NATIONAL ACADEMY OF SCIENCES

JAMES AUGUSTINE SHANNON

1904—1994

A Biographical Memoir by

THOMAS J. KENNEDY, JR.

Biographical Memoir

Courtesy of the National Institutes of Health

JAMES AUGUSTINE SHANNON

August 9, 1904–May 20, 1994

BY THOMAS J. KENNEDY, JR.

JAMES AUGUSTINE SHANNON died suddenly on May 20, 1994, just short of his ninetieth birthday at his residence in the Church Home in Baltimore, Md., of a ruptured abdominal aortic aneurysm. Survivors included his daughter, Alice Shannon Stolzberg, M.D.; his son, J. Anthony Shannon; ten grandchildren; ten great-grandchildren; and a sister, Miriam Futterlin. His spouse, Alice M. Waterhouse, M.D., died in 1976.

Born in New York City, Shannon received his primary education in the New York City public school system; his secondary education was at St. Augustine's Academy and Brooklyn Prep and College, both in Brooklyn, N.Y. He received a baccalaureate from the College of the Holy Cross in 1925 and an M.D. from the New York University School of Medicine in 1929. Following residency training with the New York University (NYU) Medical Services at Bellevue Hospital, he matriculated as a graduate student in the NYU Department of Physiology in 1931 and was awarded a Ph.D. in 1935. He subsequently served on the faculty of the NYU School of Medicine in the departments of physiology (1931-40) and medicine (1940-46).

Shannon's first scientific interests were in the physiology of the kidney. Until no more than a decade before he en-

tered the field, the level of understanding of kidney functions was primitive. Speculations and theories based principally on inference from morphology had enjoyed until about that time both currency and respectability, absent scientific evidence either to support or to resolve the conflicts between them. However, during the mid-1920s, analyses of the chemical composition of extremely small samples of fluid obtained by micropuncture from individual kidney tubules (i.e., nephrons) by A. Newton Richards and his colleagues in the Department of Physiology at the University of Pennsylvania, had demonstrated that, under the force of the hydrostatic pressure of the afferent arterial circulation to the nephron's glomerulus, an ultrafiltrate of plasma entered Bowman's capsule and the proximal tubule, whence water and solutes from the ultrafiltrate were reabsorbed by the tubular epithelial cells and returned to the post-glomerular circulation. At about the same time, E. K. Marshall and his colleagues in the Department of Pharmacology at Johns Hopkins University had provided convincing data, especially from experiments on aglomerular fish, that the tubular epithelium could also excrete compounds (i.e., transport them from the peritubular blood across the tubular epithelium into the tubular lumen). The Department of Physiology at NYU, guided by Homer W. Smith's insightful thinking, had begun to approach the quantitative study of kidney function in the intact experimental animal and in man. This groundwork of experimental studies triggered a great increase in interest in this area of physiology, so that Shannon matriculated as a graduate student in a department that would shortly become (and remain) world renowned and in a field that would engage many of the finest minds in physiology for several decades.

Shannon's publications in the field of renal physiology began in 1932 and continued for about a decade. It is ap-

parent that he rapidly achieved autonomy as an investigator. Of his twenty-odd early papers, only the first four—all submitted for publication during his first year in graduate school—and one other, in 1935, included coauthors. It was not until 1938 that the names of junior colleagues began to appear on his publications.

During the decade of the 1930s, principally in Smith's laboratory at NYU, the quantitative foundations of modern kidney physiology were established. The first and most significant contribution was the development of methods for the precise measurement of the glomerular filtration rate (i.e., the volume per unit time of plasma ultrafiltrate that, under the hydrostatic pressure in the arterial circulation, enters the kidney tubules and flows toward the urinary bladder) in a variety of species—amphibians, reptiles, birds, and mammals, including Homo sapiens. The availability of an accurate measure of the glomerular filtration rate provided for the first time the capability to examine the quantitative dimensions of the reabsorptive and excretory functions of the renal tubular epithelium, as plasma constituents in tubular urine were transported along, as well as against, chemical and electrochemical gradients.

Employing glomerular filtration rate as the standard of reference, Shannon proceeded to illuminate many of the key features in the kidney's repertoire of mechanisms responsible for maintaining the constancy of the composition of an organism's body fluids. Passive reabsorption from tubular lumen back across the tubular epithelium to the peritubular blood and thence to the general circulation, as typified by that of urea, took place by simple diffusion along the chemical concentration gradient for urea, created by the reabsorption of water. Active reabsorption, exemplified by glucose, was characterized by a limitation on reabsorptive capacity of tubular epithelial cells that was large enough so

that the urine was glucose free within the normal range of plasma glucose levels, but that, once exceeded, accounted for glucosuria. Active secretion illustrated by the dye phenolsulfonephthalein (phenol red), the rate of whose transport from the post-glomerular peritubular blood across the tubular epithelium into the tubular lumen, was, as is the case of glucose, subject to a measurable limit. Shannon's research also provided important insights into the mechanisms of tubular water transport and the influence of hypophyseal antidiuretic hormone on that process.

Shannon's work as a renal physiologist was notable for its careful and sophisticated framing of experimental questions; the broad range of its explorations of the phylogenetic evolution of excretory function; the elegance of its experimental design; the rigor of its experimental methodology; the precision and reproducibility of the experimental observations; and for the innovative insights reflected in the interpretation of the data.

After a decade in the NYU Department of Physiology, as a pre-doctoral student and then a faculty member, Shannon transferred to the university's Department of Medicine in 1940 at the academic rank of assistant professor. He was promoted to associate professor the following year, and assumed responsibility for directing the 100-bed NYU Research Service—an extraordinary research resource for the times—at a newly constructed New York City institution, the 1600-bed Goldwater Memorial Hospital on Welfare Island in the East River.

Shannon's original plan for the research program at this venue was to extend his prior studies in renal physiology, especially to normal humans, and to explore the pathophysiology of human kidney disease. Indeed, he recruited appropriate staff and made a significant start on the program. But studies in progress and future plans were abruptly

interrupted by exigencies arising out of the outbreak of World War II. Consequently, the NYU Research Service with its supporting laboratories, became the center for the clinical evaluation of new antimalarial drugs, a critical and urgent need for which had suddenly materialized. Very early in the war, Japanese conquest of Southeast Asia, the world's major quinine-producing area, had cut off the supply of that drug, then considered by far the most effective agent for treating a severe and seriously incapacitating disease that was intensely endemic throughout a huge region of the world that U.S. troops were expected to invade in the very near future.

The search for new and better antimalarial agents became, in short order, a major national effort, coordinated and funded at first by the Committee on Medical Research of the National Research Council and subsequently by the Board for the Coordination of Malaria Studies of the Office of Scientific Research and Development. The board operated through four panels for organic synthesis, biochemistry, preclinical pharmacology, and clinical trials, with the latter panel chaired by Shannon. As newly synthesized candidate antimalarials emerged from avian and simian malaria screens and animal toxicity evaluations, the most promising were administered in human subjects to assess their pharmacological characteristics, including toxicity, and, in the case of selected ones, to examine their efficacy against blood- or mosquito-induced malaria infections. Most of the pilot clinical pharmacology and therapeutic trials of the national malaria research program were carried out at Goldwater or its satellites—units at Bellevue and Manhattan state hospitals, at the Rahway Reformatory (Rahway, N.J.), and at the U.S. Army's Greenhaven (N.Y.) Disciplinary Barracks—under Shannon's direct supervision. But as the chair of the Panel on Clinical Trials, he also arranged,

coordinated, and supervised similar research activities in a nationwide network of participating institutions.

Major contributions of the Shannon-directed wartime malaria research effort included the development of highly sensitive and accurate techniques, principally photofluorometric, for measuring concentrations of drugs (cinchona alkaloids, 9-amino acridines, 4-amino quinolines, 8-amino quinolines, and several other classes) in blood, urine, and tissues; elucidation of the human pharmacology of these compounds; demonstration that in the treatment of malarial infections with quinine there was a critical level of drug in plasma above which parasitemia (and symptoms) disappeared for a finite interval and below which they cleared only evanescently or minimally; based on this observation, the design of a protocol that, when followed, produced a standardized episode of P. vivax, P. malariae, or P. falciparum malaria, reproducibly responsive to quinine when subjects never previously exposed to the disease—either patients with central nervous syphilis or volunteers from conscientious objector or prison populations—were either transfused with blood or bitten by mosquitoes previously infected with one of these strains; adoption of this protocol as the standard to which the responses of new candidate antimalarial drugs could be comparatively evaluated; definition of conditions under which the 9-amino acridine, quinacrine (Atabrine), a known and readily available antimalarial that had fallen into disrepute, was an effective agent for the suppression and treatment of malarial infections; demonstration of the utility of 4-amino quinolines as suppressive agents in the malarias and the identification of chloroquine as the best drug from the group; and the proof that 8-amino quinolines (e.g., pamaquin) was curative by virtue of its effectiveness against sporozoites, the extra-erythrocytic forms of the plasmodium. For several subsequent decades chloroquin

became the drug of choice for the suppression and treatment of malaria until its usefulness was compromised by the emergence of chloroquin-resistant strains of *Plasmodium falciparum*.

The Atabrine studies—conducted during the early days of the war when malarial infections acquired by the combat troops in the South Pacific were seriously compromising the effectiveness of U.S. military operations—had elements of high drama. Once he and his colleagues were able to develop an accurate technique for measuring its concentration in body fluids, Shannon quickly showed that the drug attained therapeutic levels only slowly, because it was extensively taken up in tissues such as the liver. The simple expedient of administering a large initial loading dose to saturate tissue-binding sites resulted in rapid achievement of therapeutic plasma levels of the drug and prompt therapeutic response. This discovery was quickly adopted by the military and it enormously enhanced the capability of U.S. military personnel to operate successfully in malaria-infested areas of Southeast Asia.

The work of Shannon and his coworkers on malaria was summarized in a series of papers in the May 1948 issue of the *Journal of Clinical Investigation*; a more detailed account appeared in the two-volume monograph *A Survey of Antimalarial Drugs, 1941-1945*, edited by F. Y. Wiselogle, which reported on all aspects of the malaria research program of the Committee on Medical Research and the Office of Scientific Research and Development.

For his World War II research on the treatment of malaria, Shannon was awarded the Presidential Medal of Merit in 1948. Although a number of able and creative colleagues collaborated with him in these malaria studies, I feel confident that they would all agree that the lion's share of the credit for the program's success was attributable to Shan-

non because of his drive, imagination and originality on conceptualizing the problems, and for highly effective leadership in a large multidisciplinary endeavor.

When the malaria project ended in 1946 and the arrangements he had struck earlier with NYU to chair its Department of Pharmacology collapsed, Shannon accepted, to the horror and against the advice of friends in academe, the directorship of the Squibb Institute for Medical Research, an entity whose research efforts were dedicated primarily to the interests of a major pharmaceutical manufacturing company. Information on this period of Shannon's career is skimpy. One major goal during his Squibb tenure, I have recently been told by several of his contemporaries at the institute, was to develop a program for antimycobacterial chemotherapy. In fact, streptomycin, the first of the aminoglycoside antibiotics, and isonicotinic acid hydrazide (isoniazid), both antimycobacterial agents, were under development at the institute during this period. Shannon also appears to have encouraged and stimulated research and development efforts on emerging antihypertensive agents, specifically rauwolfia and veratrum alkaloids and on new steroids.

In 1949, to the further dismay of his academic friends, Shannon responded positively to R. Eugene Dyer and Norman H. Topping, then director and associate director, respectively of the National Institutes of Health, who had been importuning him to accept the position of associate director (in charge of research) of the newly created National Heart Institute. The offer presented an unprecedented challenge to build from scratch a large-scale research organization. Shannon's first step was to design the dozen or so major research themes whose pursuit he felt appropriate for the fledgling intramural heart institute: cell biology, chemical pharmacology, cardiovascular physiology, kidney and elec-

trolyte metabolism, natural products chemistry, technical development, and cardiovascular surgery, to name several. He then proceeded to solicit from his vast acquaintance with national and international leaders in these fields the names of the most promising emerging young scientists and to recruit, mostly for laboratory and branch chiefs, but with an ever-open eye for other talent. In addition, in anticipation of the impending opening of NIH's new clinical center (the first hospital facility ever on the campus), he recruited a group of clinical research associates, young physicians who had recently completed residency training in (mostly) internal medicine and who were to be assigned to a program in which they would divide their time between laboratory research under the mentorship of a well-established scientist and the clinical care of research patients. The "charter" staff for the National Heart Institute's intramural program, which Shannon recruited over the next several years, included two who became Nobel laureates, two who later served as directors of NIH, and almost a score of future members of the National Academy of Sciences. Shannon himself was not elected to membership in the Academy until 1965.

In 1952, three years after joining the National Heart Institute, Shannon assumed campus-wide responsibility for the intramural research activities of all the institutes at NIH. His first order of business was to subject the programs of long-established institutes to searching scrutiny to assure himself that high standards of excellence prevailed. Under his guidance the opening of the 500-bed NIH Clinical Center—an event that had engendered no small amount of apprehension within the "old timer" NIH scientific community, because it brought responsibility for the clinical care of sick human beings to an institution that had never engaged in such activity—came off with only a very few minor hitches. The most dramatic event during his tenure as asso-

ciate director occurred in the spring of 1955, when he was called on to spearhead the government's effort to deal with a major crisis precipitated by the appearance of a number of acute cases of poliomyelitis in children recently inoculated with a new polio vaccine. At that time, vaccines were licensed for commercial production by a component of NIH, the Division of Biological Standards. A quick solution to this emergency was imperative, since failure to rectify the situation promptly not only could have severely shaken public confidence in the medical research enterprise as a whole, but might also have resulted in additional infections with further disability and loss of life. His knowledge about and insights into industrial manufacturing processes acquired during his tenure at the Squibb Institute for Medical Research enabled Shannon to discern quickly the cause of the problem and to propose modifications to the manufacturing process to solve it.

While the competence and effectiveness with which Shannon had managed the large Bethesda research enterprise was widely acknowledged as being of the highest order, his handling of the polio vaccine crisis brought his unusual array of competencies strikingly to the attention of the leadership of the U.S. Public Health Service and the Department of Health, Education, and Welfare and made him the obvious candidate to succeed NIH Director W. Henry Sebrell, Jr., when he retired that same year.

Shannon brought to his new responsibilities as director of the National Institutes of Health not only a vision of what he wanted to accomplish, but also several abiding convictions: profound faith in the power of science to transform medicine into a far more effective instrument for improving the human condition; a keen sense that the scope and intensity of the national research effort was pitifully short of what it ought to be; and the persuasion, reached

during the war, that only the federal government had pockets deep enough to provide the resources necessary to mobilize the full scientific potential of the nation. The directorship gave him a position from which he could forcefully promote his concepts about the most desirable direction and magnitude of the future national biomedical research effort.

Shannon quickly identified two major impediments to the realization of his vision: shortages of research space and trained research personnel. The Health Research Facilities Construction Act of 1956 became the vehicle for eliminating the first. The initial awards under the act were made during his first year in office and the program, until it became a casualty of the Vietnam War in 1968, awarded $473 million to fund 1,485 construction projects, which remodeled, replaced, or added about 19 million net square feet of modern laboratory space to the national research space inventory. In this effort, 407 public and private nonprofit recipient institutions matched the federal awards with $635 million of their own funds. Taking inflation into consideration, the total expenditures over the lifetime of the program would equate to more than $5 billion in 1997 dollars. Training programs were expanded rapidly and were reoriented to emphasize scientific rather than clinical training; pre-doctoral training was concentrated progressively in the Division (later the National Institute) of General Medical Sciences. The research career development award and the research career award programs for fostering academic and research careers were soon inaugurated, and in 1964 the Medical Scientist Training Program, leading to dual M.D. and Ph.D. degrees, was established.

Additional changes followed quickly. The effectiveness of the extramural research grant program was enhanced by increasing allowable costs so that by 1969 these, adjusted

for inflation, approached the absolute value of a contemporary award and by creating new types of research awards (program projects and centers) that broadened the scope of a research endeavor and facilitated interdisciplinary research. It was Shannon's strong belief that the federal government as the principal sponsor of biomedical research as a public good—the improvement of the nation's health—should pay the full costs of that research and that the relatively modest financial resources available to academic institutions should not be diverted from educational commitments to underwrite the indirect costs of these federally sponsored research programs. Accordingly, he quietly sought to have limits on indirect costs lifted and eventually succeeded in persuading the Congress to repeal statutory ceilings on indirect costs and to substitute a nominal requirement that grantee institutions share—to an unspecified extent—in the total cost of every NIH-funded research project. Targeted research funded through research contracts was pioneered by the Cancer Chemotherapy National Service Center. In response to perceived special needs, a national system of Primate Research Centers was created, as were other research resource programs, such as general and special clinical research centers and biomedical computer centers. Assistance to statutorily specified categories of grantee institutions in the form of formula grants—originally called general research support and later biomedical research support grants—was initiated in 1960 to empower these institutions to allocate the funds to local projects that had been locally adjudged most likely to advance national biomedical research goals.

Increasing program complexity coupled with expanding opportunities necessitated the creation of new organizational entities: the Center for Aging Research (1957), Division of General Medical Sciences (1958), Center for Research in

Child Health (1961), Division of Research Facilities and Resources (1962), National Institute of Child Health and Human Development (1963), National Institute of General Medical Sciences (1963), Division of Computer Research and Technology (1964), Division of Regional Medical Programs (1966), Division of Environmental Health Sciences (1967), John Fogarty International Center for Advanced Studies in the Health Sciences (1968), transfer of the National Library of Medicine to NIH (1968), and the National Eye Institute (1968).

As director of the National Institutes of Health, Shannon presided over a large institution with a staff of 6,300 when he assumed the position and 13,300 when he retired. He was a hands-on manager with an omnivorous appetite for detail, but he also reposed great confidence in his staff, delegated freely, and encouraged initiative. He knew how to make big organizations work well and how to make his lieutenants act in concert for the common cause. His was always a high morale and happy ship.

The keenness of his insights into what it took to operate a big program responsibly and accountably was a source of frequent surprise and astonishment to his staff, as well as was the level of detail at which he was knowledgeable about the programs of the individual institutes of NIH. Much of his knowledge came from the intense concentration he devoted to the budget: negotiating with institute and division directors, assembling their submissions, defending the NIH submission before hierarchies in the Public Health Serve, Department of Health, Education, and Welfare (later the Department of Health and Human Services) and the Bureau of the Budget (later the Office of Management and Budget), constructing and arguing the appeals, reviewing proposed Congressional testimony of NIH units, and making his own annual statements to the House and Senate.

Shannon was seated at the witness table throughout Congressional budget hearings, reinforcing the testimony of his directors, expanding when the occasion arose on the relationship between the funds requested and the scientific objectives they were intended to underwrite, responding forthrightly to criticism and engaging in serious discussions with committee members who offered suggestions about any aspect of program or process. If asked, as he often was, to help in the preparation of Appropriations Committee reports, he volunteered with alacrity. It is doubtful that any federal official, before or since, has ever been as respected by the Congressional committee that held jurisdiction over a federal agency as was Shannon by the House and Senate legislative and appropriation committees, under whose jurisdiction NIH operated.

By the time Shannon retired in the summer of 1968, the NIH budget of about $65 million he had inherited (adjusted to account for the transfer of the National Institute of Mental Health out of NIH in 1967) had grown twenty-fold to about $1,300 million; stated otherwise, at an average annual rate of about 26%, while the comparable figure for inflation was under 2%. The number of research grants expanded from 3,300 $10,000 awards to 12,600 $50,000 awards. Training grant awards increased five-fold and the dollar value of each tripled. Fellowship awards almost followed suit. Academe had been given a significant lift, and the nation's biomedical research enterprise had been changed beyond recognition.

Much has been written about the fortuitous—and probably never likely to recur—concatenation of events that operated during Shannon's tenure. While the time, place, and circumstances might have been auspicious and while a number of other persuasive and charismatic advocates for a large federal role in the support of research in general and bio-

medical research in particular were actively involved, no one closely associated with the rapid growth of biomedical research during that epoch will ever be persuaded that any person other than Jim Shannon could have made it come to pass. The array of talents and skills that he possessed and that were probably most visible in his tenure as director of the National Institutes of Health deserve to be catalogued: intelligence; vision evidenced by his sense of where biomedical science ought to be and his convictions that getting it there was a practical and feasible ambition; a grand design of such breadth that what has been characterized as his opportunism was simply placing a tile that appeared suddenly from an unexpected quarter into the proper place in his visionary mosaic; an unusual readiness to seek and to listen to advice from the most critical thinkers he could find on the issue at hand; great self-assurance that enabled him to act with confidence and serenity, whatever the outcries might ensue; single-mindedness; mastery of the rules of the "Washington game"—a quintessential bureaucrat in the best sense of the term with uncanny ability to find the shortest distance to whatever his goal was at the moment, to identify those institutions and individuals whose help he needed to achieve his objectives, and to cultivate them assiduously, skillfully, and successfully; and, finally, a remarkably pragmatic and eclectic outlook that, keenly attuned to the need for deeper scientific penetration of medicine, made him no less a proponent for fundamental research than for attention to clinical applications of basic knowledge for the improved management of human disease.

Shannon's influence extended beyond NIH's domain. As the director, he interacted ex officio with the leadership of other federal science and science regulatory agencies—the Centers for Disease Control, Food and Drug Administration, National Science Foundation, Atomic Energy Com-

mission, Nuclear Regulatory Commission, National Aeronautics and Space Administration, etc. He represented the Public Health Service and NIH on the Federal Council on Science and Technology and as a consultant attended virtually all meetings of the President's Science Advisory Committee from 1959 to 1965. He also participated in many important international scientific activities, particularly associated with the World Health Organization and the United States-Japan Cooperative Biomedical Science Program. Perhaps his favorite foreign "entanglement" was attending as a standing (guest) member the annual meetings of the heads of the medical research councils of the Common Market countries. There is abundant testimony that in each of these fora he made his presence felt.

Shannon reached the Public Health Service's statutory retirement age in 1968. His subsequent career included seriatim appointments as a scholar in residence at the National Academy of Sciences (1968-70), professor of the biomedical sciences at the Rockefeller University (1970-76), and as a scholar in residence at the National Library of Medicine (1976-80). His bibliography includes about 100 scientific and technical publications, along with scores of contributions to the literature on the administration of research programs, to public policy with respect to science and scientific and medical education, and to relationships between government and academic institutions.

In his long career, Shannon garnered a cornucopia of recognitions: election to every important scientific society in his field, including the National Academy of Sciences (1965); many honors, among the more significant the Presidential Medal for Merit (1948), Public Welfare Medal of the National Academy of Sciences (1962), Rockefeller Public Service Award (1964), Presidential Distinguished Federal Civilian Service Award (1966), National Medal of Sci-

ence (1974), Abraham Flexner Award and Alan Gregg Lectureship of the Association of American Medical Colleges, Kober Medal of the Association of American Physicians, Hadassah's Myrtle Wreath, and a score of honorary degrees. He had the good fortune to enjoy during his lifetime the full panoply of accolades that his achievements warranted. In all probability, he will be remembered best as the architect of the modern National Institutes of Health, a superlatively well-informed and credible advocate in government for the commitment of public funds to research in the biological and medical sciences, and the manager of a sophisticated system for allocating federal funds as fairly as is humanly possible to the most worthy research proposals. Those who did not witness the events of those memorable Shannon years may find it difficult to comprehend the transformation he wrought from the time he took office in 1955. The only living scientists who have experienced the transition from the pre- to post-Shannon eras are all septuagenarians. Scientists approaching retirement today began their research careers when the Shannon-induced changes had been in progress for almost a decade. Virtually none of today's active scientists have had any experience with the environment that prevailed in the world of biomedical research in the pre-Shannon era. In fact, there is hardly a person now alive who remembers. . . . But the institution to whose structure, function, growth, and development he added such a powerful impetus has in the four or so decades since he became its director changed the face of biological and medical science, medical practice, and human health almost beyond recognition.

What manner of man? Tall, trim, quiet, soft-spoken, modest, unassuming, seemingly unimpressed by the plaudits that came his way, apparently relaxed and easy-going, open, straight-forward, undevious, dispassionate, and, above all,

intensely focused. He had a great capacity to put setbacks and unpleasantries behind him quickly, to avoid recriminations and to waste no time or energy nursing grudges. His standards and expectations were high; those who failed to meet them more than once or twice just never got any more assignments. Personal attachments never got in the way of dispassionate and objective judgement of performance. Yet, he always seemed to be able to find time to advise and counsel those who sought help; stories abound of spontaneous acts of kindness, thoughtfulness, and generosity. Virtually every individual who ever worked closely with Jim Shannon remembered him as a heroic figure and almost unanimously rated their associations with him as the most enriching and memorable of their careers.

SELECTED BIBLIOGRAPHY

1932

With N. Jolliffe and H. W. Smith. The excretion of urine in the dog. III. The use of non-metabolized sugars in the measurement of the glomerular filtrate. *Am. J. Physiol.* 100(2):301-12.

With N. Jolliffe and H. W. Smith. The excretion of urine in the dog. VI. The filtration and secretion of exogenous creatinine. *Am. J. Physiol.* 102(3):534-50.

1934

The excretion of inulin by the dogfish *Squalus acanthias*. *J. Cell. Comp. Physiol.* 5(3):301-10.

1935

The excretion of inulin by the dog. *Am. J. Physiol.* 112(3): July.

With H. W. Smith. The excretion of inulin, xylose and urea by normal and phlorizinized man. *J. Clin. Invest.* XIV(4):393-401.

The renal excretion of creatinine in man. *J. Clin. Invest.* XIV(4):403-10.

The excretion of phenol red by the dog. *Am. J. Physiol.* 113(3):602-10.

1936

Glomerular filtration and urea excretion in relation to urine flow in the dog. *Am. J. Physiol.* 117(2):206-25.

1938

The renal excretion of phenol red by the aglomerular fishes, *Opsanus tau* and *Lophius piscatorius*. *J. Cell Comp. Physiol.* 11(2):315-23.

With S. Fisher. The renal tubular reabsorption of glucose in the normal dog. *Am. J. Physiol.* 122(3):765-74.

Urea excretion in the normal dog during forced diuresis. *Am. J. Physiol.* 122(3):782-87.

1939

Renal tubular excretion. *Physiol. Rev.* 19(1):63-93.

1941

With S. Farber and L. Troast. The measurement of glucose *Tm* in the normal dog. *Am. J. Physiol.* 133(3):752-61.

1942

Kidney. *Annu. Rev. Physiol.* 4.

The control of the renal excretion of water. I. The effect of variations in the state of hydration on water excretion in dogs with diabetes insipidus. II. The rate of liberation of the posterior pituitary antidiuretic hormone in the dog. *J. Exper. Med.* 76(4):371-99.

1943

With S. H. Fisher, L. Troast, and A. Waterhouse. The relation between chemical structure and physiological and disposition of a series of substances allied to sulfanilamide. *J. Pharmacol. Exp. Ther.* 79(4):373-91.

1944

With D. P. Earle, Jr., B. B. Brodie, J. Taggart, R. W. Berliner, and resident staff of the Research Service. The pharmacological basis for the rational use of Atabrine in the treatment of malaria. *J. Pharmacol. Exp. Ther.* 81(4):307-30.

1945

The study of antimalarials and antimalarial activity in the human malarias. *Harvey Lect. Ser.* XLI:43-89.

1948

With D. P. Earle, J. V. Taggart, and R. W. Berliner. Studies on the chemotherapy of the human malarias. I. Method for the quantitative assay of suppressive antimalarial action in vivax malaria. *J. Clin. Invest.* XXVII(3):66-74.

With J. V. Taggert, D. P. Earle, R. W. Berliner, W. J. Welch, C. G. Zubrod, N. B. Wise, T. C. Chalmers, and T. C. Grief. Studies of the chemotherapy of the human malarias. II. Method for the quantitative assay of suppressive antimalarial action in falciparum malaria. *J. Clin. Invest.* XXVII(3):75-79.

With J. V. Taggart, D. P. Earle, R. W. Berliner, C. G. Zubrod, W. J.

Welch, N. B. Wise, E. F. Schroeder, and J. M. London. Studies of the chemotherapy of the human malarias. III. The physiological disposition and antimalarial activity of the cinchona alkaloids. *J. Clin. Invest.* XXVII(3):80-86.

With J. V. Taggart, D. P. Earle, R. W. Berliner, W. J. Welch, C. G. Zubrod, J. W. Jailer, B. H. Kunh, and J. Norwood. Studies of the chemotherapy of the human malarias. V. The antimalarial activity of quinacrine. *J. Clin. Invest.* XXVII(3):93-97.

With R. W. Berliner, D. P. Earle, J. V. Taggart, C. G. Zubrod, W. J. Welch, N. J. Conan, E. Bauman, and S. T. Scudder. Studies of the chemotherapy of the human malarias. VI. The physiological disposition, antimalarial activity, and toxicity of several derivatives of 4-aminiquinoline. *J. Clin. Invest.* XXVII(3):98-107.

With R. W. Berliner, D. P. Earle, J. V. Taggart, W. J. Welch, C. G. Zubrod, P. Knowlton, and J. A. Atchley. Studies of the chemotherapy of the human malarias. VII. The antimalarial activity of pamaquine. *J. Clin. Invest.* XXVII(3):108-13.

With C. G. Zubrod and T. J. Kennedy. Studies on the chemotherapy of the human malarias. VIII. The physiological disposition of pamaquine. *J. Clin. Invest.* XXVII(3):114-20.

With D. P. Earle, R. W. Berliner, J. V. Taggart, C. G. Zubrod, W. J. Welch, F. S. Bigelow, and T. J. Kennedy. Studies of the chemotherapy of the human malarias. X. The suppressive antimalarial effect of paludrine. *J. Clin. Invest.* XXVII(3):130-33.

With M. Rosenfeld, C. G. Zubrod, and W. D. Blake. Methemalbumin. I. Appearance during administration of pamaquine and quinine. *J. Clin. Invest.* XXVII(3):138-43.

1955

With L. A. Scheele. Public health implications in a program of vaccination against poliomyelitis. *J. Am. Med. Assn.* 158:1249-58.

With others. Interim report. Public Health Service technical committee on poliomyelitis vaccine. *J. Am. Med. Assn.* 159:1444-47.

1956

With C. B. Kidd. Medical research in perspective. *Science* 124(3233):1185-90.

1957

Training for careers in medical research. *The Pharos* (Oct.):9-14.

1961

The National Institutes of Health: Programmes and problems. *Proc. R. Soc. Lond.* 155:171-82.

1964

Science and federal programs: The continuing dialogue. *Science* 144:976-78.

1967

The advancement of medical research: A twenty-year view of the role of the National Institutes of Health. *J. Med. Educ.* 42:97.

1971

Medical research: Some aspects that warrant public understanding. *N. Engl. J. Med.* 284(2):75-80.

1974

Federal and academic relationships: The biomedical sciences, 1974. *Proc. Natl. Acad. Sci. U. S. A.* 71(8):3309-16.

1976

Federal support of biomedical sciences: Development and academic impact. *J. Med. Educ.* 51(7) (Part 2):1-98.