further.

Armstrong's continuing involvement with investigations in poliomyelitis was associated with his inclusion in the Committee on Scientific Research (later Virus Research) of the National Foundation. Following the incorporation of the National Foundation in January 1938, Basil O'Connor, the President, with suggestions from Paul DeKruif, directed the establishment of committees to plan and administer the diverse activities to be undertaken by the Foundation. The Committee on Scientific Research was organized initially on July 6, 1938. According to Rivers (19), Paul Dekruif (while slightly intoxicated) told him that he (Rivers) was to be invited to join the Committee (which was reorganized several times with various name changes). The original members of the Committee were Paul DeKruif, Dr. Donald Armstrong, Dr. Charles Armstrong, Dr. George McCoy, Dr. Karl Meyer, and Dr. Thomas Rivers. Several of the above had served previously on the Scientific Advisory Committee of the President's Birthday Ball Commission. The major difference from this Committee was that the new National Foundation Committee had three working virologists: Dr Karl Meyer of the Hooper Foundation, University of California, San Francisco; Dr. Charles Armstrong of the National Institute of Health; and Dr. Thomas Rivers of the Rockefeller Institute. The Committee at its first meeting discussed the major unresolved research problems that needed to be addressed in relation to poliomyelitis. After several months of discussion and collaboration, the Committee agreed on an eleven-point program (20) that, in the order of priorities, guided the National Foundation in its grants policy until the appearance of the Salk-Sabin vaccines in the 1950s-1960s.

The program as it appeared in the minutes of the Scientific Research Committee (21) was as follows: 1) Pathology of poliomyelitis in human beings. 2) Portal of entry and

exit of the virus. 3) Purification and concentration of the virus. 4) What is to be called poliomyelitis? 5) Mode of transmission of virus from man to man? 6) Transmission of virus along nerves. 7) Further attempts to establish poliomyelitis in small laboratory animals. 8) Settlement of the question of chemical blockade. 9) Chemotherapy of poliomyelitis. 10) Relationship of constitution to susceptibility. 11) Production of a good vaccine.

Armstrong served on the Committee for several decades, participating actively in its deliberations and remaining involved in the discussions relating to the grants awarded the major investigators who made important contributions in elucidating answers relating to the questions raised by the eleven-point program. His role was central in a Committee whose foresight and acumen helped to alleviate the human affliction of poliomyelitis. Of maximum importance was his addressing point-seven in the eleven-point program – the establishment of poliomyelitis in small laboratory animals.

Through the kindness of Dr. Max Peet, a neurosurgeon of the Department of Surgery, University of Michigan, Armstrong received on August 28, 1937, a portion of the brain and spinal cord from an 18-year old boy, one of several victims who succumbed to bulbar poliomyelitis in Lansing, Michigan, during that summer (22). Dr. Peet and Armstrong became acquainted with each other when, as noted previously, they both served on activities of the Scientific Committee of the President's Birthday Ball Commission. In the initial report, Armstrong indicated that he recovered in rodents a virus that had been through 15 monkey passages. This agent, by clinical characteristics and pathologic examination, was identified as poliomyelitis (23).

When he received the Lansing brain and spinal cord material in August 1937, Armstrong sought previously unused rodent species in which he would try to adapt poliovirus. On November 8, 1937, he received several species of rodents, including a limited number of cotton rats (Eastern cotton rat, *Sigmodon hispidus hispidus*), from Dr. A. Packchanian, an investigator at the National Institutes of Health. He inoculated monkey-passaged infected nervous tissue into the brain, nose and abdomen of a limited number cotton rats. A few animals developed limb paralysis after prolonged periods but Armstrong could not passage the infection further through the cotton rats. He also had a limited supply of the rats, and he stopped further attempts at passage after the first few months of 1939. He decided to try again during the polio season of 1939 (23) after he was able to accumulate more animals. This time he was able to infect rats consistently in serial passage. With the fourth rat serial passage tissue he was able to produce typical poliomyelitis in monkeys. The virus seemed to be gaining virulence with successive passages in rats.

After the successful establishment of polio in the cotton rat, Armstrong utilized this new tool to explore whether monkey antisera derived from various infecting polio strains, including some isolated by Armstrong, were able to neutralize the Lansing strain (24). He found that two of the antisera he tested neutralized the Lansing strain and one did not. This result was consistent with the belief, extant since the early 1930s, that there was more than one immunological type of poliovirus.

Armstrong also realized that, in order to gain more knowledge of the epidemiology of poliomyelitis, he would need another laboratory host available in unlimited quantities to test the immunologic and serologic status of large population

groups. He reasoned that a strain of virus adapted to the cotton rat might be pathogenic for other rodent species; he, therefore, decided to try adapting the Lansing strain to white mice. He was able to adapt the Lansing strain to white mice with considerably more ease than he was able to adapt the strain initially to the cotton rat (25). At the time of the initial reporting, he had carried the strain through 12 successful mouse transfers. Using brain and spinal cord from the fourth mouse transfer, he was able to transmit poliomyelitis to monkeys. He was able, at this point, to transfer the Lansing strain successfully back and forth among mice, monkeys and cotton rats most of which developed the characteristic clinical signs and the definitive microscopic pathologic features of poliomyelitis. The Lansing strains derived from mice, monkeys and cotton rats, originally isolated by Armstrong from a single source, had immunologic identity.

Armstrong finally had found a utilitarian laboratory host to promote and extend further poliomyelitis research (24, 25) and to bypass the cumbersome, incompletely accurate techniques using expensive, difficult monkeys. Armstrong's opinion was that from the standpoint of availability, cost, expense of maintenance, care, safety of handling and resistance to naturally acquired infections (e.g., Theiler's mouse virus, MM, and encephalomyocarditis viruses), the cotton rat compared favorably with the white mouse as a laboratory animal with the exception that it was somewhat more timid; he noted that it propagated slowly or not at all during the colder seasons which limited its availability in the laboratory. The white mouse, on the other hand, was readily available at all times, and its employment was familiar to most investigators.

Armstrong began his initial studies using mice to test for the presence of antibodies in human serums capable of neutralizing the Lansing strain of poliomyelitis.

He reported (26) the testing of a group of 293 serums, mostly by his associate Dr. Victor H. Haas. This group of 293 serums was larger than any previous series reported up to that point by a single laboratory using monkeys; Armstrong indicated that this was an initial study with more to follow. He also reported that the results in mice were usually definite, easily read and reproducible. Preliminary results in the initial group of 293 serums showed percentages similar to smaller number of serums tested in monkeys: Sixty-five per cent of serums showed full immunity, 6.5 per cent showed partial immunity and 28.5 per cent showed no immunity. Over succeeding years, as many more serums were examined, (some derived from established cases of poliomyelitis), it became apparent that some serums from definite polio patients, did not neutralize the Lansing strain. This finding reinforced the impression among polio researchers that there was more than one immunologic type of poliovirus. In 1949 (27), using 14 monkeys, Bodian, Morgan and Howe established that there were 3 types of poliovirus, designated Types I, II, and III (named Brunhilde, Lansing, and Leon after the sources from which they were isolated), and subsequent studies indicated that the Lansing represented the least prevalent strain. In summary: "The adaptation of the Lansing strain of poliovirus to cotton rats and (white) mice in 1939 was a major advance in this period, an event which opened the way to quantitative measurement of virus and neutralizing antibody on a scale that was impossible to achieve in monkeys. Finally, with the increasing use of freshly isolated poliovirus strains, a developing awareness of the occurrence of significant strain differences was created (28)."

Additionally noted in reference to the Lansing strain, Enders, Feller and Robbins (29) used Lansing strain mouse brain material in adapting poliovirus to grow in human

non-neural tissue in tissue culture. After coaxing the Lansing strain to grow in this medium, they were able also to adapt monkey brain and spinal cord tissue infected with polioviruses types I and III to grow in non-neural cell tissue culture. They received the Nobel Prize for this in 1954. Their accomplishment enhanced the possibility of the eventual development of an effective vaccine against poliomyelitis.

Dr. Armstrong's reflections on poliomyelitis in his oral history interview (18) were a bit hazy after many years, but his musings are worth a look: "Yes, I did quite a bit on polio. When I was doing epidemiology. When a plague or epidemic started in, it caused a furor, a great excitement and fear among people. They would call for help, but you couldn't do much for them except isolation, and that wasn't effective. There wasn't often when there were two cases in the family anyway. You tried to make provision for the sick. One of the first things they would suggest was building an emergency hospital. Everyone would help, and, in a couple of days, you would have a hospital that would serve the purpose, and this was better than nothing. What seemed to me what was needed was a better experimental animal. We had monkeys, but they were expensive, and expensive to feed and keep. They were unsanitary, and they had other diseases. An effort was made by many people to inoculate other animals, but without success.

"Dr. Max Pete [Peet] of Michigan, saw a boy who had polio and died. He sent in the brain to me and part to Dr. Sabin in Cincinnati. I succeeded in getting a virus out of the brain sent to me and out of the piece sent to Sabin; he failed. The virus I got, I decided to put into other animals. I had a couple of rats, pack rats and guinea pigs, all of which I inoculated. The pack rat [?] and the cotton rat both came down with something. I took the brains and preserved them and put them in glycerin and refrigerated them. It was two



years before I got back to them [EAB – He was still working with lymphocytic chorimeningitis.]. Finally, I tried again, and, sure enough, cotton rats came down again. We studied them [EAB – primarily C.A. and R.D. Lillie] and the lesions were right for polio, symptoms were just like polio, and everything indicated it was polio. It took a great deal of nerve to say polio because everybody tried it, but I said I thought it was polio. Some of my friends objected, they thought it wasn't established. They argued that I didn't do this or do that. This was true, but I thought I had enough to make an indication. One by one they came across and agreed it was polio, but type II; then, they were all supposed to be type I [EAB – the prevalent strain]. Now there are III [EAB – types] and this [EAB – the Lansing strain] was one of the rare types. Again, I just happened to hit a lucky one, having tried the right animal. I then inoculated mice, and the mouse that I inoculated 31 days before came down with paralysis. I took that mouse and transmitted it [EAB – poliovirus] to another one, and gradually the incubation period was shortened, but the symptoms were just like polio. I gave the virus to other researchers, and they all agreed it was polio. That gave us an inexpensive animal that was easy to work with. I don't know whether it would have been possible to make a vaccine without the mouse to go on. It certainly would have taken a good deal longer and been very expensive.”

In addition to this major contribution made available to other investigators, Armstrong continued his participation as a member of the Virus Research Committee of the National Foundation. In the 1940s, he contributed to the Committee's deliberations in awarding research grants to investigators studying poliomyelitis, including the talented teams at Yale and Johns Hopkins Universities, who made many of the major discoveries about the nature of poliomyelitis (30). On October 25, 1946 Armstrong received a letter

from Basil O'Connor (31) thanking him for his tireless service on behalf of the National Foundation. "You have served on the National Advisory Committee for the National Foundation for Infantile Paralysis since its organization almost nine years ago.

"Despite the other demands of the tragic times we have been through on your time and on your strength, you have attended with almost complete regularity the bi-annual meetings of the Medical Advisory Committee – all of which have been held in New York City – in each instance consuming usually two days apart from the time spent in traveling. This, of course, necessitated, at such periods, the total abandonment of your other activities.

Between bi-annual meetings you have examined and studied seriously, the many applications for grants that have been made to the National Foundation, and as a result you have come to those meetings equipped to discuss and pass on those applications intelligently and to advise the National Foundation wisely. You could not have done all this without becoming sincerely and intensely interested in the National Foundation, its activities, its policies and its future. In connection with all these things you have, from time to time, brought to us and permitted us to share that veritable warehouse of understanding, reasoning and knowledge that only one who has attained the standing in one's profession that you have possesses. All that you have done has been done voluntarily and as a contribution to the welfare of humanity without any thought of compensation on your part." ---- following further words of gratitude on behalf of himself and the Foundation, "I know that without the contribution you have made we should never have accomplished whatever of value we have accomplished. Faithfully yours, Basil O'Connor, President."



Medical Advisory Meeting, National Foundation for Infantile Paralysis, Hot Springs, Virginia, April 1949. Courtesy of Mary Emma Armstrong.

In 1948, Armstrong was a member of the Committee on Nomenclature of the National Foundation for Infantile Paralysis (32). The other members of the Committee were David Bodian, Thomas Francis, Jr., Albert B. Sabin and John R. Paul. They discussed a “Proposed Provisional Definition of Poliomyelitis” as a culmination of presentations to previous meetings on the same subject. They presented this discussion on July 14, 1948 to the First International Conference on Poliomyelitis held in New York City. The purpose of the presentation was to apply restrictions to the use of the term “poliomyelitis virus” as opposed to the terms “encephalomyelitis” or “encephalitis” virus that were used primarily to designate those viral illnesses that had been discovered in

endemic form in non-primate hosts such as rodents. The diagnostic criteria that the Committee recommended for identifying and defining a poliomyelitis strain included: 1) The clinical and histopathologic manifestation produced in monkeys. If the unknown viral agent did not produce experimental infection with clinical signs and the characteristic changes in specific parts of the brain and spinal cord, then the agent was not a poliovirus. 2) The host range. Primates are the only known experimental hosts for most strains isolated directly from human or extra-human sources. Since 1939, other than the Lansing strain, others, such as those designated MEF, Y-SK or Ph isolated from human hosts had the capacity of producing paralytic poliomyelitis in mice, hamster and cotton rats, but not in rabbits or guinea pigs. These strains, however, were found to be related immunologically to the Lansing strain. 3) Immunologic diagnosis. Any virus which was immunologically distinct from any previously established virus but which possessed the above-mentioned diagnostic properties, had nevertheless, to be considered as a poliovirus. Any virus that was immunologically identical to a previously established poliomyelitis strain had to be tentatively considered as a poliomyelitis virus. 4) Physico-chemical properties. These properties taken into consideration included small particle size (8-12m $\mu$ ), appearance under the electron microscope, and resistance to the lethal effects of ether.

These criteria helped to differentiate the mouse viruses, often mislabeled “mouse poliomyelitis,” from the strains responsible for human and animal primate poliomyelitis. Dr. Max Theiler of the Rockefeller Institute, who adapted the yellow fever virus to mice, thus enabling the production of a non-virulent vaccine for humans, discovered these mouse viruses (strains variously designated TO, FA, GD VII). Theiler suggested using

the term for these strains he had used originally, “spontaneous mouse encephalomyelitis.” There were other mouse viruses including the Columbia SK, MM virus, and EMC or “encephalomyocarditis” virus, all immunologically similar to each other but which did not fulfill the criteria for poliomyelitis viruses (32).

By the late 1940s (33), there were hundreds of strains exhibiting the above criteria for poliomyelitis viruses that had been isolated in the United States. In view of the recent adaptation of the growth of poliovirus in non-neural tissue culture media by Enders group and the potential for vaccine development, it became important to determine precisely how many immunologic types of polioviruses existed among the many isolated strains. On July 10, 1948, the National Foundation Typing Committee was organized (33). Its members included Drs. Charles Armstrong, David Bodian, Thomas Francis, Jr., Louis Gebhardt, John Kessel, Charles F. Pait, Albert Sabin, Jonas Salk, and Herbert Wenner. The Committee as a whole had the overall responsibility of administering the program and the actual physical implementation of the typing program. The latter was funded through National Foundation grants of \$1.25 million dollars given to Drs. Gebhardt, Kessel, Salk and Wenner who undertook the actual labor of typing the strains in their own laboratories. This proved to be a monumental task considering the number of isolations involved and the tension working with large numbers of irascible, uncooperative monkeys who were indispensable for this type of operation. The workers finally confirmed what had been shown previously experimentally on a smaller scale (34), namely, that there were three distinct immunologic types of poliomyelitis virus. This fact helped ease the selection of potential components for use in a vaccine against poliomyelitis.

On January 2 and 3, 1958, Charles Armstrong was inducted into “The Polio Hall of Fame” (36) at the Georgia Warm Springs Foundation in celebration of the Twentieth Anniversary of the incorporation of the National Foundation for Infantile Paralysis. Dr. Armstrong’s wife and daughter accompanied him to this event. The Hall of Fame consisted of a linear grouping of sculptured busts of 15 scientists and 2 non-scientists who made major contributions to the knowledge and control of poliomyelitis. The busts, in the order of their placement from left to right in the monument, were those of Drs. Jacob von Heine, Oskar Medin, Ivar Wickman, Karl Landsteiner, Thomas M. Rivers, Charles Armstrong, John R. Paul, Albert B. Sabin, Thomas Francis, Jr., Joseph L. Melnick, Isabel Morgan, Howard A. Howe, David Bodian, John F. Enders and Jonas E. Salk; the two non-scientists were President Franklin D. Roosevelt and Mr. Basil O’Connor. Dr. Enders was the only one of the still living scientists who was unable to attend the ceremony. Mrs. Eleanor Roosevelt, the President’s widow, represented the late President at the ceremony.

A buffet luncheon followed the unveiling of the monument. In the afternoon, the Warm Springs staff provided guided tours of the grounds and treatment facilities of Georgia Warm Springs, The Little White House (where FDR stayed on his frequent visits and where he suffered his fatal stroke), and the Ida Cason Callaway Gardens. A 5:30 PM Reception occurred at the Golf Club. Dinner at 7:30 PM in the Main Dining Room, Georgia Hall, concluded with an after-dinner address by Mr. Basil O’Connor entitled “Threescore Years and Ten.”

The concluding session the next day consisted of a 10:30AM “Demonstration of Modern Rehabilitation Techniques” by Dr. Robert L. Bennett. A post-luncheon session,

chaired by Mr. O'Connor, featured Mrs. Roosevelt who introduced the main speaker, Dr. Jonas E. Salk. The title of his talk was "What Are the Questions for the Future?"

The artist who designed the Hall of Fame was Mr. Edmond Amateis of Clermont, Florida. He sculpted the busts in bronze and positioned them in an irregular linear pattern on a white marble wall. He became friendly with Dr. Armstrong and very graciously took photographs of Dr. Armstrong, Mrs. Armstrong and Miss Mary Emma Armstrong, posing them under Dr. Armstrong's bust. At Armstrong's request, Amateis also included photographs of himself and his wife. A few days later Amateis sent the developed prints back to Armstrong with a warmly worded letter (35) saying how honored he felt to have been chosen to create the sculptures commemorating the group of men he portrayed in the Hall of Fame.



Clay model of Dr. Charles Armstrong's head for the Polio Hall of Fame, late 1957.  
Courtesy of March of Dimes.



This event at Warm Springs Georgia represents a culmination of appreciation by the public for Charles Armstrong and his distinguished contemporaries for their untiring efforts to tame the scourge of poliomyelitis (36).



Scientists who have played leading roles in poliomyelitis research meet beneath bronze busts at the dedication of the Polio Hall of Fame in Warm Springs, Georgia. Left to right: Dr. Thomas M. Rivers, Dr. Charles Armstrong, Dr. John R. Paul, Dr. Thomas Francis, Jr., Dr. Albert B. Sabin, Dr. Joseph L. Melnick, Dr. Isabel Morgan, Dr. Howard A. Howe, Dr. David Bodian, Dr. Jonas E. Salk, Mrs. Eleanor Roosevelt, and Mr. Basil O'Connor. The busts left or right: Dr. von Heine, Dr. Medin, Dr. Wickman, Dr. Landsteiner, Dr. Rivers, Dr. Armstrong, Dr. Paul, Dr. Francis, Dr. Sabin, Dr. Melnick, Dr. Morgan, Dr. Howe, Dr. Bodian, Dr. Enders, Dr. Salk, President Franklin D. Roosevelt, and Mr. O'Connor. February, 1958. Courtesy of March of Dimes.



Grouping on Wall of the Polio Hall of Fame, from left to right: Dr. Karl Landsteiner, Dr. Thomas M. Rivers, Dr. Charles Armstrong and Dr. John R. Paul. Courtesy of Mary Emma Armstrong.



Left: Standing left to right under busts including Armstrong's: Mrs. Charles Armstrong, Dr. Armstrong, Mary Emma Armstrong and Mrs. Edmond Amateis, wife of the artist. Right: Mr. and Mrs. Edmond Amateis standing under the busts of Dr. Thomas M. Rivers and Dr. Charles Armstrong. Courtesy of Mary Emma Armstrong.



Ms. Mary Emma Armstrong at the Wall of the Polio Hall of Fame, January 2-3, 1958.  
Courtesy of Mary Emma Armstrong.

#### Notes – Poliomyelitis

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- 2) Rivers, Ibid., pp. 180-186, 281, 311, and 317-318.
- 3) Smith, J. S., Ibid., pp. 256-258.

- 4) Poliomyelitis prevention in the United States. Updated recommendation of the Advisory Committee on Immunization Practices (ACIP) *MMWR (Morbidity and Mortality Weekly Reports (CDC)*, May 19, 2000.
- 5) “March of Dimes Birth Defects Foundation”. Web site <http://www.modimes.com>
- 6) Rivers, *Ibid.*, pp. 236, 251, 252.
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- 8) Armstrong, C. and Harrison, W. T.: Prevention of experimental intranasal infection with certain neurotropic viruses by means of chemicals instilled into the nostrils *Public Health Reports* 51: 203-215, February 28, 1936.
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- 36) The press media covered Armstrong's activities in poliomyelitis extensively, initially with nasal spraying and then the adaptation of the virus to rodents. Some representative news articles primarily during the spraying period include: *The Literary Digest* August 8, 1936; *The Youngstown Telegram* January 14, 1936; *United Press* 1936; *Birmingham, Alabama, Herald* August 15, 1936, (cartoon); *Science Service* July 14,15, 1936; *The Washington Post* September 13, 1936; *The Washington Herald* June 1, 1936. Many early articles occurred in the Washington, DC area newspapers in 1935.

## Hail to the Chief

Following Charles Armstrong's adaptation of poliomyelitis to the cotton rat and white mouse in 1939, he made no further major scientific discoveries; nevertheless, he maintained an active involvement in his ongoing laboratory investigations. The period from about 1940 until the gradual discontinuation of his laboratory activities in the early 1950s was punctuated with awards that recognized his many significant contributions. In 1941, he received the Sedgwick Medal of the American Public Health Association (1 A, B), and in 1944, he was one of the first NIH scientists elected as a Member of the National Academy of Sciences (2). In December 1942, he advanced to the commissioned rank of Medical Director in the United States Public Health Service (equivalent to U. S. Army Colonel or U.S. Navy Captain), and he was also appointed Chief of the Division of Infectious Diseases (later renamed Laboratory) earlier the same year. He served in that position until November 1948. In 1947, he presided over the move of the Laboratory (Division) from NIH Building No. 5 to the new state-of-the-art "biosafe" Building No. 7, "The Memorial Laboratory." He administered the Laboratory efficiently and frugally during the World War II years and beyond. He collaborated with and gave advice freely to younger members of the laboratory who were at the beginning of their careers. He maintained collegial relationships with medical practitioners in the Washington, D. C. area and served as a helpful resource to some who had encountered puzzling infectious disease problems. His legal retirement was in 1950 but he was allowed to keep a small laboratory suite, and he continued coming into the laboratory for several more years. His



last subject of interest was the study of the relationship of season and climate to the yearly prevalence of poliomyelitis (3).

The American Public Health Association (APHA)(1 A) is the oldest and largest organization of public health professionals in the world currently representing more than 50,000 members from over 50 occupations of public health. It brings together investigators, health service providers, administrators, teachers, and other health workers in a multidisciplinary environment of professional exchange, study and action. The APHA has been progressively and incrementally concerned, since its founding 125 years ago, with a broad set of issues affecting personal and environmental health, including federal and state funding for health programs, pollution control, programs relating to chronic and infectious diseases, a smoke free society and professional education in public health.

“The Sedgwick Memorial Medal (1 B), established in honor of the late Professor William Thompson Sedgwick, was awarded by the American Public Health Association since 1929 for distinguished service and advancement of public health knowledge and practice. Professor Sedgwick was President of APHA in 1915 and Head of the Department of Biological and Public Health at Massachusetts Institute of Technology from 1883 to 1921. The *Sedgwick* award, one of the highest honors bestowed by APHA, is a true accolade of the profession – the recognition by an individual’s colleagues of outstanding accomplishments in the field of public health.” The award consists of a symbolic medallion and a custom designed certificate and is usually presented at the Annual Meeting and Exposition of the APHA. Members of the constituent sections of the APHA are encouraged to submit nominations of individuals as candidates for the

*Sedgwick* award. Other associates or contemporaries of Armstrong who worked at NIH and who received the *Sedgwick* award included Milton J. Rosenau, Wade Hampton Frost and Rollo Eugene Dyer (4).

Charles Armstrong received his award Tuesday evening, October 14, 1941, at the opening general session of the 70<sup>th</sup> Annual Meeting of the APHA in Atlantic City, New Jersey. On September 20, 1941, Armstrong had received a confidential letter from Dr. Thomas Parran, the Surgeon General, who was also Chairman of the APHA Awards Committee, saying that he had been selected as the recipient of the 1941 Award (5). On September 23, 1941 Armstrong replied (6) that he was keenly appreciative of the Committee on Awards for selecting him. Armstrong said that the honor was especially felt in view of the distinguished individuals who had received this medal in the past. The Committee on Awards was composed of the last five living recipients of the Award who selected a new recipient from among the nominations they had received.

Dr. Parran, as Chairman of the Committee, presented the Award (7) with the inclusion of these laudatory remarks: "To a greater or lesser degree we are familiar with research work in the field of human diseases but comparatively few of the workers in this field are personally known to any one of us. It has been my good fortune to know a few of these men well, and one in particular I have known for almost a quarter of a century [EAB – since 1916 when Armstrong received his commission in the USPHS]. I have followed his outstanding work on botulism, tetanus, dengue, influenza, psittacosis, encephalitis, choriomeningitis and poliomyelitis. He is unique in that he has made a distinct contribution to our knowledge of every disease with which he has worked. I know his adequate preparation, his careful procedure and his rigid criticism of his own

work. I know him also as an essentially human person, very modest, thoroughly kind, completely unselfish and of unfailing equanimity.

“Your scientific achievements, Dr. Armstrong, have won for you a place in the front rank of investigators, and your personal qualities endear you to scientist and layman alike – to all who seek after truth.”

Armstrong accepted the Award with some brief, modest, gracious remarks, the capstone of which was, “I have only been doing my day’s work.” He received congratulatory letters from many sources, including prominent investigators in academic positions, the National Foundation for Infantile Paralysis and extensive press coverage including *The New York Times* (8 A), *The Washington Post* (8 B), *The Charlotte Observer* (North Carolina) (8C), and many other newspapers. *The New York Times* (8 A) remarked that Armstrong did not speak of the dangers that were part of his day’s work. The author quoted Armstrong’s friend, Paul DeKruif’s testimonial article in the *Ladies Home Journal* written long before the Award to Armstrong became known: “On blue days when the hunt for truth about people becomes futile, or when I fear the consequences my more and more open expression of dangerous truth may have for me, I’m bucked up by the memory of Charles Armstrong’s chuckle. After he had just dodged dying from the parrot fever he was fighting, he came back to trap the deadly virus of Saint Louis sleeping sickness. Then a mysterious brain malady, caught while studying his sleeping sickness monkeys, knocked him over. But Armstrong got up off the floor.” Armstrong contracted infection from many of the pathogens with which he worked, but fortunately recovered from all of them. Some members of the press suggested ungraciously at various times that Armstrong infected himself in order to study the

effects of the agents (“human guinea pig”). These accusations demonstrated complete ignorance of Armstrong’s investigative integrity.

Armstrong was the recipient of another prestigious honor several years later in April 1944. He was one of the first NIH investigators at that time elected as a member of the National Academy of Sciences (2). “ The NAS is an honorific society of distinguished scholars engaged in scientific and engineering research, dedicated to the furtherance of science and technology and to their use for the general welfare. The NAS was signed into being on March 3, 1863 at the height of the Civil War. As mandated in its Act of Incorporation, the NAS has since 1863 served to ‘investigate, examine, experiment and report upon any subject of science or art’ whenever called upon to do so by any department of the government. Scientific issues would become more contentious and complex in the years following the war. To keep pace with the growing roles that science and technology would play in public life, the institution that was founded in 1863 eventually expanded to include the National Research Council in 1916, the National Academy of Engineering in 1964, and the Institute of Medicine in 1970. Collectively the four organizations are known as the National Academies.

“The National Research Council is the body called upon most frequently for advice on scientific and technological issues that pervade policy decisions sought by the United States Government. The NRC works outside the framework of government as a non-profit organization by enlisting committees of prominent scientific professionals to provide advice on complex issues of science, technology or medicine. At the present time the Academy membership is comprised of approximately 2000 members and 350 foreign associates of whom more than 200 have won Nobel Prizes.

“Election to membership is by nomination only submitted by an Academy member. The candidates are selected primarily only in recognition of their distinguished and continuing achievements in original research. Election to the Academy is considered one of the highest honors that can be accorded a scientist or engineer.”

Armstrong’s election to the NAS occasioned again the outpouring of congratulatory letters from former college teachers (9), Alliance, Ohio friends, and colleagues. It was also duly noted again by Surgeon General Thomas Parran (9) who wrote on May 1, 1944, “Dear Charlie, I was delighted to hear from Gene Dyer [Rollo Eugene Dyer, Director of NIH] that you have recently been elected to membership in the National Academy of Sciences. Congratulations on this well deserved recognition. Sincerely yours, Thomas Parran, Surgeon General.”

As noted previously, although Armstrong made no major scientific discoveries in the decade starting in 1940, this period was one of continued productivity. He continued his ongoing studies with the rodent-adapted Lansing poliovirus strain and the virus of lymphocytic choriomeningitis. He continued his laboratory activities during the move of the old Hygienic Laboratory (NIH) from its Washington, D.C. location to Building No. 5 of the new Bethesda, Maryland campus in late 1940. It was during this year that he had his initial unfortunate encounter with Q fever. He was one of the infected victims during NIH’s first laboratory outbreak of this disease. Fortunately, he had a benign course and was able to participate with Dr. R. D. Lillie in describing the animal and human pathology of the infection (10). During this outbreak the Division sustained its first casualty, Mr. Asa Marcy, a laboratory technician. The Division first hosted this organism in 1938 when Dr. Dyer showed that the agent isolated from ticks in Hamilton, Montana

was identical to the organism first isolated in Australia in 1936. Work on the organism was halted during World War II when the Division focused its attention on other war-related rickettsial problems such as epidemic and scrub typhus. Work resumed on Q fever after the War, and laboratory outbreaks recurred in 1946 and 1948. These latter outbreaks were correlated with antigen preparation from Q fever-laden chicken embryo yolk sacs that resulted in infectious aerosols (11 A, B). Despite the 1948 outbreak's having occurred in the new supposed "biosafe" Building No. 7 among uninvited visitors, the rickettsial unit discontinued work on Q fever; however, studies continued at the Rocky Mountain Laboratory in Hamilton, Montana where on one occasion infection was exported in contaminated laboratory garments to workers in a local laundry (12).

In early 1942, Armstrong became Chief of the Division of Infectious Diseases when Dr. Dyer was appointed Director of NIH. On December 22, 1942 Armstrong advanced in commission rank to Medical Director (Army = Colonel, Navy = Captain). He continued as the Chief of the Division until November 1948 when Dr. Karl Habel succeeded him. During Armstrong's tenure as Chief of the Division he acquired the reputation as an efficient and frugal administrator. He was responsive to the legitimate needs of the investigators in the Division and was responsive to their requirements for equipment and personnel essential to their research. He also offered them broad emotional and intellectual support at critical times. He had the reputation of overseeing an economical operation and was supposed to have had annual surpluses at the end of each fiscal year; according to some of the scientists in the Division, the fiscal and administrative staff had problems about what to do with the surplus funds (13).

In May 1942, Charles Armstrong became almost fatally ill from pneumonia caused by the bacterium that causes tularemia. He was stricken shortly after arriving in Hamilton, Montana while on a periodic inspection trip to the Rocky Mountain Laboratory that was still part of the NIH/Division of Infectious Diseases. The Rocky Mountain Laboratory was actively engaged in the production of vaccines, especially yellow fever vaccine, for the United States Armed Forces during World War II. Armstrong was continuing the oversight and support activity for the vaccine that originated with his predecessor, Dr. R. E. Dyer who still maintained interest in the Rocky Mountain Laboratory's wartime efforts. The Hygienic Laboratory, the NIH and the Rocky Mountain Laboratory were largely responsible for the existing knowledge of the tularemia organism and its epidemiology (14). Its nomenclature is *Francisella tularensis*, named after Dr. Edward Francis of the NIH-Hygienic Laboratory and Tulare County, California where the organism was encountered in early studies. Dr. George McCoy (15) discovered the bacterium in 1911 when he described a "plague-like disease of rodents" while investigating bubonic plague among ground squirrels in California. In 1912, McCoy and Chapin (16) recovered the organism from rodents in Tulare County and named it *Bacterium tularense*. Wherry and Lamb (17) reported the first bacteriologically confirmed human case in 1914. Francis (18), while studying the plague-like disease in rodents and deerfly fever in Utah in 1919 and 1920, realized that both were manifestations of an illness that was frequently bacteremic, coined the name "tularemia" and commented on the role of the deerfly in transmission. Francis, a colleague and close friend of Armstrong, spent the rest of his career in study of the laboratory aspects of the organism and eventually had a non-fatal laboratory-acquired infection with tularemia. In

1924, Drs. R. R. Parker, R. R. Spencer with Francis, working at the Rocky Mountain Laboratory, reported that wood ticks (*Dermacentor andersoni*) in the Bitterroot Valley, Montana were naturally infected and were able to transmit the disease (19). Subsequent studies have shown that the organism is widespread in other world areas of the Northern Hemisphere and is carried by many rodent species, especially rabbits and squirrels. Humans most frequently acquire tularemia after contact with the tissues or body fluid of an infected mammal (e.g. a hunter skinning an infected rabbit with his bare hands) or from the bite of an infected arthropod (e.g. ticks, deer flies, mosquitoes).

The organism is a small, gram-negative, non-motile coccobacillus, tending to be pleomorphic in culture and difficult to culture because of fastidious nutritional growth requirements. Tularemia may occur in several clinical presentations; e.g. an ulcer on a hand with a painful lymph gland in the arm pit or elbow; a general enlargement of lymph glands not accompanied by ulcers; inflammation of an eye from rubbing with an infected hand; or a non-localizing febrile illness. Pneumonia may accompany any of these clinical features of tularemia, is often the most debilitating manifestation and carries a high mortality. Excellent clinical and microbiological descriptions of tularemia can be found in recent texts (20).

The mystery remains about how Armstrong may have been exposed to tularemia. He was unaware of possible sources of infection. There was no current work on this organism at the Division in Bethesda (21) since all investigations of low priority projects that were unrelated to the war effort had been suspended temporarily. There was no current work on tularemia at the Rocky Mountain Laboratory but cultures were maintained on the premises. Armstrong, however, had no exposure to these cultures.



Armstrong arrived in Hamilton, Montana on May 24, 1942 (22). His first symptoms began within 24 hours on May 25, 1942. He did not report his symptoms immediately and continued his inspection at the Laboratory. He grew worse progressively, and he became confined to his hotel room. On the morning of May 27, when he did not appear for a scheduled meeting at the Laboratory, several of the meeting participants went to his hotel room in town where they found Armstrong, fully clothed, lying on his bed and desperately ill. He was transferred immediately to the Marcus Daly Memorial Hospital in Hamilton (22). In several days the RML was able to make a diagnosis of pneumonia due to the tularemia bacterium. His clinical course was extremely stormy. He remained acutely ill with high fever, cough, and shortness of breath. He had periods of minor remissions and followed by severe exacerbations of his symptoms. During one of the frightening exacerbations, Dr. Dyer, who was skeptical about Armstrong's survival, contacted Mrs. Armstrong and daughter Mary Emma and suggested that they come to Hamilton quickly in order to be with Armstrong in his possible last mortal moments. They came to Hamilton immediately and stayed for about a month during June 1942. Mary Emma Armstrong described how impressed she was with the friendliness and caring attitude of the townspeople in Hamilton. On several occasions when she was "downtown," townsfolk whom she did not know would approach her with well wishes and inquire about Dr. Armstrong's progress in the hospital.

Armstrong improved gradually but was weakened greatly by the infection. There was no effective antibiotic treatment against tularemia in 1942. Dr. Selman Waksman (23) did not discover streptomycin, the preferred effective agent, until 1944. Armstrong remained hospitalized in Hamilton for several months. He then returned to the

Washington, D. C. area where he entered the newly constructed United States Naval Hospital in Bethesda, Maryland on August 10, 1942. He remained hospitalized one more month for further convalescence. He then stayed home for an additional two months until he felt sufficiently well to return to work. For one week from November 6 to about November 14 he had a mild illness characterized by indeterminate symptoms and for which he recorded some notes (24). After this final episode he remained in good health, ready to resume his full responsibilities as Chief of the Division of Infectious Diseases. During the World War II era the Division's Bethesda laboratory locus was focused largely on research efforts related to wartime problems, the most prominent of which were the rickettsial diseases, epidemic typhus and scrub typhus. Dr. Norman H. Topping became Chief of the Rickettsial Unit in 1941 following Dr. Dyer's appointment as the Director of NIH. Dr. Topping had developed an improved epidemic typhus vaccine from organisms grown in chick embryo yolk sacs that was used successfully to immunize Armed Forces troops (25). He had also worked extensively with Rocky Mountain spotted fever, developing a hyperimmune rabbit for human treatment prior to the appearance of successful antibiotic therapy and studying the epidemiology of the disease in the Northeastern United States as well as elsewhere in the country. He helped establish the identical nature of the Eastern and Western strains of Rocky Mountain spotted fever (26). The unit was trying to develop effective vaccines for scrub typhus because of the prevalence of the disease among troops in the South Pacific Theater with its attendant morbidity and mortality. Awards and selective election to prestigious professional organizations duly recognized Topping's research in rickettsial diseases (27).

A young Public Health Service physician, Dr. Richard G. Henderson, assigned to the scrub typhus project, acquired a fatal laboratory infection with the organism. He died October 20, 1944. His laboratory assistant, Leroy Snellbaker, also became ill but he recovered (Snellbaker later became the author's laboratory technician). A few days prior to these events (28) Topping encountered Henderson and Snellbaker in the laboratory and was aghast when he found them grinding scrub typhus infected yolk sacs in a Waring blender on an open desktop without taking protective precautions. Topping was doubly perturbed since he and Charles Shepard had designed and built a functioning isolation cabinet (to be described later in the chapter) for use with highly infectious, virulent organisms.

In November 1944, Dr. Armstrong recruited Dr. Robert J. Huebner (29) from the USPHS Out Patient Ear, Nose and Throat Clinic into the Division of Infectious Diseases and assigned him to the Rickettsial Unit. The unit discontinued work with scrub typhus when World War II ended and then resumed investigating Q fever. A second large laboratory outbreak occurred soon thereafter (30), carefully documented by Huebner, the new unit member. Topping left rickettsial research after investigating an outbreak of Q fever in Amarillo, Texas with Shepard in 1946 (31). The Rickettsial Unit continued until about the middle of 1949 under the brilliant direction of Huebner who solved the riddle of the new mystery disease, *Rickettsialpox*, (also known as Kew Gardens spotted fever) and who discovered how Q fever spread from its natural host, the dairy cow, to the unfortunate population of Los Angeles County, California (29). The recent biography of Huebner (29) describes these accomplishments in detail including Armstrong's help with the investigation of rickettsialpox (29).

During Armstrong's tenure as Chief of the Division from 1941 to 1948, and for several years beyond, the Division had many distinguished investigators. Dr. Karl Habel (32) succeeded in cultivating the mumps virus in fertilized chicken eggs and devised serological tests for its presence. Mumps was an important disease of military recruits during World War II. From Habel's discoveries others were able to develop vaccines that are now used widely and effectively to prevent mumps. Habel also studied rubella (German measles) (32). He succeeded in isolating and passing the virus through fertile chicken eggs and then successively through monkeys. This accomplishment enabled the development of a vaccine that helped reduce the threat of infant malformation (congenital rubella syndrome) caused by this virus in pregnant women. Habel succeeded Armstrong as Chief in 1948. Armstrong also provided help and guidance when Huebner began to study the Coxsackie viruses in 1949 (33).



Group photograph, taken October 1946, on the steps of the NIH Administration Building (No. 1) in Bethesda, MD at the Dedication of the new Memorial Laboratory (Building No. 7). Dr. R. Eugene Dyer, the Director of the NIH, is in the middle of the first row. Dr. Leonard Scheele, the Surgeon General is third from the right in the second row, and Dr. Charles Armstrong, now Chief of the Division of Infectious Diseases, is third from the left in the second row. Courtesy of Mary Emma Armstrong.

In the field of mycology (fungi, yeasts), Dr. Chester W. Emmons made a number of significant observations and discoveries during this same 1940-1950 decade. He first pointed out the reservoirs of histoplasmosis in soil (34) and bats (34), of coccidiomycosis in soil (34), and of cryptococcus in soil (34) and pigeon droppings (34) – thus supplying crucial information on sources of infection by these pathogenic fungi.

Several pioneering bacteriologists were also still active during this period and were gradually closing out their professional careers. Dr. Ida A. Bengston was the first woman

hired to the staff of the Hygienic Laboratory in 1916. Her most notable contribution was refinement of the complement-fixation serological test used primarily in testing for antibodies stimulated by rickettsial infections such as typhus and Q fever. She collaborated with the Rickettsial Unit during the initial investigations of Q fever and, during World War II, on the typhus vaccine studies. She appeared as author and co-author on many of the publications related to these studies (35). The name of Dr. Sarah E. Branham (*Branhamella* species) is closely associated with the early studies of the genus *Neisseria* (gram negative, bean-shaped bacteria in pairs – one species, *Branhamella catarrhalis*, a bacterium found in the throat is named for her) in which she illuminated the taxonomy, described a new species in meningitis, explored properties of immune sera, and especially distinguished the three basic serotypes of the meningococcus (36). Another widely recognized longtime association has been that of Dr. Margaret Pittman with the genus *Hemophilus* (*e. g. influenzae* and various other similar species, and *Bordetella pertussis* or whooping cough) and with various aspects of pertussis (37). She continued to contribute to pertussis (whooping cough) following relocation from NIH/Division of Infectious Diseases to FDA's Bureau of Biologics and even after retirement.

In early December 1942, a trapper's wife (38) living on the Little Chenier in the isolated coastal bayou country of Louisiana came down with an apparent form of pneumonia, was transferred to a sanitarium 120 miles inland and died several weeks later. A local epidemic spread rapidly in the Louisiana parishes from this index case, including the patient's nurse. Most of the symptomatic persons died from similar lung

manifestations. The Louisiana State Department of Health sent a request for aid to the Public Health Service in Washington because the wartime possibilities of this epidemic were ominous. The epidemic zone was in the middle of one of the most crucial military and shipping areas in the United States, including Army camps, war plants, the Port of New Orleans and the large population area of New Orleans itself.

In early March 1943, Dr. Byron J. Olson arrived from the Division of Infectious Diseases. He began working immediately with the Epidemiologist of the Louisiana State Department of Health, Dr. Waldo L. Treuting. They began to study the patients who were still living, and they collaborated with the physicians who had been treating the patients. The disease had a rather distinctive pattern. It started with benign symptoms until shortly before the patients died when they became suddenly more severely ill leading to rapid death. Patients who recovered often experienced mental symptoms and personality changes. The attending physicians observed that only fatal cases could transmit the disease and the route was most likely by respiratory spread. In view of this mode of spread, Drs. Olson and Treuting instituted strict isolation and quarantine of patients' contacts. Some contacts, who left the area prior to the establishment of the quarantine, were checked quietly by local health authorities in order not to create panic.

Patients who died were transported to the United States Marine Hospital in New Orleans where Dr. Chapman H. Binford, the hospital pathologist performed autopsies. Dr. Olson took lung specimens from the autopsied patients as well as sputum, throat washings, and blood from symptomatic patients injected at the scene into experimental animals, and he brought these materials back to the NIH laboratory in Building 5 for further study. He conducted this work together with Dr. Carl L. Larson for the next two years. They sealed

off the top floor of Building 5 in the manner reminiscent of Dr. Armstrong's attempt to isolate the basement rooms of the old Hygienic Laboratory in Washington, DC in 1929, when he was investigating psittacosis. Drs. Olson and Larson also donned rubber boots, gloves and facemasks. Before leaving the laboratory they took showers and put on complete changes of clothing.

Drs Olson and Larson were able to isolate an agent that they hypothesized was a virus. It has gone by the name of "The Agent of Louisiana Pneumonitis." The organism possessed resemblances to psittacosis and was thought to represent a new member of the psittacosis-lymphogranuloma venereum group now designated as Chlamidia. The pathologic changes in the organs found at autopsy were similar to those found in psittacosis. The organism has not been known to recur since the original outbreak. Drs. Olson and Larson apparently were able to make a vaccine that protected laboratory animals from infection with the organism. If the organism reacts like other members of the Chlamydia group, it should respond to treatment with current antibiotics.

There was speculation about the origin of the organism. The investigators noted that the first recognized site of occurrence was near old ocean beaches stranded in the Louisiana coastal marshes. The Chenieres are the winter home of varieties of northern birds and are along the path of one of the great "fly ways" for migratory birds moving to and from the two Americas. It was not unreasonable to speculate that an organism similar to psittacosis could have been hosted by an unknown migratory bird group.

The decade 1940 to 1950 was a time of many organizational and administrative changes at the National Institute of Health as the scientific campus expanded in Bethesda.



The author, arriving in 1948, was largely unaffected by these changes, observing that apparent progress was indicated by the frequent changes in the headings of the official stationery of all the new laboratories and institutes. In addition to the activities noted previously, Armstrong still oversaw the laboratory studies of the investigators studying encephalitis, influenza, bacterial pneumonia, chemotherapy, brucellosis, rheumatic fever, tuberculosis, acute diarrheal diseases, the new epidemiology unit headed by Dr. Joseph A. Bell, and the extensive programs at the Rocky Mountain Laboratory. In addition, the Tropical Medicine Laboratory, Biologics, and the residual Dental Unit studies were still constituent components of the Division of Infectious Diseases (39). The Rocky Mountain Laboratory had a major program of vaccine manufacture and distribution, ongoing projects in the rickettsial diseases, encephalomyelitis, relapsing fever, other diseases transmitted from animal hosts to man and continuing studies of medical entomology and parasitology. In 1948, in anticipation of the expansion to the National Institutes of Health, the reorganization removed heart and dental disease from the Division of Infectious Diseases into their own institutes, i.e. National Heart Institute and the National Institute of Dental Research. The Division of Tropical Diseases and the Biologics Control Laboratory were separated from the Division of Infectious Diseases, and the Rocky Mountain Laboratory was no longer controlled administratively as part of the Division of Infectious Diseases. On November 1, 1948 the Division became the Laboratory of Infectious Diseases, and together with the Divisions of Tropical Medicine, Biologics Control, and the Rocky Mountain Laboratory combined to form the new National Microbiological Institute (NMI) (40). The NMI later morphed into NIAID (National Institute for Allergic and Infectious Diseases) with the advent of the Clinical Center in

1953-1954 and offshoots from the Laboratory of Infectious Diseases. Biologics Control later became part of the Food and Drug Administration (FDA).

Certain traditions transferred from the Hygienic Laboratory to the new research quarters in Bethesda. There was a general atmosphere of collegiality with free discussion of ideas among the investigators working on their various projects. One of the customs that persisted was the lunchtime gathering of the laboratory members for relaxation and nourishment of body and mind. There was animated discussion, primarily of current events and all shades of political opinion. Religion and the Civil War (War Between the States) were generally avoided. The participants carried their lunches in brown paper bags or, more commonly, in metal lunch boxes equipped with thermos bottles. Dr. Armstrong ate with the group frequently. He had an 18-acre property on Montrose Road in Rockville, Maryland where he grew fruits and vegetables. In season he brought to the luncheon table the largest most delicious strawberries that he distributed to the group; he also provided other homegrown products to some of the laboratory helpers. (A list of the frequent lunch attendees, the “Luncheon Group,” is included in Appendix C.) The luncheon group was extensive when the author arrived in August 1948 to begin work in Building No. 7; later, however, the space for the lunchtime gathering became lost in the 1950s when space became a problem with the expansion of the respiratory virus studies and the arrival of new personnel. The lunchroom was divided into small cubicles for the secretaries and offices for the new investigators.

On October 27, 1946 (41), Dr. Charles Armstrong officiated at the formal dedication of Building No. 7, The Memorial Laboratory, for the study of infectious

diseases at the National Institute of Health. The building was designed and constructed as the result of an intensive effort on the part of the United States Public Health Service to provide a safe environment for research personnel. The designers planned and equipped the building to control and contain infections at their source, thereby affording greater protection for every individual in the laboratory. Dr Armstrong had outlined the need for such a facility. In the 59-year history of the NIH, at least two workers in each decade had died of laboratory-acquired infections. In the 1940-1950 decade, four had already died, including Dr. Richard G. Henderson, described previously. Armstrong also emphasized the two laboratory outbreaks of Q fever, the first in 1940 (42) with 16 cases and one death and the second in 1945 (42) with 47 cases that were both attributed to air-borne transmission. The hope in the construction of Building No. 7 was that airflow could be controlled and air-borne diseases confined within a small area. However, despite the building's unique construction features and the philosophy of infection control, a third outbreak of Q fever occurred in 1948 (42) when uninvited guests entered the working area of the ongoing Q fever studies, and one of the workers brought infection home through fomites. Human frailty and indifference to infection control protocol contributed to the failure of the building's original purpose, i.e., to contain infection.

Prior to the outbreak of Q fever in 1945, the Division of Infectious Diseases was shaken badly by traumatic events that occurred in the fall of 1944. Three employees died within a period of six weeks. Bacteriologist Rose H. Parrott died from a tularemia infection acquired in her laboratory at NIH on September 11, 1944. Eighteen days later, Philip L. Jones, Scientific Aide, died of scrub typhus at the Rocky Mountain Laboratory in Hamilton, Montana. Twenty-two days later Dr. Richard G. Henderson was fatally

infected in Bethesda, Maryland. This upsetting sequence of fatalities from laboratory-acquired infections dictated the need to provide full protection to the workers exposed to hazardous infections. In response, Dr. Thomas Parran, Surgeon General of the USPHS, approached Congress to obtain funds (\$1,200,000) for a building especially designed to protect persons engaged in research on infectious diseases. The Surgeon General (Dr. Parran), Dr. R. E. Dyer, Director of the NIH, his assistant, Dr. L. F. Badger, Armstrong and senior members of the Division of Infectious Diseases laboratory staff all contributed ideas to the final plan of the building. In addition, Drs. Badger and Topping toured a number of new laboratories in the United States seeking innovative ideas for adaptation to the new building. Prior to the construction of The Memorial Laboratory, Drs. Norman Topping and Charles Shepard (43) had improvised a protective cabinet for use in the Rickettsial Unit, a refinement of which later became a standard feature in the new building work units.



Dr. Charles Armstrong in midyears, dates not recorded.  
Courtesy of Mary Emma Armstrong.

Although the building over time did not fulfill its intended purpose, it, nevertheless, was a prototype for structures intended to provide strict biological safety to workers in microbiology. Armstrong outlined four main concerns that DID/NIH wanted the building to address. First, it wanted to spatially separate research on different diseases. Second, it wanted to control the airflow in and out of every room and working space in the building. Third, it needed equipment, not designed previously, to protect the worker against infection. Fourth, it needed an easily enforceable set of rules affecting the movements of personnel about the building. Armstrong felt that the Laboratory, at the time of the dedication, provided solutions to these problems.

There were six individual research units, each dedicated to a specific disease or group of diseases; two units were located on each of three floors and separated by a

“clean” (non-contaminated) area housing administrative facilities and personnel. Each unit had separate elevators for refuse to be dropped into incinerators at opposite ends of the building. Refuse cans were sterilized in the basement by steam before being returned to the floors.

The air and airflow were under control from the time the air entered the building through intakes in the roof until it was drawn off by outlets also on the roof. The clean areas contained a higher pressure than the contaminated areas so that the air drift was always toward and not from the location of the infected materials. The air entered at low velocities through special openings and was drawn toward the infected material on workbenches and exhausted through a wall slot at the rear of the benches.

The problem of air control not only influenced the architectural scheme of the Laboratory, but was also a prime consideration in the construction of the newly designed protective equipment.

Each of the six units had an identical layout. From the clean areas, a double set of doors served as an air lock for entrance into the working spaces. Once inside, the worker changed to his distinctive work clothes in a clean dressing room and then entered the unit proper. Upon leaving the unit, the worker reversed the procedure leaving his work clothes in the contaminated dressing room where he could also take a shower. He then put on his other garments in the “clean” room. These procedures did not work out in practice. The investigators from 1948 onward wore the same blue coveralls going to and from the work areas. There were no recommendations for wearing head or shoe coverings, nor were workers encouraged to do compulsive hand washing. Most of the investigators took their showers at home instead of in the units. Fortunately there were no major infectious

catastrophes after the Laboratory opened, until it eventually closed down around 2004, primarily because of less virulent organisms under investigation.

Each of the units contained sterile cubicles and protective cabinets enclosing 30-watt ultraviolet light to sterilize the air. Workbenches were provided with glass hoods, fluorescent illumination and ultraviolet irradiation to destroy exposed pathogens. Water, gas and electricity controls were installed on the near face of the bench, making it unnecessary to reach over infectious material. An electric grill air exhaust, also present in the protective cabinet and sterile cubicle, drew the air away from the bench and sterilized it at temperatures exceeding 500C before releasing it through the roof outlet.

Other facilities in each unit included an autopsy room, one constant “high” room (70F to 120F), one constant “low” room (10F to 60F), one large and two small animal rooms, a storage room, a cage washing and sterilizer room, a water distillation room, a serological laboratory, and an office and library-conference room.

The initial research operations in the six units were: 1) Rickettsial diseases; 2) Pathogenic molds; 3) Psittacosis and related diseases; 4) Brucellosis; 5) Poliomyelitis and other central nervous system diseases; and 6) “The common cold” (with reservations). The units became fully operational within a short period after the dedication and the completion of construction.

The following anecdote may be apocryphal, but several of the senior investigators, in conversation with the author (EAB), attested to the veracity of the described event. Armstrong, with his critical thinking and questioning character, apparently had some reservation about the efficiency of the airflow control in the new building. In order to see whether the airflow control was working efficiently, he decided

to check it with a “non-pathogenic” organism. He chose the bacterium *Serratia marcessans*, at that time thought to be a harmless commensal germ but now known to be highly pathogenic for humans. This particular bacterium produces a distinctive red colony on agar bacteriologic media. He scattered open agar-containing Petri dishes in the attic of the building. He then put a suspension of the *Serratia* organisms into the building ventilation system’s intake and inspected the open Petri dishes at regular intervals. In about 24 hours he noted that all the Petri dishes contained the distinctive red colonies of the growing bacteria. From this observation, Armstrong concluded that the building’s airflow control was working improperly. There was no follow through as to whether any corrective action was ever taken.

In the mid-1950s the interior architecture of Building No. 7 changed appreciably when the research emphasis changed to respiratory viruses and when there was an influx of many new, young investigators. The author participated in an audio-video taping of the interior of the building around 2003 and could hardly recognize any of the old unit architecture. The central areas had been divided and sub-divided into multiple smaller spaces. The animal rooms had been relocated to the basement and eliminated from the units in order to make more working benches and cubicles. The old clothes-changing air locks had also been subdivided and some of the included sanitary facilities eliminated, leading to daily inconvenience for the people working in the corresponding research units. The working areas of the units were changed the least, and the author readily recognized features that he remembered. When the building was finally shut down, the personnel were transferred to other sites on and off the main NIH campus.



The otherwise impeccable research reputation of the Hygienic Laboratory-NIH-Division- Laboratory of Infectious Diseases became tarnished in the early 1950s by the fraudulent activity of an investigator working in an anomalous research and administrative entity housed within the new Memorial Laboratory. This entity, although physically within the Laboratory of Infectious Diseases, was under the control of the Office of the Associate Director of NIH, Dr. Norman H. Topping. He had achieved honors and recognition for his work on typhus vaccine and Rocky Mountain spotted fever. Among these honors was the Bailey K. Ashford Research Award in Tropical Medicine in 1943. This award, financed by the Eli Lilly Company, was awarded to young investigators under the age of 35 years who had made significant scientific discoveries. Topping's career advancement also suggested political influence or favoritism either within or without the Public Health Service. In April 1948, he was promoted to the rank of medical director (Navy equivalent of captain) and eight months later to assistant surgeon general, equivalent of rear admiral. In 1948, Dr. Thomas Parran named him Associate Director of the National Institutes of Health. Topping, apparently, was very friendly with Dr. Parran and with Dr. Dyer, the Director of NIH, who was scheduled to retire in several years (44). The relationship between Armstrong and Topping never seemed to have been particularly cordial, and was apparently cool and distant from the time when Topping first arrived at the NIH in July 1937 (45). The author (EAB) met Topping on two occasions. The first was on August 1, 1948 in his Associate Administrator's office where the author received a very perfunctory welcome to the NIH. The second occasion was in July 1950 at the Rocky Mountain Laboratory in Hamilton,

Montana. At this meeting Topping exuded charm, congratulations and sincere advice on the current research that the author was doing in Dr. Robert J. Huebner's laboratory.

In 1945, by his own account (46), Topping lost interest in doing further work on rickettsias. He decided to study viruses and selected the "common cold" as the preferred entity for investigation. The discussion that followed in his autobiography about the "common cold" research was a complete whitewash of the events that occurred in the next several years. Topping organized or outlined a plan of investigation with the assistance of a new associate, a physician who had just completed his internship in internal medicine, named Leon Trotsky Atlas. The author was acquainted casually with Dr. Atlas when Atlas interned at the Massachusetts Memorial Hospital in Boston from July 1945 to July 1946. The author was a medical student at the time and interned at the same hospital two years later from 1947 to 1948. Topping had apparently arranged for one of the six work units in Building No. 7 to be assigned for common cold research. The first mention of studies of the "common cold" appeared in the 1947 Annual Report of the Surgeon General (47): "Limited studies on the common cold were started in January (1947). The unit for the study consists of two sections, one engaged primarily in laboratory investigations and the other consisting of human volunteers in one of the local correctional institutions (District of Columbia Correctional Institution, Lorton Reformatory, Lorton, Virginia). The infectiousness of nasal washings from individuals suffering from the common cold was investigated in the human volunteer group. In turn, nasal washings from them were inoculated into fertile eggs and serial passages were performed. At least one agent has been isolated which probably originated from humans.

This agent is being investigated as possibly one of the causes of minor upper respiratory disease in man.”

An interesting corollary to the above is an excerpt from Surgeon-General Leonard A. Scheele’s solicitation for Congressional funds in 1949: “In 1948 for the first time in history, scientists of the National Institutes of Health succeeded in isolating a virus of the common cold. In addition, they have developed techniques for measuring the potency of this and other viruses, which open up new possibilities for research into the whole field of virus diseases. This is the opening wedge driven by basic research.”\*

The following account and discussion of subsequent events in the saga of the “common cold” research is based on the author’s autobiographical notes prepared for the Office of NIH History around 1996-1997: Dr Atlas acquired a dubious reputation during his internship in Boston in 1945-1946. He had the reputation of being very bright, but also brash, conceited and arrogant. He was unpopular with his fellow interns. In the same intern group were two fellow Texans, both very capable physicians, former college football players who made Atlas the butt of their practical jokes. The author was not aware that Atlas had any additional advanced scientific training other than that acquired in college or in medical school.

When the author arrived at NIH in 1948, he was pleased that he at least knew people whom he had encountered previously. In addition to Atlas, the author had the good fortune to find Dr. John P. (Jack) Utz who had preceded him at the Boston internship in 1946-1947. Jack Utz was working with Dr. Dorland Davis on an influenza study. The author tried to establish a new collegial relationship with Atlas. While waiting

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\* Excerpt from Dr. Scheele’s presentation before the Labor-Federal Security Subcommittee on Appropriations, House of Representatives, 81<sup>st</sup> Congress, January 28, 1949.

until it was safe to start working with Q fever infected laboratory material, the author used to visit with Atlas in his unit (which the author inherited several years later). Atlas was very voluble during these visits, and he enjoyed discussing the “important progress” that he was making with his research. He claimed to have isolated an agent in the fertile chicken egg that was consistently producing the symptoms of the common cold in human volunteers at the correctional institution in nearby Lorton, Virginia. Atlas worked alone with one laboratory technician in Building No. 7. Dr. Topping spent fulltime in his office in Building No. 1, the NIH Administration Building; he was rarely, if ever sighted in Building No. 7.

Atlas did not supervise the human volunteer program on a daily basis; he left the administration of test material and clinical observations to a young laboratory assistant named Costello. Atlas, however, had shown great energy and initiative in establishing and organizing his laboratory, and the human volunteer program at Lorton. He was also a talented tinker. He devised a very clever apparatus for administering test samples into the nose and for retrieving nasal washings from the volunteers. He also invented a very efficient aspirator tip for suctioning and harvesting fluids (allantoic and chorionic) from fertile chicken eggs. He actually published descriptions of these artifacts in the scientific/technical literature. He gave reprints of these articles (subsequently lost) to the author but Atlas never managed to provide a reprint of the description of the isolation of the “cold virus” agent. During Atlas’ relaxed moments in the laboratory, he would take out his violin and play selections from a few classical compositions. He also “fiddled” with his very attractive laboratory assistant (whom he later married). Because of his first and middle names, his political orientation or that of his parents may have been suspect.

According to Topping (49), Atlas was summoned for questioning before the Congressional House Un-American Activities Committee but was cleared of any incorrect political activities or utterances.

During the early visits, Atlas became aware that the author was a novice in virological knowledge, and he would admonish the author to read more extensively about virology. However, novice that he was, the author discovered a chink in Atlas' armor. In all innocence, the author asked about the controls that Atlas used in his human volunteer program. Atlas erupted like an angry volcano, spewing forth many well-chosen expletives. The gist of his reply was that he did not need controls since he was very familiar with the signs and symptoms of the common cold, and he knew when colds developed in his volunteers. Despite the author's status as a novice, he had enough training to realize that scientific experiments, especially those dealing with biological systems, required adequate controls in order to establish the validity of the observations. Repelled by Atlas' arrogance, the author did not press the discussion further. Inasmuch as the time had come for the author to begin work in the Q fever unit, he felt that he could no longer spare the leisure moments, nor did he have the inclination to visit again with Dr. Atlas after the above conversation.

After a period of several months or longer, Atlas started talking about another "momentous development." He claimed that he had developed a chemical test to detect the presence of the cold virus agent growing in the eggs (see Surgeon General Scheele's remarks above to the Congressional Committee). Atlas had enlisted the help of a biochemist, Dr. George Hottle, to aid in the development of the technique. Dr. Hottle was a very quiet, unassuming, apparently competent biochemist whose personality contrasted

sharply with Leon Atlas'. Dr. Hottle had been assigned to the Laboratory of Infectious Diseases for several years. At a viral research meeting that the author attended at the Walter Reed Army Institute of Research (WRAIR), Atlas, without presenting supporting data, verbally announced his "chemical test." Dr. Joel Warren, an experienced virologist, who was then associated with Dr. Joseph Smadel at Walter Reed, expressed his astonishment and exclaimed, "If this is true, then it is a bomb shell advance in virology." And, so it went. Volunteers were "infected" with "colds", and "viruses revealed" their presence chemically in the chicken egg. On rare occasions Atlas would boastfully join the luncheon group meeting in the conference room in Building No. 7. On one occasion, Dr. Jack Utz, who was well acquainted with Atlas, remarked. "Leon! Some day the bubble is going to burst." Among the senior investigators in Building No. 7 there was much skepticism about the common cold study both from the scientific and administrative aspects. Many of them felt that a stronger, less volatile hand was needed at the helm to provide adequate direction, but the study supervisor in the "front office" (Dr. Norman Topping) would not tolerate interference.

Some time in early 1951, an English physician associated with Sir Christopher Andrewes, the most prominent investigator of the common cold, visited the National Institutes of Health. Dr. Andrewes group operated the Common Cold Unit in Salisbury, England and had made many careful clinical and epidemiological observations of colds in volunteers given infected nose or throat washings. The visitor requested a meeting with Dr. Atlas since, apparently, word of Atlas' work had spread to England. Specifically, he asked to see the volunteer program at Lorton and to see the induction of colds in patients. After several days of observation, he returned to NIH, and said, the author believes, to

Dr. Charles Armstrong, who was now the Chief emeritus, “I did not see any common colds at Lorton.”

The author was uncertain what decision process occurred at that time, or by whom, but shortly thereafter Drs. Charles Armstrong and Robert Huebner, the author’s immediate superior, delegated (ordered) the author to conduct an independent study, using the volunteers at Lorton, to determine whether there was an infectious agent in Atlas’ eggs capable of producing the syndrome of the common cold. (The role of Dr. Karl Habel—who succeeded Dr. Armstrong as Chief of the Laboratory in 1948—in this situation was not clear.) In order to accomplish this, the author designed a double blind, controlled study in the volunteers using “infected” and non-infected fluid from fertilized eggs. The two experimental volunteer groups were housed in separate wards of the prison infirmary. The author then examined the volunteers daily for 10 days making detailed observations and clinical notes about each participant. At the end of the study observation period, there were no observed clinical differences between the two groups; possibly more symptoms occurred in those volunteers who had received the control fluids. Of course, the author did not know which group had received which inoculum until the study code was broken. During the study, the author noticed that the assistant, Costello, was making suggestive, prompting statements to the patients; the author demanded that he stop this practice or leave the ward. The results of this study cast doubt on all the previously recorded uncontrolled trials among the volunteers.

The next step in the process of probing the existence of the elusive “cold virus agent” was to determine the validity of the quantitative chemical test. The author also executed this step as a double blind, controlled study. Inoculums from “infected” and

control eggs were injected into a batch of young fertile (embryonated) chicken eggs. Fluid from the allantoic cavity of several eggs from each group was harvested at daily intervals. Dr. Hottle received these fluids for chemical analysis. The actual chemical details of the test were rather complex, and the author was unsure what precise chemical reaction was being tested. The end point of the chemical reaction was the intensity of the development of a blue color measured in a colorimeter. In any event, the observed intensity of the chemical endpoint seemed to correlate with the age of the developing chick embryo, and there was no difference in the color reaction at each embryonic age of the developing chick between those infected with the test or control inoculums. It would appear, then, that the level of chemical reaction was related to some product developed and was related to the growth of the chick embryo and did not indicate the proliferation of an infectious agent.

These two simple controlled studies were instrumental in demolishing the elaborate hoax that masqueraded as research related to the “common cold.” A few days following the conclusion of the studies, both Drs. Atlas and Hottle disappeared from Building No. 7; other researchers in the building had no information on the destinations or subsequent careers of the two discredited investigators. Dr. Hottle was somewhat an innocent victim in these events but he probably should have recognized his vulnerable engagement in the flawed activity in which he played a part.

Shortly after the departure of Drs. Atlas and Hottle, a guest virologist, Dr. Edwin Schultz of Stanford University, was invited to NIH to review the laboratory observations generated by the Cold Virus Unit to determine whether anything could be salvaged from the debacle. Dr. Schultz and Dr. Armstrong were contemporaries who worked in the mid-



1930s on the attempts to prevent poliomyelitis in humans by chemical blockade of the nose (see the chapter on Poliomyelitis). Dr. Armstrong may have suggested Dr. Schultz for presentation of an outside of institution, objective, impartial analysis of the research. After several months, Dr. Schultz could not corroborate any evidence that an infectious agent producing colds was ever isolated in eggs. At one point in his investigation, a rumor circulated that something might be growing in eggs but there was no substantial confirmation of this rumor.

A non-event occurred possibly as a result of the cloudy circumstances surrounding the entirety of the controversial common cold research. Dr. Norman Topping, the Associate Director, did not become Director of the NIH when Dr. R. E. Dyer retired in 1951. In his last few years at NIH, Topping was actively involved in planning for the new Clinical Center, the new special Institutes, physical structures, research goals, and a myriad of other administrative functions. In 1952, Topping left NIH to become Vice President for Medical Affairs at the University of Pennsylvania where he remained for six years. In 1958, he returned to his alma mater, the University of Southern California, where he had an illustrious career, including President, until he retired. In his autobiography (50), Topping described, in some detail, the reasons, primarily political, why he did not become Director of NIH without mentioning in that discussion his association with the cold virus research. Dr. William H. Sebrell succeeded Dr. Dyer as Director of NIH in 1951 with Topping and Dr. David E. Price as Associate Directors. Dr. Sebrell was a young associate of Dr. Joseph Goldberger, of pellagra prevention fame, in the old Hygienic Laboratory. He was the Director of the Experimental Biology and Medicine Institute before that morphed into the National Institute of Arthritis and

Metabolic Diseases in 1951. Later, during an oral history interview (51), the interviewer asked Dr. Sebrell why Dr. Topping never became the Director of NIH. Sebrell became very evasive and circumspect, never providing a definitive answer to the question. The question unanswered, thus, has become a subject for speculative romance.

Investigations into the etiology of the common cold have met with success elsewhere following the dismal events discussed above. In subsequent years, around 1970, with the availability of tissue culture techniques, Sir Christopher Andrewes, by simulating the physical conditions in the nose and by using respiratory epithelial cells in the tissue culture media, was able to isolate agents that produced the clinical syndrome of the common cold (52). This group of agents has been designated *Rhinoviruses* and exists in over 100 recognized serological types. Other viruses discovered since early 1950 by Huebner and associates (53) at the Laboratory of Infectious Diseases such as adenoviruses, echoviruses, respiratory syncytial virus, para-influenza, certain Coxsackie virus strains, and even influenza itself, have all been shown at times to produce cold-like signs and symptoms.

Dr. Armstrong received the following letter (54) intending to soften the blow for his abrupt dismissal from the position as Chief of the Division (soon to become the Laboratory) of Infectious Diseases. The letter from Surgeon General Leonard A. Scheele (through the Director of the National Institutes of Health – Dr. R. E. Dyer) was dated October 19, 1948, and read as follows:

“Dear Dr. Armstrong,

As you know the final step of the reorganization of the National Institutes of Health has been completed with the establishment of the [National] Microbiological Institute. I have selected Dr. Victor Haas to be the Director of this new Institute. [EAB – Dr. Haas had been a junior associate of Dr. Armstrong at the time that Dr. Armstrong was adapting the Lansing strain of poliomyelitis to rodents].

“The establishment of the Microbiological Institute seems an appropriate time to free you of the onerous administrative duties that you have done so faithfully since the beginning of the war. I realize that you accepted these additional responsibilities through a deep sense of patriotism for our country and loyalty to the U. S. Public Health Service. I can assure you that your service has been keenly appreciated by both Dr. [Thomas] Parran and myself.

“We of the service know, as I have heard you express, that the future of the Institutes depends upon a sound research program. You, perhaps as our outstanding scientist, should be free to apply your full energies to research. Knowing of your long interest in poliomyelitis and of your many fine contributions, it is our hope that it again will have your complete attention.

“Once again on behalf of the Service I wish to thank you for a job well done as Chief of the Division of Infectious Diseases under trying war conditions, and add the hope of even greater accomplishments in your own research program.

“Sincerely yours, Leonard A. Scheele, Surgeon General.”

The transition as Chief from Armstrong to Dr. Karl Habel went almost unnoticed. It was not until many months later that the author was even aware of the change. During this time period Armstrong’s intellectual vigor and physical stamina were

undiminished. He made significant contributions in 1946 to Huebner's unveiling the mystery of rickettsialpox (55), and, from 1947 to 1949, he was a source of strength to the investigation of Q fever in Southern California (56). He helped with the launching of the Coxsackie virus studies in 1949-1950 (33), and he played a prominent role on the Scientific Committee of the National Foundation for Infantile Paralysis (see previous chapter). He helped with several investigations of cases referred by regional physicians (57).

His formal retirement from the Public Health Service did not occur until 1950. As a courtesy, he received the use of several small rooms and access to animal facilities so that he could still conduct his research studies. He continued to come into the laboratory daily. Dr. Armstrong never seemed to demonstrate overtly any bitterness about his abrupt removal as Chief of the Laboratory of Infectious Diseases, however, his daughter confided to several senior laboratory investigators at a later date (58) that "a cabal of unspecified persons" cut off his career abruptly and prematurely. It is not known to what extent Dr. Armstrong participated in the ferment of planning for the future growth and new programs for the burgeoning National Institutes of Health but an organized, politically inspired intrigue could have blocked his participation (speculative). In any event, the clear, levelheaded reasoning of Charles Armstrong would have been sadly lacking.

Armstrong's final published contributions to information about poliomyelitis appeared in a series of papers (59) describing his theories to account for the seasonal incidence of poliomyelitis in the world's temperate zones. He indicated that there was a tendency for seasonal variation to be slight in the tropics, with a tendency for outbreaks

to be confined to the warm months of the year as one proceeds either north or south from the equator. Spread of polio is by contact, through the fecal-oral route, with the throat serving as a primary entry and exit point of virus in addition to initial infection in the lower gastrointestinal tract. The nose was generally abandoned in the 1940s as the primary point of virus entry following the demonstration of the intestine as a site of major viral multiplication, and subsequent dissemination or development of immunity (see the chapter on Poliomyelitis). However, the observation of others that poliomyelitis often occurred after tonsillectomies and that the virus could be recovered from the throat both before and after an attack of poliomyelitis, led Armstrong to theorize that local conditions in the upper airways occurred that favored the entrance of poliovirus through the throat epithelium. This might depend on the presence or absence of excess mucus in the nasopharynx to provide a protective mechanism to prevent viral attachment. Armstrong set up some laboratory models using mice and other viruses mixed with commercial mucus to determine the protective effect of mucus against herpes and rabies in mice. He further postulated that there was a change in the relative humidity in the upper respiratory passages that kept the inhaled air at a relative humidity of about 90 per cent when warmed to 90F. The relative humidity of ambient temperature air was much lower. Armstrong, consulting with the local weather bureaus in a variety of locations, obtained interval recordings of average monthly atmospheric temperatures and average monthly relative humidity at 7AM, and atmospheric relative humidity adjusted to a temperature of 88F. He correlated these figures with the incidence of poliomyelitis in various locations. These locations were Washington, DC, in 1949, New York City in 1949, combined District of Columbia and Arlington, Virginia in 1950, and Denver, Colorado in 1950 and

1951. He selected Denver to represent the atmospheric humidity in an elevated, semiarid region to contrast with northeastern United States locations with a normal rainfall pattern. In all these areas studied, where poliomyelitis epidemics occurred, Armstrong noted that when the atmospheric relative humidity rose above a certain level during the polio season months, the adjusted relative humidity of warmed inhaled air was 90 per cent.

In the various conclusions in his observations, Armstrong stated that in an attempt to explain the seasonal incidence of epidemic poliomyelitis, a hypothesis was suggested that required no assumption of an extra-human source or change of infectivity for the virus nor any assumed alteration in the susceptibility of the population to infection. On the other hand, the hypothesis attempted to relate the seasonal behavior of poliomyelitis to generally observed alterations in the upper respiratory tract due to atmospheric changes, notably, in temperature and relative humidity of inspired air. The upper respiratory passages were viewed not only as a portal of entry for the virus but also as a portal of exit for the virus most effective in transmitting the disease from person to person.

He elaborated further that when air of usual temperature and humidity was breathed, it was warmed to a rather constant temperature of 90F and through absorption of moisture from the upper respiratory tract, its relative humidity was raised to approximately 90 per cent. A definite correlation between the curve of relative humidity of atmospheric air warmed to 90F and the curve of incidence for recognized poliomyelitis for the same area, based upon either monthly or weekly intervals of time supported the view that a dry air at 90F tended to prevent infection with poliomyelitis in a population, while a moist atmosphere at the same temperature tended to favor its spread. The incidence of cases

further suggested that relative humidity of from 27 to 28 per cent for atmospheric air warmed to 90F represented a critical level below which poliomyelitis spread with difficulty.

Armstrong realized that the numbers of recognized cases of poliomyelitis in one study (including the District of Columbia, Arlington and Fairfax Counties, Virginia and Montgomery and Prince Georges Counties, Maryland) were small and that the significance of any single rise in numbers of reported cases that appeared to be related in time to a change of relative humidity at 90F was of questionable statistical significance. However, the fact that such an occurrence was repeated five times (on the graphic data) lent support to a probable significant relationship between the two phenomena. The evidence, as recorded, suggested that it might be possible to predict with some degree of probability the course of an established outbreak in a limited area for about three weeks in advance. Especially this would be possible when a fall in the relative humidity of atmospheric air warmed to 90F occurred.

Armstrong, thus, hypothesized that the general correlation between the relative humidity of air at the temperature of the nose and throat, 90F, pointed, together with much additional evidence, toward the upper respiratory tract of man as a body area significant in the seasonal spread of poliomyelitis and as possibly accounting for its seasonal incidence. The evidence for the hypothesis, though correlative, was not definitive. Nevertheless, the attempt to find a reasonable explanation for the seasonal incidence of poliomyelitis demonstrated the imagination, creativity, ingenuity, intuition and the still residual talent of Charles Armstrong's mind. This project was his last major intellectual effort. The question of the seasonal incidence of poliomyelitis was soon to

become moot with the impending advent of the new effective vaccines for poliomyelitis toward which he had made a major contribution.

Notes – Hail to the Chief

- 1) A) Web site of The American Public Health Association:  
<http://www.apha.org/about/>. B) Web site of the Sedgwick Medal:  
<http://www.apha.org/sections/awards/05awards.sedgwick.htm>.
- 2) Web site of the National Academy of Sciences: <http://www.nasonline.org>.
- 3) See reference No. 59 of this chapter.
- 4) Other National Institutes of Health Sedgwick Award recipients listed by the National Library of Medicine.
- 5) The September 20, 1941 letter from Thomas Parran was among Armstrong's personal papers.
- 6) The September 23, 1941 reply letter was among Armstrong's personal papers.
- 7) Parran's presentation remarks were among Armstrong's personal papers; quoted in the *American Public Health Association News* 3: 1331-1332, December 1941.
- 8) A) *The New York Times* October 14, 17, 1941.  
B) *The Washington Post* October 15, 19, 1941.  
C) *The Charlotte Observer* October 20, 1941. Quoted: "I have only been doing my day's work."
- 9) Among Armstrong's personal papers.



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- 21) Annual Reviews of the Surgeon General (USPHS) 1941-1943.
- 22) Account related to author by Ms. Mary Emma Armstrong; local newspapers in Hamilton, Montana.
- 23) Waksman, Selman discovered streptomycin in 1944. The Committee awarded the Nobel Prize in Physiology or Medicine to Waksman in 1952 for this discovery.
- 24) Among Armstrong's personal papers, Ibid.
- 25) Topping, *Recollections*, Ibid., Chapter: At the NIH, pp.51-134; Williams, R. C. Ibid., P.209.
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- 27) Topping, Ibid., p. 81.
- 28) Topping, Ibid., p. 90.
- 29) Huebner biography at Office of NIH History website.
- 30) See previous note 11A this Chapter.

- 31) Topping, *Ibid.*, p.97; Williams, R. C., *Ibid.*, p. 234.
- 32) Intramural Contributions, *Ibid.*, p. 41. About Karl Habel.
- 33) Huebner, R. J., Armstrong, C., Beeman, E. A. and Cole, R. M.: Preliminary report on occurrence of Coxsackie viruses in a Southern Maryland community *Journal of the American Medical Association* 144: 609-612, June 1950.
- 34) Intramural Contributions, *Ibid.*, p. 22. About Chester W. Emmons.
- 35) Williams, R. C., *Ibid.*, pp. 199, 209, 210, 234; Topping, *Ibid.*, pp. 79, 81. About Ida A. Bengston.
- 36) Intramural Contributions, *Ibid.*, pp. 19, 22. About Sarah E. Branham.
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- 38) Williams, R. C., *Ibid.*, Section on Louisiana pneumonitis pp. 228-231.
- 39) Annual Reports of the Surgeon General (USPHS), 1944-1948.
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- 41) Armstrong, C.: Memorial Laboratory, National Institute of Health *The Scientific Monthly* 64 (No. 5): 365-368, May 19 47.
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- 43) Topping, *Ibid.*, p. 89.
- 44) Annual Reports, *Ibid.*, 1944-1948.
- 45) Topping, *Ibid.*, pp. 49, 51.
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- 47) Annual Report, *Ibid.*, 1947.
- 48) Statement of Surgeon General Leonard A. Scheele before the Labor-Federal Security Subcommittee on Appropriations, House of Representatives, 81<sup>st</sup>

- Congress, January 28, 1949. Among Armstrong's personal papers, contributed separately by Ms. Mary Emma Armstrong
- 49) Topping, *Ibid.*, pp. 96, 97.
  - 50) Topping, *Ibid.*, pp. 120, 121.
  - 51) Oral history interview of Dr. William H. Sebrell, on file at the Office of NIH History.
  - 52) Andrewes, C.: *The Common Cold*, W. W. Norton and Company, New York, 1965; and recent virology texts: Mandell, *Ibid.*, and Fields, B. N.: *Virology* 4<sup>th</sup> Edition.
  - 53) Huebner, *Ibid.*, note 29 this chapter.
  - 54) Letter contained in Armstrong's USPHS Commissioned Officers Corps official service record.
  - 55) Huebner, R. J., Stamps, P. and Armstrong, C.: Rickettsialpox. A newly recognized rickettsial disease, I. Isolation of the etiological agent *Public Health Reports* 61: 1605-1614, November 8, 1946.
  - 56) Personal conversation with Dr. Huebner; sentiments expressed by Dr. Huebner in a condolence letter to Ms. Mary Emma Armstrong on the occasion of her father's death.
  - 57) Armstrong, C. and MacMurray, F. C.: Toxoplasmosis found by recovery of *Toxoplasma gondii* from excised axillary gland *Journal of the American Medical Association* 151: 1103-1104. 1953.
  - 58) Personal communication from Ms. Armstrong to author.

- 59) A) Armstrong, C.: Seasonal distribution of poliomyelitis *American Journal of Public Health* 40 (No. 10): 1296-1304, October 1950.
- B) Atmospheric conditions and the spread of poliomyelitis *American Journal of Public Health* 41: 1231-1237, October 1951.
- C) Poliomyelitis and the weather *Proceedings of the National Academy of Sciences* 38: 613-618, July 1952.
- D) (With Dixon, J. P. and Chadwick, W. L. of the Denver Department of Health and Hospitals) Poliomyelitis and atmospheric humidity in an elevated semiarid region, Denver, Colorado *American Journal of Public Health* 42 (No.10): 1246-1252, October 1952.

## Final Years and Legacy

For many years following the cessation of Armstrong's position as Chief of the Division of Infectious Diseases on November 1, 1948, he remained engaged with continuing scientific investigations, with involvement in his prior association with the National Foundation for Infantile Paralysis and other professional organizations. Until his actual official retirement from the Public Health Service in October 1950, he continued working in NIH Building No. 5 as Chief, Polio Unit, National Microbiological Institute, National Institutes of Health. It was during this period that he wrote the series of manuscripts on the seasonal relationship of the incidence of poliomyelitis, provided guidance to Huebner's studies on Coxsackie viruses and collaborated with MacMurray in isolating toxoplasmosis from a patient with a cryptic fever (see previous chapters). After official retirement, as a courtesy in recognition of his many past scientific contributions, NIH provided him with an office and several small rooms where he could continue working. He usually came into the laboratory every day, and on occasional weekends, until several years before his death when failing health forced him to abandon this routine.

He continued to carry on an active correspondence with other poliomyelitis researchers (2, 3) and various professional institutions where he was still in demand as a featured speaker (4). In addition, he continued to maintain close personal relationships with his college and friends in Alliance, Ohio. On February 22, 1954 he was one of five "favorite sons" honored by The Alliance Ohio Chamber of Commerce at their annual banquet for "outstanding achievement." (5) Mr. William M. Morgan, the President of the

Alliance Chamber of Commerce, invited Armstrong to attend the next Annual Banquet in 1955; however, since Armstrong could not attend, Mr. Morgan sent Armstrong newspapers clippings of the event instead (6). Dr. Armstrong thanked Mr. Morgan for the clippings. Morgan also happened to be Professor of Chemistry at Mount Union College. Armstrong, however, did manage to get to Alliance in June 1955 to attend the 50<sup>th</sup> Anniversary Reunion of the Alliance High Class of 1905. Fortunately, 13 of the 35 class members were able to attend (8). Armstrong had for many years maintained affectionate ties with both “town and gown” of Alliance. Going back to previous years, in July 1930 Dr. G. F. Lamb of the Geology Department of Mount Union College wrote Armstrong thanking him for the thoughtful letter that Armstrong wrote when Lamb retired (9). In February 1930, Dr. W. H. Mc Master, President of Mount Union College wrote Armstrong with well wishes for recovery from psittacosis. The letter also contained chatty anecdotes about mutual local acquaintances (10).

Armstrong still remained in the public eye, and other organizations still sought associations with him for his professional services. On May 31, 1955 the NIH Record featured him in an article entitled “Portrait of an NIH Scientist” (11) that summarized his background, career and accomplishments since joining the Public Health Service in 1916. Around the same time, the NIH Biomedicine Research Facility offered him a position to work with the group at Fort Detrick, Frederick, Maryland. Armstrong wrote to Brigadier General L. D. Worsham (14) on May 6, 1955, thanking him for the offer to work with the Frederick group. However, he declined the offer on grounds that he was still working at NIH, did not have the requisite skills to be effective with the Fort Detrick organization, and that it would be a personal hardship for him to move his family to Frederick. In early

January 1958, Armstrong was inducted into the Polio Hall of Fame in Warm Springs, Georgia (see the chapter on Poliomyelitis). In February 1960 he was a signer of the First Conference Report of the Lederle (Company) Advisory Board on Living Polio Virus Vaccine (11).

Armstrong was also able to attend and participate in meetings of other professional organizations to which he belonged. He attended the 46<sup>th</sup> reunion of the class of 1915 at Johns Hopkins Medical School (11). On May 3, 1961, he represented Mount Union College at the Inauguration of Dr. Thomas Henry Carroll as President of George Washington University of Washington, DC (12). On October 23, 1963 he attended the Centennial Banquet of the National Academy of Sciences at the Statler-Hilton Hotel in Washington, DC (11). On November 29, 1962 Armstrong participated in a program commemorating the 75<sup>th</sup> Anniversary of Infectious Disease Research in the United States Public Health Service (13). The speakers included past and present members of the Public Health Service as well as prominent invited guests. The Scientific Program was held in the NIH Clinical Center Auditorium; the hospitality hour was in the Officers Mess in the National Naval Medical Center across the road from the NIH. In the afternoon program, Armstrong talked about “Virology in Retrospect”, followed by Nobel Laureate Dr. John F. Enders who addressed the subject of “Virology in Prospect”.

Charles Armstrong, around the mid-1960s, became a person of interest for historians. His associate and friend of many years, Dr. James P. Leake, also now retired, was a volunteer at the National Library of Medicine. Dr. Leake was writing, doing research and annotating subjects contained in Armstrong’s bibliography (1). On August 3, 1964, Armstrong received a letter from Dr. Saul Benison, then Professor of History at



Brandeis University Graduate School of Arts and Sciences, Waltham, Massachusetts

(11). Dr. Benison was the author of “Tom Rivers”, the oral biography of Dr. Thomas M. Rivers, Armstrong’s medical school classmate at Johns Hopkins (see previous chapters and notes). Dr. Benison wrote as follows: “Dear Dr. Armstrong, I want to thank you for your thoughtfulness in sending me off your papers relating to poliomyelitis. They will be very helpful to me in my work. Receipt of these papers reemphasizes to me the importance of preserving your correspondence, laboratory protocols, diaries, etc. for the history of contemporary science and medicine.

“When last I was in Washington I discussed this with Dr. Martin Cummings and Dr. John Blake of the National Library of Medicine. They agreed with me that the National Library of Medicine could begin its Manuscript Collecting program in no better way than by preserving your correspondence, diaries and protocols. I know that many scientists have a tendency to denigrate the importance of such materials and all too often destroy them. As an historian of medicine and science I can unequivocally say that the very growth and development of my discipline is predicated on the preservation of just such materials. I hope that you will in the future take steps to preserve and store your correspondence etc. with the National Library of Medicine. Again let me thank you for your kindness to me. Sincerely”. Fortunately, much, but not the total amount of such material (Armstrong’s), has been salvaged.

In Armstrong’s twilight years he still did not fade into obscurity. He was featured in The Surgeon General’s Bulletin of the U. S. Department of H. E. W. November/December 1964. Surgeon General Luther L. Terry, noted initially for his attack (report) on tobacco use and abuse, appeared in the Bulletin greeting Armstrong as

a Five Decade PHS Scientist at a recent (11) Senior Level Orientation Program. A regular speaker for the orientation series, Armstrong's talk was entitled "The Growth of the Service. A Bird's Eye View." A brief outline of Armstrong's career followed in the Bulletin. A former PHS colleague, Dr. Michael L. Furculow (15) saw the Bulletin and corresponded with Armstrong. Dr. Furculow was a student of the epidemiology of histoplasmosis and tuberculosis in the Ohio River Valley. He wrote that it was a pleasure to see Armstrong's picture with Surgeon General Terry, that Armstrong looked "just as young as you did 25 years ago, or more exactly, 24 years ago when I first went with you in the old NIH." Furculow was delighted that Armstrong was in such "good health" and was still able to continue his usual productive work.

The years however were beginning to take their toll, and his health was beginning to fail. Nevertheless, he was able to enjoy a celebration of his 80<sup>th</sup> birthday (September 25, 1886) on September 27, 1966 (16). To honor Armstrong for his accomplishments, especially research in infectious diseases, Dr. James A. Shannon, Director of NIH, and a number of Armstrong's former co-workers at NIAID attended the celebratory luncheon at the Naval Medical Center Officers Club. The group gave him an album of photographs of scientists with whom he had worked. He also received a letter of congratulations from Lyndon B. Johnson, President of the United States which said: "I would like to join your many friends in extending to you my best wishes and congratulations.

"As you celebrate your 80<sup>th</sup> birthday and the 50<sup>th</sup> anniversary of your entrance into the U.S. Public Health Service, your fellow Americans look to you with gratitude for your important contributions to the medical advances of our times.

“You have earned abiding recognition from the generations of Americans who may be assured better health and longer lives through your own dedication. On their behalf, I salute you”.

Additional letters of congratulations also followed from many friends including Cornelius B. Philip, Ph. D., Principal Medical Entomologist at the Rocky Mountain Laboratory in Hamilton, Montana, and George M. King, M. D., a private medical practitioner in Alliance, Ohio (11).

On June 2, 1967, he received his final lifetime honor (11,17). He was awarded the Distinguished Alumnus Award from his Alliance High School. The small diploma said: “Presented to Charles Armstrong. In recognition of outstanding achievement and inspiration to the students and faculty of Alliance High School. [Signed] Walter A. Wollam, William F. Rogers.” Unfortunately, Armstrong could not accept the award in person because he was too infirm in the last few days of his terminal illness.

The final two years of Armstrong’s life became uncomfortable because of rapidly declining vigor and recurrent hospitalizations related to his illnesses. Also, his wife of 45 years, Elizabeth Rich (Bess), passed away on April 14, 1965, 26 months before his own death. He steadfastly nursed and cared for her during her final few months before she succumbed to severe heart disease. Despite his own failing health, he assumed many of the household chores and duties to relieve his daughter who lived at home and who was teaching school fulltime in Montgomery County, Maryland. He tended the family yard and lawn, continued gardening and farming on a limited basis, cooked meals, did the shopping and relieved his daughter’s busy schedule as much as possible. Painful and debilitating illnesses began to appear. He developed painful compression fractures of the

bodies of the 9<sup>th</sup> thoracic and first lumbar spinal vertebrae due to osteoporosis. This condition required his wearing a stiff supportive back brace so that he could be ambulatory. He had a strange history related to his renal system. In 1963, for undisclosed reasons, he had an exploration of the left kidney area that showed an unusual tissue formation of the left ureter (the tubular structure from the kidney to the bladder). The diagnosis was localized amyloidosis. (Amyloid is a starch-like protein-polysaccharide complex disseminated locally or generally in the body either as a primary, idiopathic process or secondary to a chronic inflammatory infectious illness such as a draining, pustular wound.) The condition appeared to be progressive but his physicians never established whether it was related to any of his previous illnesses.

In 1966, he developed diabetes mellitus and diverticulosis of the colon. That year he was hospitalized at the U. S. Public Health Service Hospital in Baltimore because of bowel obstruction. During this hospitalization his physicians found a double right ureter (congenital anomaly) and Bence-Jones protein in his urine (an abnormal protein often found in multiple myeloma, leukemia, lymphoma, and Hodgkin's Disease). Armstrong was re-hospitalized in 1967 at Baltimore because of symptoms related to worsening kidney function and the development of the signs of congestive heart failure. His final hospitalization was in June 1967 at the National Naval Medical Center in Bethesda, Maryland with terminal uremia and uremic pericarditis. He died after two days on June 22, 1967. He was interred next to his wife in the family burial plot in the Senecaville (Ohio) cemetery among friends and neighbors.

Mary Emma Armstrong described one regret associated with her father's death. An autopsy was performed on Dr. Armstrong (in the presence of his longtime friend and

associate, Dr. James P. Leake) at the USPHS Hospital in Baltimore; many individuals waited with scientific interest the autopsy findings that might answer to what degree, if any, the major illnesses acquired in the laboratory might have contributed to the ailments leading to his death. Unfortunately, the pathologist in charge of the autopsy shortly thereafter became incapacitated, and the autopsy findings were never recorded officially. Miss Armstrong described with gratitude the many doctors and friends who guided Armstrong's medical care during his final two years. She acknowledged two men with affection and appreciation: Dr. Norman B. McCullough and Dr. James P. Leake, both members of the Public Health Service. Dr. McCullough first came to the Laboratory of Infectious Diseases in 1951 when he succeeded Dr. Birdsall Carle as Chief of the Brucellosis Unit. He had been previously at the University of Chicago where he worked with Dr. C. Wesley Eisele studying salmonella infections in volunteers. He became Chief of the NIAID Clinical Unit when the Clinical Center opened in 1953. He later became Chief of the Laboratory of Bacterial Diseases of NIAID. He left NIH in the late 1960s and became Professor of Microbiology and Public Health and Professor of Medicine at Michigan State University in East Lansing, Michigan. Drs Leake and Armstrong went back together many years from their days at the Hygienic Laboratory and were close personal friends as well as professional colleagues. Although "retired", Dr. Leake, as already described, kept himself busy with his activities at the National Library of Medicine.

Charles Armstrong's passing was duly noted in prominent newspapers with detailed obituaries: *The New York Times*, June 23, 1967 (18); *The Evening Star* (Washington) June 23, 1967 (19); and *The Washington Post*, June 23, 1967, (20). A very

personal tribute appeared in the *Mount Union College Bulletin* (21) written by a fellow alumnus, Dr. Howard B. Andervont, class of 1923. Dr. Andervont was a contemporary of Armstrong. He worked in the National Cancer Institute and was well known for his studies of the Bittner mouse mammary tumor, later recognized as caused by a retrovirus. His peers and associates have provided previously their evaluations of Charles Armstrong as a scientist and dedicated investigator. His daughter (1) provided her insight of him as a father with deep personal moral and ethical principles. He came from a family guided by spiritual values, and he married into a family with similar values. His gentleness of spirit and reverence, however, enabled him to wear his religion lightly in a non-proselytizing manner. At home, and for his daughter, he was a ready source of maxims and Poor Richard's Almanac-like aphorisms to guide the activities of daily living. Because of his obvious love and enthusiasm for his research activities, he was grateful for his family's strong support and encouragement. He was in harmony with himself ("comfortable in his own skin"), felt that his professional endeavors were worthwhile and that he was making significant contributions to the community. He was gregarious but enjoyed solitude especially when he was working alone in the laboratory, in his home garden, or on the small "farm" he loved so much in nearby Maryland. It was at these times that he had some of his most creative ideas when he had opportunities for relaxed meditation and quiet contemplation. Mary Armstrong (1) related Mrs. Bess Armstrong's stating that Dr. Armstrong's first love was his job and that she came next; however noted, that among the world of people, Dr. Armstrong's wife came first in his affections and his daughter second. His private world and his home life were for study, rest, refreshment, support and relaxation. The love was there mutually and abundantly; both women tried, as much as

possible, to relieve Armstrong of any domestic burdens or worries that might encroach on his time or might interfere with his work. The family was a pillar of strength during his many laboratory-acquired illnesses.

Those who knew Dr. Armstrong in his personal life were aware that he was a “man of many parts” in addition to being a physician-scientist, a teacher, a person of great physical strength and endurance. He was a legendary humorist given to optimism and laughter, and an engaging raconteur with an endless supply of jokes. He enjoyed making hand-drawn Valentines that he used to distribute in season to members of the Division of Infectious Diseases when he was its Chief. (He also sent them to his daughter.) These have been collected and kept by his long-time secretary, Miss Virginia Burlingame. He was tolerant, non-prejudiced, a responsible citizen and an adamant participant in exercising his voting rights regularly in scheduled county, state, primary and federal elections. He was also a handy man and domestic jack-of-all-trades. As a carpenter, he put a roof on his first home after marriage, and he painted the same house twice on the outside. He put a roof on the garage of his second house. As a mechanic, he kept his automobile, farm tractor, family washing machine, clocks and fans in working order, but he never mastered the maintenance of radios. He also wired the home of his wife’s parents in rural Ohio near Senecaville. In summary, he was an extraordinarily gifted, well-rounded person.

In his written autobiography, Armstrong listed in chronological order what he considered to be his major, lifetime, scientific contributions. Other sources (1, 22) round out the list:

- 1) In 1919, he demonstrated by epidemiological and laboratory proof that commercially canned ripe olives had induced severe and fatal botulism. The result was that the California olive packers spent several hundred thousand dollars in studying and revamping their canning methods in such a way that the danger from this product was eliminated.
- 2) In 1920, he described an influenza epidemic in an isolated island community, clarified the method of spread and the characteristics of immunity.
- 3) In 1922-1923, he helped control a typhus outbreak among Navajo Indians in New Mexico.
- 4) In 1925-1927, he demonstrated methods for eliminating tetanus following smallpox vaccination. In 1925, he demonstrated that a number of cases of post-vaccination tetanus were attributable to the employment of bunion pads as vaccination dressings. Tetanus spores were found in the glue of such pads. In 1927, he demonstrated on epidemiological grounds that post vaccination tetanus peculiar to the United States was always confined to primary vaccinations that were covered with some sort of shield or dressing strapped to the vaccination site. Experiments showed that the vaccine intentionally seeded with tetanus spores permitted the development of tetanus only if the site was covered by some sort of occlusive dressing strapped to the vaccination site or if the vaccination was administered in a traumatic fashion. Elimination of vaccination dressings and discontinuation of the



manufacture of celluloid vaccination shields eliminated post-vaccination tetanus. Armstrong also conducted experiments to suggest a possible mechanism for the dangerous complication of encephalitis following vaccination.

- 5) In 1927, he helped complete a compilation of milk-borne outbreaks of diseases such as scarlet fever and undulant fever (brucellosis).
- 6) In 1929-1930, he isolated the agent of psittacosis (parrot fever) demonstrating that it was a filterable, non-bacterial, virus-like organism. He conducted laboratory and field work that provided the data for an Executive Order issued by President Herbert Hoover in 1930 prohibiting the importation of psittacine birds into the United States unless subjected to regulations then prescribed by the Secretary of the Treasury.
- 7) In 1933, he led the effort along with others to isolate the previously unknown virus that caused the epidemic of Saint Louis encephalitis. He isolated the virus initially in monkeys and then in white mice.
- 8) In 1934, he isolated from brain material originating in the Saint Louis encephalitis epidemic a new completely unknown virus that he labeled “lymphocytic choriomeningitis” based on the unique location and pathology of the infection’s involvement in the brain and meninges. He continued the study of this agent for many years and contributed the bulk of early information about its biology, epidemiology and behavior

in mice and men. The French scientific community honored Armstrong by naming the clinical entity “La Maladie d’Armstrong”.

- 9) In 1936, he demonstrated that various astringent chemicals instilled into the nostrils of monkeys would produce a marked temporary protection against poliomyelitis virus instilled by the same route – thus affording a useful means of blocking the nasal route of infection in experimental studies. This modality was unsuccessful in influencing the course of a concurrent ongoing community poliomyelitis epidemic.
- 10) In 1939, for the first time, he was able to adapt and transmit a human strain of poliomyelitis (the Lansing type 2 strain) virus from monkeys to small rodents, first to the cotton rat and then to white mice. This accomplishment was revolutionary in facilitating the study of many aspects of infection and immunity in humans that could scarcely have been carried out with monkeys, the only susceptible experimental animal known up to that time. The discovery also stimulated the renewal of efforts to adapt and establish the other immunologic types of poliomyelitis, leading to methods that resulted in the eventual developments of successful vaccines for poliomyelitis.
- 11) In 1946, he assisted Robert J. Huebner and others in discovering and elucidating the nature of a newly recognized disease named “Rickettsialpox”. The complete elucidation of this disease in record time (seven months) has been recognized as a modern classic of investigative microbiology.

- 12) In 1950-1952, he developed a hypothesis to help explain the commonly observed late summer-early fall incidence for poliomyelitis in the temperate climate zones. He postulated changes in the relative humidity of inspired air, correlated with official weather reports, to explain the acquisition of poliomyelitis infection and possibly of other viruses transmitted in a similar fashion.
- 13) In 1953, he demonstrated *Toxoplasma gondii* organisms in a superficial lymph gland from a patient with a cryptic fever thus indicating one method by which this elusive ailment in adults might be identified.
- 14) In the 1950s, he tried to determine the etiology of cat scratch disease without making any progress in cultivating the organism

During the course of Armstrong's field and laboratory activities, he contracted the following infections: a) Malaria, b) Dengue fever, c) Psittacosis, d) Encephalitis (He developed antibodies to both Saint Louis encephalitis and lymphocytic choriomeningitis.), e) Q fever, f) Tularemia.

In paying tribute to his numerous accomplishments, many media articles and obituaries seemed to attribute primary importance to his eminence in poliomyelitis research. In the oral history recorded late in his life (1966), Armstrong, on reflection, was of the opinion that his most significant contribution to public health was the promotion of methods to prevent tetanus following smallpox vaccination; this was perhaps a far too modest self-evaluation considering the totality of his accomplishments.

The author of the Johns Hopkins Epidemiology Letter (22a) stated that the legacies of Charles Armstrong were evident, not only in his contributions to infectious

disease epidemiology and to public health in general but in the role played as mentor to other outstanding epidemiologists. Exposed in his early and subsequent career to outstanding practitioners of the science, he was one of the premier epidemiologists of his time and represented an ideal combination of qualities that still prevails in the discipline today; these qualities include the excitement of discovery that is the essence of research, the commitment to the future represented by teaching and scholarship, and the sincere dedication to service for the improvement in public health. Armstrong's devotion to his work and the conscientious persistence in pursuing his ideas were also representative of the above qualities. These plus his exemplary personal life are indicative of an altogether admirable person.

During the course of many years spent in academic and medical study, laboratory research, the clinical practice of medicine, participation in teaching and academic duties, this author has encountered many brilliant teachers, investigators, stimulating educators and physicians but he has recognized only two individuals whom he considers to be true heroes. Charles Armstrong is one of them.

#### Notes – Final Years and Legacy

- 1) Dr. Armstrong's daughter, Mary Emma Armstrong carefully assembled, tabulated and evaluated much of the information relating to Dr. Charles Armstrong's life after his formal retirement from the Public Health Service. She also provided an intimate glimpse into his domestic life, family relationships and his guidelines for social behavior and personal relationships outside the laboratory.

- 2) Letter from Dr. David Bodian, Johns Hopkins University, April 18, 1951, among Armstrong's personal papers.
- 3) Letter from Dr. Herbert Wenner, University of Kansas, April 12, 1951, among Armstrong's personal papers.
- 4) Letter from Dr. Horace M. Gezon, U.S. Naval Medical School, December 18, 1951, among Armstrong's personal papers.
- 5) The Alliance (Ohio) Review, February 24, 1954.
- 6) Letters from William M. Morgan, February 22, 1955 and March 22, 1955, among Armstrong's personal papers.
- 7) Letter from Armstrong to Professor W. M. Morgan April 6, 1955, among Armstrong's personal papers.
- 8) The Alliance (Ohio) Review, Monday, June 20, 1955.
- 9) Letter to Armstrong from Dr. G. F. Lamb, July 28, 1930, among Armstrong's personal papers.
- 10) Letter to Armstrong from President W. H. McMaster, February 13, 1930, among Armstrong's personal papers.
- 11) Among Armstrong's personal papers.
- 12) Letter from Armstrong April 18, 1961, to President Carl C. Bracy, Mount Union College, Alliance, Ohio, among Armstrong's personal papers.
- 13) Anniversary Program, NIH Record, December 5, 1962.
- 14) Letter to Brigadier General L. D. Worsham, Facilities Operation Division, Frederick, Maryland, May 6, 1955, among Armstrong's personal papers.

- 15) Letter from Michael L. Furculow, M. D., Professor of Epidemiology, University of Kentucky Medical Center, Lexington, Kentucky, January 5, 1965, among Armstrong's personal papers.
- 16) NIH Record, October 18, 1966 – Dr. Armstrong is cited by the President and honored by former NIH colleagues.
- 17) The Alliance (Ohio) Review June 2, 1967, AHS (Alliance High School) Honors First "Class" of Distinguished Alumni. Fourteen honored.
- 18) The New York Times, June 23, 1967, Dr. Charles Armstrong, 80, Dies, Public Health Aide Fought Polio.
- 19) The (Washington) Evening Star, June 23, 1967, Dr. Charles Armstrong, 88 (?), Pioneer in Polio Research.
- 20) The Washington Post, June 23, 1967, Dr. Charles Armstrong, Pioneer Polio Worker.
- 21) Mount Union College Bulletin, August 1967, Dr. Charles Armstrong '10, Dies at Bethesda Naval Hospital, Research Pioneer in Poliomyelitis.
- 22) A) Epidemiology Newsletter, Johns Hopkins University School of Hygiene and Public Health, autumn, 1996. B) Surgeon General's Bulletin No. 42. C) Armstrong, C. and MacMurray, F. M. *ibid.*

## Appendices

### Appendix A

#### Charles Armstrong Curriculum Vitae

Name: Charles Armstrong

Date and Place of Birth: September 25, 1886; Alliance (Stark County), Ohio, USA

Date and Place of Death: June 23, 1967; United States Naval Hospital, Bethesda, Maryland, USA.

Citizenship: United States of America

Marital Status: Married Alberta A. Rich, June 21, 1920 to April 1965

Children: One daughter, Mary Emma

#### Education:

1905—Graduated from Alliance High School

1905-1906—Mount Union College Preparatory School

1906-1910—Graduated from Mount Union College, Alliance, Ohio, B.S. degree

1911-1915—Graduated from Johns Hopkins Medical School, M.D. degree

1815-1916—General Internship, Yale New Haven Hospital

#### Civilian Work Experience:

1910—Superintendent, Special School District, Greentown, Ohio

#### Assignments in the United States Public Health Service:

October 16, 1916—Commissioned.

1916—Six weeks, Immigration Station, Ellis Island, New York.

November 1916-September 1918—Medical Officer, United States Coast Guard Cutter (CSG) SENECA, assigned to Cuban and European waters for 17 months when the ship was transferred to the U.S. Navy, 1917-1918, during World War I.

Fall 1918-Winter 1919—Investigating local outbreaks of pandemic influenza.

1919-1921—Assigned as an Epidemiological Aide to the Ohio State Department of Health.

1921-1950—Assigned to the Hygienic Laboratory, remaining there through its administrative and name changes to the National Institute of Health, Division then Laboratory of Infectious Diseases until his retirement.

#### Ranks of Dr. Charles Armstrong in the U.S. Public Health Service

1916-1920	Assistant Surgeon (Commission: October 29, 1916)
1920-1924	Past Assistant Surgeon (Commission: October 27, 1920)
1924-1936	Surgeon (Commission: August 13, 1924)
1936-1942	Senior Surgeon (Commission: October 27, 1936)
1942-1950	Medical Director (Commission: October 27, 1942)
1941-1948	Chief, Division of Infectious Diseases, National Institute of Health
1949-1950	Chief, Polio Unit, Microbiological Institute, National Institute of Health.
1950	Retirement from Active Duty
1950-1963	Daily researcher at National Institutes of Health without compensation (until December 1963). (This excepts retirement income)
1963	Closing out of all research and work at the National Institutes of Health

#### Honors Received by Dr. Charles Armstrong

1933 Honorary Doctor of Science Degree, Mount Union College; Alliance, Ohio  
1938 Election into the Society of the Sigma Xi.  
1938-9 Appointment to General Advisory Committee of the National Foundation for Infantile Paralysis.  
1941 Recipient of the Sedgwick Memorial Gold Medal  
1944 Election into the National Academy of Sciences  
1954 Recipient of an honor by the Chamber of Commerce of Alliance, Ohio  
1956 Election to the Polio Hall of Fame, Dedicated in Warm Springs, Georgia, January 2, 1958  
1966 Presentation of Distinguished Alumnus Award to Dr. Armstrong (and others) by the Alliance High School, Alliance, Ohio  
1966 Letter from President of the United States from the White House

#### Lectureships by Dr. Charles Armstrong

“The Complications of Smallpox Vaccination.” DeLamar Lectures on Hygiene. School of Hygiene and Public Health of the Johns Hopkins University, Baltimore, February 15, 1932.

“The Complications of Smallpox Vaccine.” Cutter Lecture on Preventative Medicine of 1931-1932. Harvard Medical School, Boston, March 31, 1932.



“Studies on Choriomeningitis and Poliomyelitis.” James M. Anders Lecture XV, The College of Physicians of Philadelphia, Philadelphia; January 3, 1940.

“Studies on Choriomeningitis and Poliomyelitis.” Harvey Lecture, 1940-1941. Delivered under the auspices of the Harvey Society of New York under the patronage of the New York Academy of Medicine, New York, October 31, 1940.

“Some Recent Research in the Field of Neurotropic Viruses with Especial Reference to Lymphocytic Choriomeningitis and Herpes Simplex.” Kober Lecture of 1942. Delivered at Gaston Hall, Georgetown University, Washington, D.C., May 5, 1942.

“Seasonal Distribution of Poliomyelitis.” The Don W. Gudakunst Memorial Lecture (first in the series). Delivered at the School of Public Health, University of Michigan; Ann Arbor, Michigan, May 8, 1950.

#### Speeches by Dr. Charles Armstrong

November 22, 1924. “Standardization of Pollen Extract by the Complement Fixation Test,” by Charles Armstrong and W.R. Harrison. Read before the Society for the Study of Asthma and Allied Conditions, New York.

June 1928. “Vaccination,” by Charles Armstrong. Read before the Annual Conference of Public Health Officers and Public Health Nurses of New York State, Saratoga Springs.

June 3, 1929. “The Role of the Vaccination Dressing in the Production of postvaccinal Tetanus,” by Charles Armstrong. Read at the 27<sup>th</sup> Annual Conference of State and Territorial Health Officers with the Public Health Service, Washington, D.C.

June 3, 1929. “Postvaccinal Encephalitis,” by Charles Armstrong. Read at the 28<sup>th</sup> Annual Conference of State and Territorial Health Officers with the Public Health Service, Washington, D.C.

June 18, 1930. “Psittacosis: Epidemiological Considerations with Reference to 1929-1930 Outbreak in the United States,” by Charles Armstrong. Read at the 28<sup>th</sup> Annual Conference of State and Territorial Health Officers with the Public Health Service, Washington D.C., jointly with the 45<sup>th</sup> Annual Conference of State and Provincial Health Officers of North America.

March 24, 1931. “Post Vaccination Encephalitis,” by Charles Armstrong. Presented at the Baltimore Meeting of the American College of Physicians.

October 6, 1932. “Diagnosis of Mild Smallpox and Scarlet Fever,” by Charles Armstrong. Read at the Annual Meeting of the Vermont State Medical Society, Burlington, Vermont.

June 6, 1933. "Education and Research," by Charles Armstrong (at the time he received an Honorary D.Sc.) Address delivered at Annual Alumni Banquet, Mount Union College, Alliance, Ohio.

June 15, 1934. "Etiology of the 1933 Epidemic of Encephalitis," by Ralph S. Muckenfuss, Charles Armstrong, and L. T. Webster. Read before the Section on Preventive and Industrial Medicine and Public Health at the 85<sup>th</sup> Annual Session of the American Medical Association, Cleveland, Ohio.

October, 1934 (day not known). "Smallpox and Postvaccinal Encephalitis," by Charles Armstrong. Presented before a class at the Army Medical Center, Washington, D.C.

November 17, 1936. "Experience with the Picric Acid-Alum Spray in the Prevention of Poliomyelitis in Alabama, 1936," by Charles Armstrong. Read before the Southern Branch of the American Public Health Association at the 5<sup>th</sup> Annual Meeting; Baltimore, Maryland.

June 10, 1937. "Benign Lymphocytic Choriomeningitis: Laboratory Studies with the Virus and Their Possible Bearing on the Infection in Man," by Charles Armstrong and Jerald G. Wooley. Read before the Section on Nervous and Mental Diseases at the 88<sup>th</sup> Annual Session of the American Medical Association at Atlantic City, New Jersey.

October 5, 1940. "Cotton Rats and White Mice in Poliomyelitis Research," by Charles Armstrong. Read at a joint session of the Laboratory and Epidemiological Sections of the American Public Health Association at the 69<sup>th</sup> Annual Meeting; Detroit, Michigan.

April 8, 1941. "The Etiology of Poliomyelitis, Infantile Paralysis," by Charles Armstrong. A symposium delivered at Vanderbilt University for the National Foundation for Infantile Paralysis.

September 27, 1948. "Progress in Virus Control," by Charles Armstrong. Delivered at the 19<sup>th</sup> Annual Scientific Assembly of the Medical Society of the District of Columbia.

June 1950. "Studies on Cocksackie Viruses; Preliminary Report on Occurrence of Cocksackie Virus in a Southern Maryland Community," by Robert J. Huebner, Charles Armstrong, Edward A. Beeman, and Roger M. Cole. Read by Dr. Beeman before the Section on Pediatrics at the 99<sup>th</sup> Annual Session of the American Medical Association; San Francisco, California.

April 30, 1952. "Poliomyelitis and the Weather," by Charles Armstrong. Read before the National Academy of Sciences, Washington, D.C.

Dr. Charles Armstrong's Membership in Professional and Scholarly Organizations

- 1906 Sigma Alpha Epsilon Fraternity (SAE)
- 1927 Association of Military Surgeons of the United States.  
Member: Dec. 24, 1927 to Feb. 1, 1950
- 1928 American Epidemiological Society.  
Active Member, April 30, 1928  
President, 1932 [*American Men of Science* says 1939]
- 1932 American Public Health Association  
Member: 1932  
Fellow: 1935
- 1933 American Medical Association  
Member: 1933  
Fellow: 1935
- 1933 American Association for the Advancement of Science  
Fellow: 1933
- 1935 Society for Experimental Biology and Medicine  
Member: "many years" terminating in 1967
- 1938 National Foundation for Infantile Paralysis  
General Advisory Committee: January 1938-December 1950  
Committee on Virus Research: June 1938-June 1947  
Committee on Epidemics and Public Health: Nov. 1940-June 1947  
Committee on Virus Research and Epidemiology: July 1947-Dec. 1950
- 1938 The Society of the Sigma Xi
- 1938 New York Academy of Sciences  
Associate Member: December 1938  
Active Member: October 28, 1948
- Washington Academy of Medicine  
Member: 1943 [or before] to 1967  
Vice President: 1964-1966
- 1944 National Academy of Sciences
- 1945 Clinico-Pathological Society: Washington, D.C.

1952 Society of American Bacteriologists: Washington Branch.  
[Now—the American Society for Microbiology]  
Life member.

Commissioned Officers Association of the Public Health Service  
Charter member: Life member  
[dates for membership not kept in Association files]

Alumni Association of Mount Union College  
Alumni Association of Johns Hopkins University (Medical School)  
Alumni Association of Yale University (Medical School)

Health History of Dr. Charles Armstrong (1886-1967)

Major Illnesses:

1927 Malaria

1928 Dengue fever

1930 Psittacosis: Hospitalization—Navy Hospital, Washington, D.C.

1933 Encephalitis: Hospitalization—Navy Hospital, Washington, D.C.  
Choriomeningitis (Date not known).

1940 Q Fever: Probable hospitalization—USPHS Hospital, Baltimore, MD

1942 Tularemia (pulmonary type):  
Hospitalization—Marcus Daly Hospital, Hamilton, Montana  
Naval Medical Hospital, Bethesda, Maryland

Other Illnesses or Conditions

1930 Prostatitis

1932 Ulcers of bladder.  
Treatment: New Haven General Hospital, New Haven, CT (Dr. Demming,  
physician)

1950 Removal of abscessed tooth. USPHS Clinic, Washington, D.C.

1950 Appendectomy. Hospitalization: Garfield Memorial Hospital, Washington, D.C.

1960 Vaccine made by Dr. McCullough and Dr. Armstrong at NIH for Dr. Armstrong

1962 X-ray finding of “spot” on kidney

1963 Left renal exploratory operation: results—finding of unusual formation of normal tissue. (During course of the surgery done by Dr. William P. Herbst, 3<sup>rd</sup>, at the Naval Medical Hospital in Bethesda, Maryland, amyloidosis of the kidney of the kidney ureter was discovered.)

1966 Bowel obstruction  
Diabetes mellitus  
Bence-Jones Protein  
Osteoporosis

(All of above) Hospitalization: USPHS Hospital, Baltimore, Maryland

1967 Uremia  
Cardiac difficulties  
(All of above) Hospitalization: USPHS Hospital, Baltimore, Maryland

1967 Uremia  
Uremic Pericarditis  
Death

(All of above) Hospitalization: Naval Medical Hospital Bethesda, Maryland

## Appendix B

### Charles Armstrong Bibliography

Armstrong, Charles; R. V. Story and Ernest Scott: Botulism from eating canned ripe olives. Pub. Health Rep. **34**:2877-2905, Dec.19, 1919.

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Armstrong, Charles: Dengue fever. Pub. Health Rep. **38**: 1750-1734, Aug. 3, 1923.

Voegtlin, Carl: Charles Armstrong and Helen A. Dyer: The curative action of sulpharsphenamine in experimental syphilis. Pub. Health Rep. **38**:815-1817, Aug. 10, 1923.

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Payne, C. C. and Charles Armstrong: Epidemic transient diaphragmatic spasm; disease of unknown etiology, epidemic in Virginia. Jour. Amer. Med. Assoc., **81**:746-748, 1923.

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Armstrong, Charles: Tetanus following vaccination against smallpox and its prevention with special reference to the use of vaccination shields and dressings. Pub. Health Rep. **42**:3061-3071, Dec. 16, 1927.

Armstrong, Charles: Postvaccination tetanus and its prevention. Jour. Amer. Med. Assoc. **90**:738-740, Mar. 10, 1928.

Armstrong, Charles: Intradermal (injection) vaccination. Is its suitability for general use established? Jour. Amer. Med. Assoc. **91**:1530-1531, Nov. 17, 1928.

Armstrong, Charles: Vaccination. Hospital Social Service, XIX, 390-398, 1929.

Armstrong, Charles: The selection of a heat-resistant strain of vaccine virus (rabbit testicular). Pub. Health Rep. **44**:1183-1191, May 17, 1929.

Armstrong, Charles: The role of the vaccination dressing in the production of postvaccinal tetanus. Pub. Health. Rep. **44**:1871-1884, Aug. 2, 1929.

Armstrong, Charles: Postvaccinal encephalitis. Pub. Health Rep. **44**:2041-2044, Aug. 23, 1929.

Armstrong, Charles and R. D. Lillie: Vaccine virus pneumonia in rabbits. Pub. Health Rep. **44**:2635-2647, Nov. 1, 1929.

Lillie, R. D. and Charles Armstrong: The pathology of generalized vaccinia in rabbits. National Institute of Health Bull. No. 156, 1930.

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Armstrong, Charles: Psittacosis. Epidemiological considerations with reference to the 1929-30 outbreak in the United States. Pub. Health Rep. **45**:2013-2023, Aug. 29, 1930.

Branham, Sara E.; George W. McCoy and Charles Armstrong: *Bacillus psittacosis* Mocard 1893. Failure to find it in the 1929-30 epidemic in the United States. Pub. Health Rep. **45**:2153-2160, Sept.12, 1930.

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Armstrong, Charles: Post-vaccination encephalitis. Ann. Int. Med., **5**:333-337, 1931.

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Armstrong, Charles: Modification of the vaccine response in rabbits by the application of diphtheria toxin to the vaccination site. Pub. Health Rep. **48**:1-7, Jan. 6, 1933.

Armstrong, Charles: Psittacosis. *Amer. J. Nurs.* **33**:97-101, Feb. 1933.

Armstrong, Charles and W. T. Harrison: Heterologous experience (immunization) as a factor in resistance to disease. *Pub. Health Rep.* **48**:597-609, June 2, 1933.

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Muckenfuss, R. S.; Charles Armstrong and H. A. McCordock: Encephalitis: Studies on experimental transmission. *Pub. Health Rep.* **48**:1341-1343, Nov. 1933.

Armstrong Charles: The production of specific immunity in white mice by intranasal inoculation with encephalitis virus (St. Louis type). *Pub. Health Rep.* **49**:959-960, Aug. 17, 1934.

Armstrong, Charles with Pathology by Ralph D. Lillie: Experimental lymphocytic choriomeningitis of monkeys and mice produced by a virus encountered in studies of the 1933 St. Louis encephalitis epidemic. *Pub. Health Rep.* **49**:1019-1027, Aug. 31, 1934.

Muckenfuss, Ralph S.; Charles Armstrong and L. T. Webster: Etiology of the 1933 epidemic of encephalitis. *Jour. Amer. Med. Assoc.* **103**:731-733, Sept. 8, 1934.

Wooley, J. G. and Charles Armstrong: The distribution of immunity against encephalitis virus of the St. Louis type in the United States as determined by the serum-protection test in white mice. *Pub. Health Rep.* **49**:1495-1505, Dec. 14, 1934.

Armstrong, Charles: Effect of experimental local irritation upon susceptibility to vaccine and encephalitis virus (St. Louis type). *Pub. Health Rep.* **50**:43-50, Jan. 11, 1935.

Armstrong, Charles and, J. G. Wooley: Studies on the origin of a newly discovered virus which causes lymphocytic choriomeningitis in experimental animals. *Pub. Health Rep.* **50**:537-541, Apr. 19, 1935.

Armstrong, Charles and W. T. Harrison: Prevention of intranasally inoculated poliomyelitis of monkeys by instillation of alum into the nostrils. *Pub. Health Rep.* **50**:725-730, May 31, 1936.

Armstrong, Charles and Paul F. Dickens: Benign lymphocytic choriomeningitis (acute aseptic meningitis). A new disease entity. *Pub. Health Rep.* **50**:831-842, June 21, 1935.

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Armstrong, Charles and R. D. Lillie: Encephalitis virus (St. Louis type): Effect of partial specific immunity upon the clinicopathologic picture in intracerebrally inoculated white mice. Pub. Health Rep. **51**:1069-1075, Aug. 7, 1936.

Armstrong, Charles and W. T. Harrison: Prevention of intranasally inoculated encephalitis (St. Louis type) in mice and of poliomyelitis in monkeys by means of chemicals instilled into the nostrils. Pub. Health Rep. **51**:1105-1112, Aug. 14, 1936.

Armstrong, Charles: Experience with the picric acid-alum spray in the prevention of poliomyelitis in Alabama, 1936. Amer. Jour. Pub. Health, **27**:103-11, Feb. 1937.  
Also Jour. Mad: Assoc. Alabama, 6:278-285, February 1937.

Armstrong, Charles and J. G. Wooley: Benign lymphocytic choriomeningitis, laboratory studies with the virus and their possible bearing on the infection in man. Jour. Amer. Med. Assoc. 109:410-412, Aug. 7, 1937.

Wooley, J. G., Charles Armstrong and R. H. Onstott: The occurrence in the sera of man and monkeys of protective antibodies against the virus of lymphocytic choriomeningitis as determined by the serum-virus protection test in mice. Pub. Health Rep. **52**:1105-1114, Aug. 13, 1937.

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Armstrong, Charles: Studies on the mechanism of experimental intranasal infection in mice. Pub. Health Rep. **53**:2004-2012, Nov. 11, 1938.

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## Appendix C

### Armstrong Laboratory Staff

The Author's Recollection of the Rickettsial Unit Personnel During His Tour of Duty at the Laboratory of Infectious Diseases, National Microbiological Institute, National Institutes of Health from August,-1948 to September, 1952.

This list of people is intended as a chronology of those associated with the laboratory during this particular time period. It includes the people with whom the author worked while assigned to Dr. Robert J. Huebner's unit, and also the individuals in Buildings 5 and 7 who attended the daily luncheon sessions on the second floor conference room of Building 7. This was a time of socializing and exchanging views on a variety of subjects not necessarily related to work. The previous careers of many are detailed in the history of the Commissioned Corps of the Public Health Service by Ralph C. Williams.

#### Viral and Rickettsial Unit Professional Personnel

Dr. Robert J. Huebner, M.D. - Chief, Senior Surgeon, USPHS.  
Dr. Edward A. Beeman, M.D. - Research Associate, S.A. Surgeon, USPHS  
Dr. Lauri Luoto, D.V.M. - Research Associate, USPHS.  
Worked in Bethesda and Downey, California in the Q Fever Laboratory.  
Dr. Angela Briefs, Ph.D. - Part time visiting scientist, 1951-1952 -special projects.

#### Laboratory Associates

Sara Elizabeth (Betty) Ransom, M.S. - Chief Bacteriologist.  
Horace (Chick) Turner - Chief of the Serology Section.  
William Baker - Laboratory Technician.  
John D. Estes - Laboratory Technician.  
Richard K. Lynt - Laboratory Technician.  
Leroy Snellbaker - Laboratory Technician.  
Julius (Rudy) Kasel - Laboratory Technician- later Ph.D.  
Charles F. Knauff - Chief Animal Handler.  
Frank J. West - Animal Handler.  
James M. Turner - Animal Handler.  
Toby Bowman - Factotum and Gopher.

Secretary

Ruth Bell

Epidemiology Section

Dr. Joseph A. Bell, M.D. - Chief, Medical Director, USPHS.

Dr. Roger M. Cole, Ph.D., M.D. - Surgeon, USPHS, - assigned to section; later Chief of Streptococcal Research Unit.

Dr. Paul Beigelman, M.D. - S.A. Surgeon, USPHS, - assigned to section 1951 - 1952.

Chief of the Laboratory of Infectious Diseases

Dr. Charles Armstrong, M.D. - Medical Director, USPHS

Secretary

Virginia Burlingame

Administrator

Mr. Kenneth Brown

Members of the "Luncheon Group"

Karl Habel, M.D. - Virologist: later Chief of the laboratory.

Alexis Shelokov, M.D. - from 1950; worked with Dr. Karl Habel.

Dorland Davis, M.D. - Chief of the Influenza Unit; later Director of NIAID.

John P. Utz, M.D. - worked with Dr. Davis; later in Clinical Laboratory of NIAID.

Carl Larson, M.D. - head of a laboratory unit; later Director of the Rocky Mountain Laboratory.

J. Frederick (Fritz) Bell, M.D. - worked with Dr. Larson and transferred to the Rocky Mountain Laboratory.

Chester Emmons, Ph.D. - Chief of the Mycology Unit.

Samuel Salvin, Ph.D. - worked with Dr. Emmons.

Birdsall Carle, M.D. - Chief of the Brucellosis Unit until 1951.

Norman McCullough, M.D. - succeeded Dr. Carle in 1951; later became Chief of the Clinical Laboratory of NIAID.

Charles C. Shepard, M.D. - various studies; later transferred to CDC; co-discoverer of Legionella.

Leon T. Atlas, M.D. - Chief Investigator, "Cold Virus" Unit.

George Hottle, Ph.D. - Biochemist, worked with Dr. Atlas.

Edwin Schultz, M.D. - visiting scientist from Stanford University to evaluate "Cold Virus" Unit.

Lawrence Kilham, M.D. - Virologist, 1950 - 1951; returned to Dartmouth Medical School.

Herman Dubuy, Ph.D. - Biologist, Biochemist.

Dean Woods, Ph.D. - Biologist, Biochemist.

Roderick Murray, M.D. - Chief, Division of Biologics; later FDA.

John Hornibrook, M.D. - Division of Biologics.

Robert Hannan, M.D. - temporary assignment in USPHS.

Frederick Germuth, Jr., M.D. - Immunologist, temporary assignment

Carl F. (Ted) Mattern, M.D. - starting USPHS career.

Elizabeth Verder, Ph.D. - Salmonella Bacteriologist; made potent punch for Christmas parties.

Ernest Jawetz, M.D. - 1948-1949; left NIH for an academic position in San Francisco.

G. Robert Coatney, Ph.D. - Malariologist, Laboratory of Tropical Medicine.

Leon Jacobs, Ph.D. - parasitologist, Laboratory of Tropical Medicine.

Edward Hamm, Ph.D. - Bacteriologist with the National Dental Institute.

Francis Arnold, D.M.D. - Chief of the National Dental Institute.

#### Tragedies

Carl Schultz, M.D. - Chief of the Streptococcal Unit; committed suicide.

John Oliphant, M.D. - Division of Biologics; committed suicide.