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FREDERIC C. BARTTER

1914—1983

A Biographical Memoir by
JEAN D. WILSON AND CATHERINE S. DELEA

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September 10, 1914–May 5, 1983

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FREDERIC CROSBY BARTTER was born in the Philippine Islands on September 10, 1914, and died in Washington, D.C., on May 5, 1983, of complications resulting from a cerebral hemorrhage that occurred while he was attending the annual meeting of the National Academy of Sciences. With his death, clinical science lost one of its most imaginative investigators and charismatic personalities. His achievements were both broad and deep. He devoted a major portion of his career to investigating the interrelation between the kidney and various endocrine systems and contributed to aspects of clinical science as diverse as chronobiology, the physiology of taste and smell, and mushroom poisoning. At the National Institutes of Health he collaborated with more than a hundred investigators (friends), enriching the lives and scientific stature of each through his ability to stimulate, guide, and enhance the talents of others.

EARLY LIFE

George Bartter, an Anglican minister from England, and his wife, Frances Buffington, an American teacher, had two children—George and Frederic—both born in Manila and raised in the remote mountain village of Baguio, Philippine Islands, which became the family home. Bartter's early edu-

cation was supervised by his father, his mother (a Smith college graduate and classical scholar), and priests at a nearby Catholic monastery. Early in life he acquired a love of poetry and good writing and, in later years, was able to recite from memory long passages from Shakespeare, St. Teresa, and Rupert Brooke. At age thirteen he and his brother were sent to the United States and enrolled at the Lennox School in Lennox, Massachusetts, from which he graduated in 1930. He returned to the Philippine Islands for a year and worked in the English school before entering Harvard College. After receiving a Bachelor of Arts degree in 1935, Bartter spent a year in the Department of Physiology, Harvard School of Public Health. His interest in an investigative career and his first paper on lymph sugar stemmed from this experience. He obtained his M.D. degree from Harvard Medical School in 1940 and spent his internship at Roosevelt Hospital in New York from 1941 to 1942.

ACCOMPLISHMENTS IN BIOMEDICAL RESEARCH

Bartter's first paper after graduation from medical school resulted from his service as an officer in the U.S. Public Health Service during World War II. The paper concerned plasma volume and the speed with which plasma is reconstituted after donation of blood, the control of blood volume being an important topic throughout his subsequent career. The Public Health Service then assigned him to the Pan American Sanitary Bureau to investigate the physiology of parasitic diseases, one result of which was a pioneering study of the treatment of onchocerciasis.

There can be no doubt that both the style and the focus of his investigative career were profoundly influenced by his subsequent association with Fuller Albright, first as a research fellow from 1946 to 1950, then as a junior member of the faculty at the Massachusetts General Hospital and the

Harvard Medical School. Many have described the unique environment Fuller Albright created on Ward Four at the Massachusetts General Hospital, including Bartter, who wrote several moving accounts.[1]

At least three distinguishing features of Bartter's work stem directly from his relationship with Albright. First, he performed virtually all of his work directly on humans. Indeed, his bibliography of over 400 papers lists only a few studies using experimental animals and fewer still experiments in vitro. Though clinical physiologists usually draw clinical deductions from animal studies, Albright, whose model Bartter followed, deduced physiological principles from physiology deranged by the disease process. Secondly, Bartter used few patients in each study, but every patient was studied intensively over a long period of time with the most advanced methodologies and techniques. Finally, Bartter benefitted from his mentor's remarkable breadth of interests that encompassed electrolyte and renal physiology, endocrinology, intermediary metabolism, the control of blood pressure, biological rhythms, and neurophysiology.

The last of a school of clinical investigation built on the metabolic balance technique, Bartter was yet uniquely adept at applying new technologies to in vivo studies, from isotope dilution to radioimmunoassay procedures.

During his years with Albright, Bartter developed a number of interests that would continue throughout his career: the metabolic effects of ACTH in man, parathyroid pathophysiology and bone metabolism, the control of blood volume in disease, and the metabolic effects of androgens, estrogens, and adrenocortical steroids in various disorders.

An outstanding example of Bartter and Albright's joint

[1] See "Fuller Albright," in *The Massachusetts General Hospital, 1955–1980* (Boston: Little Brown & Company, 1981), p. 86; and "Fuller Albright," *Endocrinology* 87 (1970):1109.

creativity was their deduction that the common virilizing form of adrenal hyperplasia is fundamentally a type of adrenocortical insufficiency arising from a metabolic error in the biosynthetic pathway for cortisol. To compensate for the deficiency in cortisol secretion, they reasoned, the pituitary secretes excessive quantities of ACTH leading to excessive secretion of other classes of adrenal steroids by the adrenals themselves. Bartter and Albright proved their thesis by treating affected patients with cortisone to correct the hypersecretion of virilizing steroids—undoubtedly the single greatest stroke of genius in understanding and controlling adrenal hyperplasia.

In 1951, Bartter's move from Boston to the National Institutes of Health, initially in Baltimore and then Bethesda, broadened the focus of his studies of the pathophysiology of disease. When "electrocortin" (aldosterone) was discovered in 1953, it was immediately apparent to Bartter that this new hormone must be of critical importance in cardiovascular-renal physiology. He turned his attention to determining its role in health and disease and the factors controlling its secretion. Without neglecting the importance of other aldosterone regulatory factors, Bartter, together with Grant Liddle, reasoned that extracellular fluid volume is a major determinant of aldosterone secretion. This deduction ultimately led several groups to the discovery that the aldosterone regulatory influence of extracellular volume is mediated by the renin-angiotensin system.

In 1960, Bartter described the syndrome of hyperplasia of the juxtaglomerular complex—in which hyperaldosteronism and hypokalemic alkalosis coexist with normal blood pressure: now commonly termed Bartter's syndrome. His findings added to the growing body of evidence that adrenal cortical secretion is influenced by the renin-angiotensin system. He further proposed a hypothesis for the paradox of

normal blood pressure in the presence of high concentrations of aldosterone and angiotensin, a paradox still being investigated today.

Adrenal hyperplasia, with all its complexities, held a continuing fascination for Bartter. He realized that a third of all the patients he studied with primary aldosteronism also had adrenal hyperplasia. Originally it was hoped that plasma renin determinations might differentiate between aldosteronism produced by tumor from that produced by hyperplasia. The low plasma renin values measured in several patients with proven adrenal hyperplasia suggested that, in these patients, *all* adrenal tissue responds to a tropic stimulus other than ACTH or the renin-angiotensin system. This, too, continues to be an active field of investigation.

While many of the seventy papers on calcium and phosphorus metabolism coauthored by Bartter relate to the diagnosis and treatment of hyperparathyroidism, pseudohypoparathyroidism, and metabolic bone diseases, several significant studies deal with the renal handling of phosphorus and calcium under the influences of parathyroid hormone, vitamin D, large doses of phosphate, and calcium infusions. Bartter's laboratory also explored the physiology of thyrocalcitonin and its relation to disease states, the solubility and composition of bone mineral, and the gastrointestinal absorption of calcium and its role in metabolic diseases. In the late 1960s he and Charles Y. C. Pak began a pioneering series of studies on the classification, pathogenesis, and treatment of kidney stones.

During these years at the NIH, Bartter's studies covered a broad range of metabolic topics: renal concentrating mechanisms, steroid-hormone binding and transport, urinary acidification mechanisms, regulation of aldosterone biosynthesis, the effect of adrenal hormones on taste and auditory thresholds, vitamin D metabolism and action, phosphorus

depletion, mechanisms of edema formation, cystine metabolism, magnesium metabolism, radiographic measurements of bone minerals, prostaglandin and catecholamine metabolism, and collagen formation in bone. The common theme in all these studies was Bartter's passion for analyzing the disease process.

A highlight of his investigative career came in 1957, when—with William B. Schwartz of Tufts University—he described the syndrome of inappropriate secretion of antidiuretic hormone (ADH, or vasopressin). Hyponatremia and renal sodium loss unrelated to renal or adrenal disease were seen in two patients with bronchogenic carcinoma. The data from a series of studies of these patients suggested overexpansion of the body fluids, probably as a result of sustained, inappropriate secretion of ADH. Bartter and Schwartz characterized this clinical entity, now known to occur in a variety of pathophysiological settings, in a trenchant series of clinical experimental and didactic studies developed over more than two decades. The syndrome is found with various tumors; in disorders affecting the central nervous system or the lungs; and in adrenal, thyroid, or pituitary insufficiency. It is now known that the tumors produce an antidiuretic substance directly and that some of the other disorders are associated with an abnormal release of ADH from the pituitary gland. From its immediate impact upon medicine, Bartter's description of inappropriate ADH secretion was perhaps his most important discovery.

During the last decade of his scientific career, Bartter focused on the control of blood pressure and the derangements that underlie the hypertensive disorders of man—a line of investigation that continued after his 1978 move to the University of Texas Health Science Center in San Antonio and was cut short by his untimely death. It is an irony that he discovered his own hypertension during these studies.

PERSONAL QUALITIES

Fred Bartter's curiosity and quest for intellectual expansion extended well beyond his professional interests. He had a great love and knowledge of music and sang with several musical groups, an interest he shared with his family. A devotee of mathematician and philosopher Alfred North Whitehead (under whom he studied), he read widely in philosophy and poetry. He was a perpetual student who insisted, both in his public speaking and writing, that clarity of expression reflects clarity of thought. He was a strict adherent of correct grammar, and everyone who worked with him became aware of his meticulous attention to detail. Yet his subtle sense of humor, his joy in and excitement about life on the day-to-day level, made him particularly endearing. His warmth and sensitivity gained him the respect and loyalty of his patients, whom he treated as an integral part of the investigative team. Delighting in the diagnostic pursuit of a disease, he yet never lost sight of the person.

One of Bartter's many interests deserves special comment. During a summer vacation he picked up a book belonging to his mother-in-law, who had been a botany major at Smith College, about mushrooms. Its beautiful illustrations and the complex classification system of species and subvariants fascinated him, and he began looking for mushrooms in the woods and lawns back home. Pursuing this subject with the same intellectual vigor he applied to his work, Bartter became an authority on the subject. He could identify more than 200 varieties, and for many years he combined his avocation with his professional career, giving lectures on mycology and on the symptoms and treatment of mushroom poisoning.

Following Czech reports of lipoic acid as an antidote for *Amanita* mushroom poisoning, Bartter—and Charles Becker of the University of California, San Francisco—obtained an

investigational permit from the Food and Drug Administration to use lipoic acid as a treatment for patients who had eaten supposedly lethal mushrooms.[2] The toxins of the "Death Caps" (or "Destroying Angels," as deadly *Amanitas* are called) attack the liver, causing hepatitis and acute yellow atrophy that may progress to liver failure. Bartter and Becker treated many patients who had ingested the mushrooms, and were therefore at risk, with the agent. Although the precise therapeutic role of lipoic acid—as opposed to other supportive features of the experimental regimen—was never clarified, the treatment was successful. Bartter's experience with treating mushroom poisoning enhanced his zest as a mushroom collector, and he delighted in instructing others and in serving as a resident expert on mushroom identification.

HONORS

Fred Bartter was a member of numerous professional and scientific societies, including the Endocrine Society, the American Society for Clinical Investigation, the Association of American Physicians, the Royal Society of Medicine, the Royal College of Physicians of London, the Peripatetic Club, and the National Academy of Sciences, to which he was elected in 1979.

He received the Sandoz Contemporary Man in Medicine Award, the *Modern Medicine* Distinguished Achievement Award, the Fred C. Koch Award of the Endocrine Society, and the Meritorious Service Medal from the National Institutes of Health. These honors were followed by election as the 1981 honorary faculty member of the Epsilon Chapter of Alpha Omega Alpha—the medical honorary society at the

[2] See B. J. Culliton, "The Destroying Angel: A Story of a Search for an Antidote," *Science* 185(1974):600; and "Dr. Bartter Tries Thioctic Acid as Antidote to Fascinating Fatal Wild Mushrooms," *NIH Record* (November 4, 1975):6.

University of Texas Health Science Center in San Antonio—and, in 1982, election as an Honorary Fellow of the American College of Cardiology. In 1982, the American College of Physicians conferred on him the John Phillips Memorial Award "in recognition of his outstanding career as an investigator and teacher and for his memorable contribution to the understanding of hormonal regulation of renal function and salt and water homeostasis."

Bartter was also asked to give many honorary lectures, including the 1980 Arthur B. Corcoran Award of the High Blood Pressure Council and the 1982 Fuller Albright Lecture of the Peripatetic Club. The San Antonio Veterans Administration Medical Center named its Bartter Clinical Research Center in his memory—a posthumous tribute that surely would have pleased him.

Fred Bartter is survived by his wife, the former Jane Lillard; three children, Frederic C. Bartter, Jr., of Baltimore, Dr. Thaddeus C. Bartter of Boston, and Mrs. George (Pamela) Reiser of Lincoln, Massachusetts; and three grandchildren.

Fred Bartter will be remembered by his associates for his persistence, imagination, endless curiosity, and bottomless fund of knowledge. The ability to perceive a disease in a set of slightly aberrant numbers, the unshakable faith that, in metabolic balance studies, what goes in must eventually come out, and the optimism that all is eventually discoverable—this is "Bartter's Syndrome," and we are all the better for having been exposed to it.

CHRONOLOGY

POSTGRADUATE TRAINING AND FELLOWSHIPS

1941–1942 Medical intern, Roosevelt Hospital
1942–1945 Medical officer, U.S. Public Health Service
1945–1946 Staff member, Laboratory of Tropical Diseases, National Institutes of Health
1946–1948 Research Fellow in Medicine, Massachusetts General Hospital
1968–1969 Overseas Fellow, Churchill College, University of Cambridge

PROFESSIONAL APPOINTMENTS

1948–1950 Assistant in Medicine, Massachusetts General Hospital
1951 Associate in Medicine, Massachusetts General Hospital
1951–1973 Chief, Endocrinology Branch, National Heart and Lung Institute, National Institutes of Health
1970–1976 Clinical Director, National Heart and Lung Institute, National Institutes of Health
1973–1978 Chief, Hypertension, Endocrine Branch, National Heart and Lung Institute, National Institutes of Health
1958–1978 Associate Professor and Professor of Pediatrics, Howard University
1960–1978 Associate Professor and Clinical Professor of Medicine, Georgetown University
1978–1983 Professor of Medicine, University of Texas Health Science Center, San Antonio, and Associate Chief of Staff for Research, Audie L. Murphy Memorial Veterans Administration Hospital, San Antonio

MEMBERSHIPS

Endocrine Society
Laurentian Hormone Conference
American Society for Clinical Investigation
Association of American Physicians
Salt and Water Club

Peripatetic Society
American Physiological Society
Royal Society of Medicine-Endocrinology Section
Royal College of Physicians of London
National Academy of Sciences
Alpha Omega Alpha

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1949

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1950

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1951

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1953

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1956

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1958

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1959

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1973

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