NATIONAL ACADEMY OF SCIENCES

PAUL RUFUS BURKHOLDER

1903—1972

A Biographical Memoir by

JAMES G. HORSFALL

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February 1, 1903–August 11, 1972

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DISTINGUISHED SCIENTISTS don't just happen. Paul Rufus Burkholder wasn't just accidentally elected (1949) to the National Academy of Sciences. He didn't have his greatness thrust upon him; he earned it.

In him was a concatenation of factors that characterize many members of the Academy: (a) He was born into and raised in an intellectual family. His father had a "library" that young Burkholder devoured. (b) He was a bright boy. (c) He was a prodigious worker as witness the extensive bibliography attached. (d) He was an introvert at heart, a loner if you please. This allowed him the time to work. (e) He was stimulated by his early teachers to pursue science. (f) He had a devoted wife who shared his hobbies, his life, and his lab. She worked as hard in biology as he did and raised three sons besides.

I knew Burkholder in the graduate school at Cornell. I knew him again when I was an adjunct professor in his department at Yale. I always admired "Burkie," even though he was difficult to "know" well.

When he was in graduate school, he compensated for some of his introvert tendencies by joining Gamma Alpha, a graduate student fraternity. There he found another "Burkie" (no relative), whom I also knew. This may not have helped Paul too much, for the second Burkie was a very tall man and Paul was a little short. Promptly the two were distinguished as "big Burkie" and "little Burkie." It must be discouraging to be called a "little Burkie." On the other hand, it drives the little Burkies to excell the big Burkies.

At any rate, Paul fought the little-man complex so hard that he was able to put on giant shoes and take giant strides in science.

HIS INTELLECTUAL BASE

The Burkholder forebears, religious refugees from the German section of Switzerland, came to Pennsylvania during its early colonial period. William Rankin Burkholder, Paul's father, was born in 1857, just before the Civil War, on a farm in central Pennsylvania. As a young man, Paul's father and an older brother operated a successful general store in Middleburg. William was small, quick, and very strong, taking delight in wrestling, hunting, and driving fast horses. To play cards and drink hard liquor was not to be scorned either. Money was plentiful and life was full, strenuous, and satisfying.

In some way, William's older brother became convinced that he should forsake this way of life and become a minister in the church. He brought influence to bear on William to do likewise. This was a difficult problem. Could he give up all those things that he enjoyed? The diary he kept at the time bears witness to his struggle. His brother—positive, eloquent, and persuasive—showed him his duty. Once the decision was made, he went off to college, as very few did a century ago. In time he was ordained as a minister in the United Brethren Church by Bishop Wright, the father of the famous Wright brothers. As his son was to do later, he pursued a solitary, dedicated life of service to the small communities in south-central Pennsylvania. There, when he was thirty-nine years old, he met and married Mary Ellen Schubert, a young girl of twenty-one. Their son, Paul, an only child, was born seven years later, on February 1, 1903, at Orrstown, Pennsylvania.

Mary's father, George Schubert, came from Germany as a young boy. Because the children made fun of his accent, he left school to become a farmer, married a girl of French descent, and raised a family of seven children. Mary, the oldest, like her son later, had an alert mind and a desire to become a teacher. Her mother pressured her to stay safely at home, however, to help with the family and the aged grandparents.

In spite of her bitter disappointment, her sense of responsibility won out and she did not rebel. Thus, her formal schooling came to an end and she turned to church work for an outlet. Here, William found her. Typical of ministers' families, they had very little money, but a house was always provided, along with space for a garden and a farm to keep a cow and a few chickens. Here a small boy could grow in an atmosphere of freedom and with no real sense of hardship. The environment, if somewhat spartan, was intellectual and enriched by visitors to the home and church. Paul read and reread his father's library, consisting mostly of books on religious subjects. Sundays he spent in church, where three times a day he listened to his father's sermons or found the time well spent in meditation.

He understood what his father was trying to do and admired him for his tireless, if often frustrating, efforts to help the people in their individual, everyday problems and to keep the churches growing and active. Paul knew that the basic principles were right, but there must be more than this. Questions were left unanswered, and Paul went out to find the answers.

School and learning were important. Rightly or wrongly, he felt that he was not so bright and must work extra hard to compensate. He took full advantage of the knowledge exhibited by the schoolmasters of the little village schools. Summers, while still very young, he started working for farmers, weeding and picking vegetables and fruit and helping to harvest hay and grain. He came to be known as swift and dependable, so there was no problem in procuring work. Always he saved the money he earned. His spare time was spent roaming in the mountains with his gun, shooting small game for food, and enjoying nature.

Ready for high school, he walked three miles to a train that took him to Chambersburg and three miles home every day. This schedule kept him busy from early until late, but he enjoyed the work and did well in his classes.

COLLEGE DAYS

In 1920 he enrolled in Dickinson College in Carlisle, Pennsylvania. His classes ranged over a great variety of subjects as available in a small liberal arts college. He worked in the library for expense money. He appreciated this easy access to the books and he used them to good advantage. Like many boys, he worked summers as a laborer.

During his four years at Dickinson, he decided to become a botanist. This decision was influenced no doubt by his early and continuing interest in plants. In 1949 Dickinson College recognized his work with an honorary D.Sc.

GRADUATE SCHOOL

At Cornell, he came under the enthusiastic tutelage of O. F. Curtis and Louis Knudson and almost automatically became a plant physiologist. Of his contemporaries who took plant physiology with him at Cornell, at least four, including himself, were later elected to the National Academy of Sciences.

Cornell was surely the happy hunting ground for biologists. There was the science in the laboratory, but the campus and surrounding hills were laced with gorges through which streams cascaded down to the lake from "far above Cayuga's waters"—to quote the old Cornell song.

What vegetation to study! It was different on the sunny north side from the shady south side of the gorge. Paul's Gamma Alpha house was on the south edge of Cascadilla gorge. He could collect specimens for his classes almost at his doorstep, or he could go across campus to the Fall Creek gorge to collect plants on the north edge or swim in Beebe Lake and be eyed by the Tri Delta girls from their house on the rim above. And besides he helped the brothers make wine during prohibition days. He was surely a chip off his father's block.

Like all graduate students in the twenties, before National Science Foundation student fellowships, he needed money. A job offer introduced him to the excitement of aquatic biology.

The New York State Conservation Department offered him a summer job in the limnological survey of the state watersheds, beginning with the Cayuga Lake basin, with which he was already familiar. He did the phytoplankton studies. He and his colleagues worked hard, had fun, earned money, and published their papers. This work was to influence him throughout the rest of his life.

THE DEPRESSION

He received his Ph.D. in 1929, the year of Black Friday and the collapse of the stock market, but it did not discourage him. He was able to continue with the limnological survey. It was extended to Lake Erie in cooperation with the Buffalo Museum of Natural Sciences, where he became a curator of biology and continued plankton studies on the lake. The government boat, *Sheerwater,* manned by a discrete crew and carefree young scientists, came to be known to the "rum runners" on Lake Erie as a friend in time of need. There were adventures aplenty on the waters and opportunities for firsthand observation of an epic in our history. Buffalo society added to the fun and frolic.

While at the Museum, he planned and installed exhibits and participated in the teaching program. Continuing his plankton studies, he spent one summer working in northern New York waters and another working in some lakes of the upper Hudson watershed. The last summer he did a study of the phytoplankton of Frenchman's and Penobscot bays, in Maine, near Bar Harbor.

In 1930 he married Lillian Miller, a lady who shared his biological enthusiasms for the rest of his life and who survives him. With the acquisition of a wife and a little later a son, Franz, life took on a more serious aspect. He wished to return to a more academic environment. In the meantime the depression had deepened and no jobs were available. A National Research Council Fellowship saved him, however, and he spent two rewarding years, one at Harvard, where a second son, Peter, was born in 1935, and one at Columbia, where he came under the influence of E. W. Sinnott, a member of the Academy. While at Columbia, he took a course in bacteriology. This became another influence on the rest of his career.

TO CONNECTICUT COLLEGE

Even after two fellowship years, jobs were still scarce, but one appeared in the nick of time. A young Ph.D., George Avery, had recently begun teaching at the Connecticut College for Women, at New London. (This college has now been "liberated" to Connecticut College and men go there.) Being alone among all those women, Avery shouted for help to Sinnott at Columbia. Sinnott sent him Burkholder.

Burkholder promptly made his late-blooming course in bacteriology pay off. He taught the girls about germs, but now his interest in plant physiology returned. Avery started his work on plant hormones at Connecticut College and since it was a timely subject, they collaborated on work in this field and produced a book on it. The next three years yielded an impressive return in papers published.

BACK TO AQUATIC BIOLOGY

While at New London, Paul purchased a small farm near Falmouth, Massachusetts, on Cape Cod. Falmouth harbor was near, and so Burkholder bought a sail boat and returned to the water. Wood's Hole was near, too, and here was the opportunity to return to the study of the creatures that live in the water.

This lasted only three years, however. In 1938 Dr. Rickett left the post of plant physiologist at the University of Missouri and the boy from the hills of Pennsylvania went to the hills of Missouri. This seemed a logical move. A large well-staffed agricultural school provided many interested students for the botany courses. Despite much teaching to be done, he managed to carry on research work, mostly in plant nutrition. Here the third son, Karl, was born in 1940. When he left, Dr. Tucker, chairman of botany, jokingly said, "I will have to hire two men to take your place, a day man and a night man."

A YALE MAN

In 1940 Sinnott entered his life again. Dr. Sinnott went to Yale as chairman of the botany department and asked Burkholder to go with him as plant physiologist.

Botany at Yale was at an all-time low ebb, partly because of the depression and partly because of a failure to bring in new faculty members, but mostly because the university had no agriculture program to send the students of botany on to jobs. Zoology was strong at Yale because there was a medical school to beckon the students from that department.

The next few years were spent in building up the faculty of botany. Norman Giles, a new Ph.D. in plant genetics, came from Harvard; Reader came as a taxonomist in charge of the herbarium. Ed Tatum brought his *Neurospora* work and Dave Bonner followed. Burkholder taught a new course in microbiology that became very popular. Galston came to teach plant physiology. Paul Sears set up a program in conservation.

The department was on the way. Graduate students appeared. Joshua Lederberg, who discovered sex in bacteria; Ed Adelberg, now head of microbiology at Yale; Guillard at Wood's Hole; Sy Pomper; Lou Nickell; Ina May Martin from Jamaica; Joyce and Ralph Lewin; and many others received degrees from the department.

The years were good at Yale. Burkholder was made Eaton professor of botany. His research moved apace, especially in microbiology, production of vitamins by yeasts, and production of antibiotics by lower fungi.

CHLORAMPHENICOL DISCOVERED

Burkholder soon made a dramatic discovery. Fleming's penicillin had arrived during the war. Penicillin came from a fungus. What other antibiotics from microorganisms could be found? Waksman had discovered streptomycin and received the Nobel Prize. Burkholder soon discovered chloramphenicol in an actinomycete, which he isolated from a Venezuelan soil. The Parke-Davis Company developed, purified, and synthesized it.

Chloramphenicol was discovered just in time to save the lives of soldiers in the Korean War from scrub typhus, a classical killer of soldiers in wartime.

Chloramphenicol is a dramatic case in biology for another reason. Chemists like to chlorinate and nitrate compounds. In 1947, when chloramphenicol was discovered, dogma said that no organism could do these chemical tricks. They couldn't attach a chlorine or a NO_2 group to carbon as chemists could. Chlorine and nitro were the substituents chemists used to make killers for organisms—note dinitrophenol wood preservative or chlorinated hydrocarbon insecticides.

Burkholder's actinomycete proved the dogma wrong. Not only could it chlorinate a compound, it could nitrate it, too; and besides it could put both substituents in the same molecule.

This only proves that chemists were a million years late in learning these tricks.

A PALACE REVOLUTION

In the meantime, Yale botany was not all serene. Burkholder became the unfortunate victim of a palace revolution. Sinnott had held a brilliant group of thinkers together, but then he moved up to be dean of the Sheffield Scientific School. Having always supported Burkholder, Sinnott made him chairman of the botany department, but Burkholder had no liking for scientific politics and had not developed administrative skills.

Severe unhappiness showed in the microbiological contingent. And Burkholder didn't really hold a union card in microbiology. He came into it late as a plant physiologist. This problem was tied to the national picture as well. The bacteriologists of the country had arrogated to themselves the term microbiology. People working with other microorganisms like protozoa, fungi, and one-celled algae were low in the pecking order; and Burkholder's specialty was fungi.

Bacteria are mostly dealt with in two university disciplines—medicine and agriculture. Yale had no agriculture. Medicine, therefore, became a magnet for the new microbiology created by Burkholder at Yale in the botany department. And so it was natural for friction to develop within classical botany. Whereupon, botany lost another child that it had begotten.

The explosion was severe. Tatum left, Galston left, Naylor left, Burkholder left, and Bonner deserted the botany department for the medical school and a new department of microbiology. It seems ironical that Bonner was later elected to the National Academy of Sciences through the botany section, not through microbiology.

GEORGIA BECKONS

Georgia beckoned to Burkholder and Burkholder listened. He labored strenuously there to build up science in general and microbiology in particular, but it went too slowly for him.

The Sloan-Kettering Cancer Institute in New York thought so, too. Cornelius Rhoades, its director, suggested to George Avery, by then director of the Brooklyn Botanic Garden, that Burkholder could be moved. He could be and was.

The next five years at the Garden, with his old friend George Avery and with Sloan-Kettering cooperation, saw an intensive program of screening soil organisms for antibiotics that might have the potential for chemotherapy of cancer.

There is a fascinating sequel to the Sloan-Kettering phase. They kept Burkholder's cultures "on deposit" when he left. Rhoades chanced to mention this to Jasper Kane, then a research executive with the Pfizer Company. Kane procured the cultures for futher screening. In one of these was the fungus that produces Terramycin for Pfizer.

BACK TO COLUMBIA

Since the cancer idea did not pay off, Burkholder returned in 1961 to Columbia and to his old love for the sea and marine biology. Perhaps the inhabitants of the sea could provide the hoped-for antibiotics that fungi from the worked-over soil could no longer supply. He affiliated with the new biology laboratory in the Lamont Geological Observatory at Columbia, situated up the Hudson River from New York. He was no longer landlocked. He had come full circle back to the organisms in the water.

He spent a season in the Antarctic working with Sieburth on his problems. Why do penguins have so few bacteria in their intestines? Sure enough, as expected, an antibiotic produced by a phytoplanktonic organism was passed in the short food chain to krill and on to the penguins, in which it inhibited growth of bacteria in the gut.

Burkholder marveled at the plankton growing so thick in the sheltered waters of the Antarctic. This was the foodstuff that supported the whalers for so many years.

He isolated bacteria from the waters of the Antarctic Sea and from Atlantic waters, from the Gaspé Peninsula to Puerto Rico. He learned to scuba dive and examined corals, sponges, and seaweeds from the Caribbean to the Great Barrier Reef of Australia and the Philippines for possible sources of chemotherapeutic drugs.

At the age of sixty-five, he retired from his Lamont Geological Observatory post and went to the University of Puerto Rico as a professor of marine biology at its laboratory in La Parguera and lastly to the College of the Virgin Islands. In both locations he taught graduate students and continued to study the beautiful life in the warm seas.

He was still hard at work at marine biology when leukemia, a disease for which he had attempted to find a cure, suddenly struck him down. He died on August 11, 1972, and thus was closed the life of a very productive biologist. He couldn't lick cancer, but cancer licked him. He came close to being struck down with his boots on, as he surely would have preferred.

Dr. Burkholder is survived by his wife of forty-two years, Lillian, and by three sons, all in scientific endeavors. Franz Burkholder, formerly a computer programmer with Minneapolis-Honeywell now has his own company in Boston. Peter Burkholder is a professor and chairman of the department of pathology in the hospital of the University of Wisconsin. Karl Burkholder is a clinical psychologist in the school system of Arlington Heights, Illinois.

AN OVERVIEW

George Avery has said to me that Burkholder was an imaginative and inspired teacher, always colorful in his lectures. Richard Benoit, one of Burkholder's former students has expressed my thoughts for an overview better than I could. He wrote me, "Dr. Burkholder truly believed that the business of science was discovery and he was essentially an explorer, like the great botanist–explorers of the generations before his own." Even as a boy he explored the mountains of Pennsylvania. As a graduate student, he explored the gorges and forests around Ithaca. He explored Lake Erie for phytoplankton and later the waters of the Atlantic, the Caribbean, the South Pacific, and Antarctica.

In between, he explored soils for antibiotics and discovered chloramphenicol. He explored land and water plants and hog stomachs for vitamins—zeroing in on vitamin B_{12}, the therapeutant for pernicious anemia. Bushwhacking his way through a forest of hog and human stomachs, he found out how to administer B_{12} orally instead of intravenously.

Benoit continues, "Others may remember Burkholder for his successes; I will remember him for his seeking, his exploring. He did not always reach his goal, but he carried the light far up the mountain."

I agree with Benoit. Science has lost a great frontiersman!

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KEY TO ABBREVIATIONS

Am. J. Bot. = American Journal of Botany
Ann. N.Y. Acad. Sci. = Annals of the New York Academy of Sciences
Appl. Microbiol. = Applied Microbiology
Arch. Biochem. = Archives of Biochemistry
Bot. Gaz. = Botanical Gazette
Bot. Mar. = Botanica Marina
Bull. Buffalo Soc. Nat. Sci. = Bulletin of the Buffalo Society of Natural Sciences
Bull. Mar. Sci. Gulf Caribb. = Bulletin of Marine Science of the Gulf and Caribbean
Bull. Torrey Bot. Club = Bulletin of the Torrey Botanical Club
J. Antibiot. = Journal of Antibiotics
J. Bacteriol. = Journal of Bacteriology
J. Org. Chem. = Journal of Organic Chemistry
Limnol. Oceanogr. = Limnology and Oceanography
Mar. Biol. = Marine Biology
Plant Physiol. = Plant Physiology
Proc. Natl. Acad. Sci. = Proceedings of the National Academy of Sciences
Spec. Sci. Rep. Fish. = Special Scientific Report, Fisheries

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