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ELI KENNERLY MARSHALL, JR.

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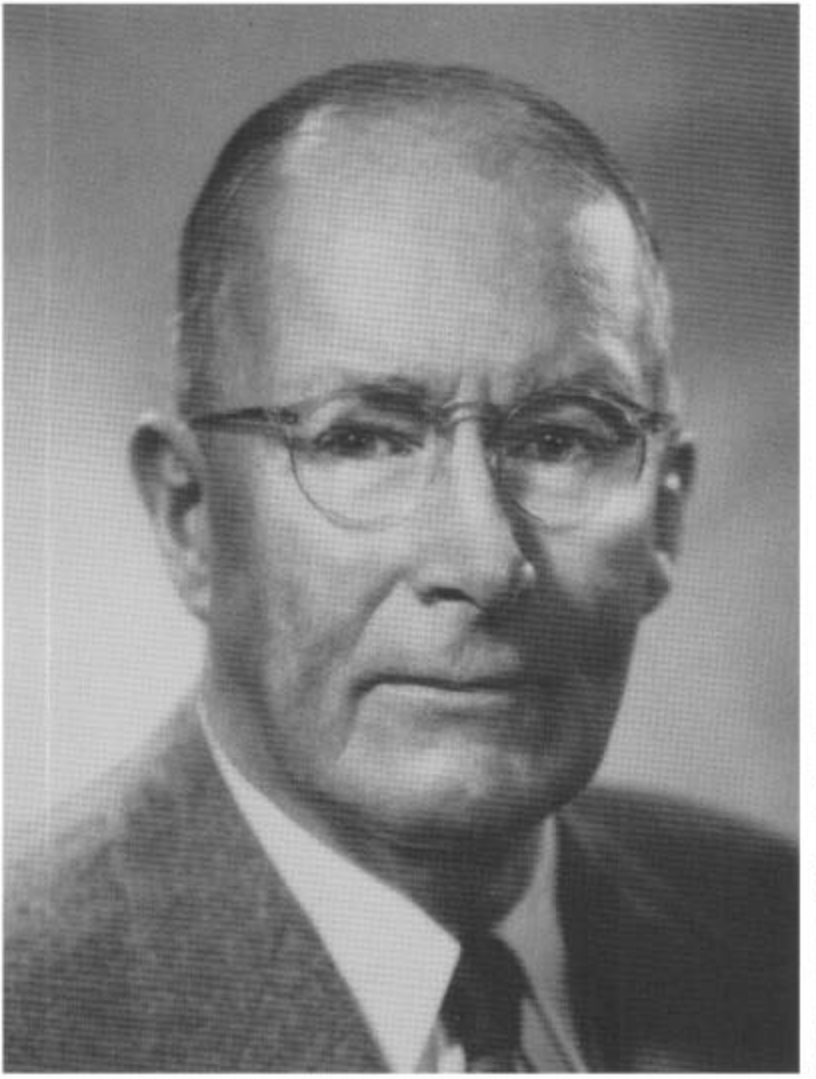
A Biographical Memoir by

THOMAS H. MAREN

Biographical Memoir



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E K Marshall Jr.

ELI KENNERLY MARSHALL, JR.

May 2, 1889–January 10, 1966

BY THOMAS H. MAREN

THE IDEAS AND IDEALS of the nineteenth century are embodied in many men and women born in late Victorian times, and so live on to the present. In this tradition was Eli Kennerly Marshall, Jr., who served the Johns Hopkins University School of Medicine for thirty-five years, first as professor of physiology, then of pharmacology and experimental therapeutics. Now near the end of our own century, it is fitting to review and celebrate the life of a scientist who made giant strides toward the twenty-first.

Marshall was born in Charleston, South Carolina, on May 2, 1889. His father's family came from England in the early part of the century. His paternal grandmother, Susan, was the daughter of Eli Kennerly, a Virginian who migrated to South Carolina. His mother's family was more varied. One side of her family was English—his merchant grandfather (Brown) was a descendant of the Rev. Samuel Andrew, a founder of Yale, and George Treat, one-time governor of Connecticut. His maternal grandmother (Beckmann) appeared more exotic; Marshall's notes say her family included members of German, French, and Russian descent. He once mentioned that he was part Russian—a rather incongruous note—and there was no whiff of the East in his character. He retained throughout his life the accent and many of the at-

titudes common in Charleston, which in the days of his upbringing was a somewhat unique cultural enclave.

On both sides his family was "in trade" in Charleston. His father ran the successful shoe business built up by his mother's father, and they all lived in the maternal grandparents' pleasant home, surrounded by aunts and (mostly) female children. Life moved in stately and routine fashion; there were large, early breakfasts; dinners at 3:00; and late, cold suppers. An isolated and shy boy, he went to private schools and graduated first in his class from Charleston High School. No effort seems to have been made to widen his horizons; he was sent to the small but excellent College of Charleston. He graduated at the age of nineteen in 1908, the only chemist in a class of eight men. As he describes those days: "I was devoted to books, took no interest in athletics, and really led a rather narrow life of the mind. College, except in an intellectual way, was for me a failure. No lasting friendships were made, and as I see it now, my college was a high school and my post-graduate years in chemistry, a poor makeshift for college."

He embarked on these graduate years at Johns Hopkins in 1908; there had been some Hopkins teachers and acquaintances in the city of Charleston and at college. He lived in a boarding house near the old University on Little Rose Street; again he was quite isolated. It would be most agreeable to say, from the vantage of seventy-five years, that this unspoiled innocent found, at the golden dawn of Johns Hopkins, the inspiration he craved and deserved. Alas, this first year was "a shattering of illusions." Ira Remsen, who had been director of the Chemistry Department, was now president of the University and kept partial control of the department, with no strong successors. Marshall was assigned to a thesis advisor and a topic that he deemed "unthinkable,"

and he returned to Charleston the next summer in the fierce indignation that was to become so characteristic. He arranged to complete his graduate work at the University of Chicago, but his old college professor, Francis Parker, interceded at Hopkins and arranged for Marshall to choose his own thesis advisor, Associate Professor of Organic Chemistry S. F. Acree. He returned to Baltimore, but his notes about the time, written thirty-five years later, were full of exclamation points and attacks on those "old men" who dared threaten his freedom.

The next two years, finally, "were extremely happy and pleasant," despite the ebb of the department. Acree gave him plenty of independence and he read widely in the excellent library, including the works of Emil Fischer, Nef, and Gomberg. He had planned to go into industry, but unaccountably he became interested in physiological chemistry. In 1911 he took an assistantship in that subject in the Medical School with Walter Jones,[1] beginning the association in three departments that was to last forty-five years.

He received the Ph.D. in chemistry and sailed to Europe in the summer of 1912, with a letter of introduction (but with no advance notice and no place to stay) to Abderhalden at the Physiology Institute at Halle. He was accepted, but again seemed isolated: little English was spoken, his German was weak, and he did not care for the system in which Herr Professor gave directions each morning to the staff for the day's work. But the loner was to triumph: "I spent time reading in the small department library. . . . I wanted to study enzyme action . . . ran across literature on urease and decided to work with it when I returned to Baltimore in the fall." But if only Marshall could have visited Paul Ehrlich at Frankfort-am-

[1] "Walter Jones," in *Biographical Memoirs of the National Academy of Sciences*, vol. 20 (Washington, D.C.: National Academy of Sciences, 1943), pp. 79–139.

Main! Did he even know then of Ehrlich, whose name was to be coupled with his a quarter of a century later?

Back in Baltimore that winter, Marshall did just as he planned and attacked the urease problem with great force. It turned from a purely chemical exercise into a methodological triumph for physiology and chemistry (Section I below). Marshall wrote, "It was quite worthwhile to be on the mountaintop for a short time."

Marshall thought Jones unimaginative and not interested in his work. Had he stayed with Jones, would he have slid off that mountain? Jones thought there wasn't much left to do in physiological chemistry, and he couldn't do much for Marshall anyway. But there was a deus ex machina, or more accurately, a godlike figure on the floor below—John Jacob Abel,[2] professor of pharmacology, already a world figure. Abel was a gentle farmboy and school principal from Ohio who had gone to Europe for seven years "to prepare myself for the 20th century." There he studied medicine, chemistry, physiology, and pathology before becoming one of the founding chairmen at Johns Hopkins in 1893. He had isolated epinephrine from the adrenal, begun work on the artificial kidney, studied chemotherapy of trypanosomiasis with antimony compounds, crystallized insulin, pioneered work on the posterior pituitary, and founded both the American Society of Biological Chemists and the American Society for Pharmacology and Experimental Therapeutics. Most significantly, he believed that "the investigator is the man whose inner life is free."

Marshall had caught Abel's eye; indeed, the two departments lunched together, an important tradition that was to last many years. Abel arranged for Marshall to transfer to pharmacology, but with the most significant and serious pro-

[2] "John Jacob Abel," in *Biographical Memoirs of the National Academy of Sciences*, vol. 24 (Washington, D.C.: National Academy of Sciences, 1947), pp. 231–57.

viso: that Marshall would study medicine. Rather complicated arrangements had to be made, because at that time faculty were not permitted to study for a degree. Marshall ended up doing the basic sciences (except biochemistry, physiology, and pharmacology, which he never took!) at Wisconsin and Chicago during the summers, but somehow the rule was relaxed so that he did his clinical work at the Johns Hopkins Hospital. Marshall's medical training had profound implications for him, as well as for generations of his students; he never ceased to bless Abel for this advice. He received the Hopkins M.D. in 1917.

During those years he lived most contentedly at the old Johns Hopkins Club at the corner of Monument and Howard streets. Intellectually and socially, it was a rich period. There was a host of young scholars from the medical school and the university, who traded shoptalk, gossip, and beer on Saturday nights. Much later he recalled Barnett (statistics), Mustard (Latin), and Lovejoy (philosophy). An appealing scene is that of Edgerton, a Sanskrit man and later professor at Yale, reading Hindu stories to Marshall at midnight, over crackers and cheese.

This episode in Marshall's life ended with three events: his graduation from medical school, service in World War I, and marriage to a Hopkins classmate, Berry Carroll, of Columbus, Ohio. She later made a career as psychiatrist to the Children's Court in Baltimore, while raising three children. Marshall was assigned, with the rank of captain, to the Chemical Warfare Service in Washington, where he worked until the end of the war.

In this unlikely setting, Marshall made a major, independent discovery—Homer W. Smith,[3] who was destined to be-

[3] "Homer W. Smith," in *Biographical Memoirs of the National Academy of Sciences*, vol. 39 (New York: Columbia University Press for the National Academy of Sciences, 1967), pp. 445–70.

come the world leader in renal physiology. But in 1918, Smith was an enlisted man from Cripple Creek, Colorado, where he had sold vacuum cleaners. Marshall noticed that a light always burned late in the back laboratory; investigation one night revealed a tall skinny young man (not unlike the captain himself) who stuttered and had a passion for chemistry, literature, and music. If the captain was burdened with two doctorates, the sergeant had none at all, and Marshall resolved to repair this. Meanwhile, they published three excellent papers on mustard gas, prepared in the quantitative and chemical spirit that was to characterize the work of both in the years ahead. There was some effort to get Smith into medical school after the war, but he ended with the D.Sc. from the Johns Hopkins School of Hygiene and Public Health, where he worked on the pharmacology of arsenic. Seven years later, when both were involved in the study of renal physiology, they met again in Maine, where they collaborated briefly in a pioneering study of vertebrate evolution in light of the development of the glomerulus. They were neighbors, friends, antagonists, colleagues, and rivals at the Mount Desert Island Biological Laboratory for thirty-five years. To ask for more would be unrealistic, in view of their very different characters.

Back at Hopkins in early 1919, Marshall and his new family happily faced a gas-lit apartment on West Baltimore Street, a low budget, and some interesting decisions. He thought of going with a drug company as research director, but there were no offers and Abel was unsympathetic to this. He was offered a professorship in the Peking Union Medical School, with responsibility for the combined departments of physiological chemistry, physiology, and pharmacology (the curriculum of the twenty-first century?), but turned it down with little thought. Only at the close of his life did he speak

sadly of this—quite out of character for him—as a great missed opportunity. He took the more conventional way and accepted the chair of pharmacology at Washington University in St. Louis. But in less than two years, too little time for lasting impressions on Marshall or Washington, the offer came from Hopkins, through Abel, to succeed Howell in the chair of physiology. His single, short journey outside Hopkins was over. His only reservation in returning was that somehow he had never taken a course in physiology, but he reasoned that he had never taken physiological chemistry or pharmacology either and had already taught both.

There must have been a very special quality in Marshall that brought him to this distinguished chair at age thirty-two and led Hopkins to pass over the more orthodox candidates. His papers up to that time were surely of good quality, but there were no outstanding contributions to physiology. Of course, his training was remarkable; it may be noted that he was not an M.D.–Ph.D. in the modern sense of a combined degree. He had two separate and significant tracks to a career in pharmacology: chemistry *and* medicine. His scholarship, vigor, singleness of purpose, and forthright honesty could not have failed to impress.

His bibliography from 1910 to 1920 charts his gradual transition from pure chemistry to physiology and pharmacology. The urea method had opened the door to these later studies, notably on the effects of adrenalectomy on the kidney (Section I). It was not long before this promise and these gifts came to fruition. In October 1922 he read to the Johns Hopkins Medical Society the "Proof of Secretion by the Convoluted Tubules": he had discovered active transport! Some details of this finding and the ensuing controversy are given below (Section II). In the published paper (1923) he seems to have leapt fifty years over the heads of his contemporaries

to bring an entire new field into focus. It was to be another twenty-five years before it gathered the great impetus that it has now.

In January 1923, just as his great paper with Vickers on the proof of secretion was published, Marshall sailed to Europe—"carefree and happy"—with his family. In this memorable year he met most of the scientists who had been only names to him. "E. H. Starling of University College was particularly nice to me . . . we sat in his little office in front of a small fire . . . we discussed Physiology . . . my going into it without orthodox training. Starling said 'we need men bringing gifts, a new point of view.' I then felt that maybe I could do something."

The next few months were spent in Cambridge. "Here, I worked with Joseph Barcroft (with whom I had had much correspondence, during the war, on gas warfare). This was a delightful time. We took a furnished house—had a 'general' and excellent nurse for the children. I enjoyed dining in College at the high table. My wife says that if I had not been married, I should have pulled every string possible to become a Fellow of one of the Cambridge Colleges and live the delightful life there."

He went to Edinburgh to confront Arthur R. Cushny, whose book, *The Secretion of Urine,* and "modern theory" were widely accepted. The theory embraced filtration and reabsorption only, even though Bowman and Heidenhain had spoken of secretion much earlier. Cushny was unmoved by Marshall's visit, or his papers, and still rejected secretion in the 1926 edition of his book. It is clear that Cushny could not accept the idea that cells reabsorbed *and* secreted or that different substances could be handled in different ways.

Marshall spent "several delightful weeks" in the leading physiology laboratory of Europe—August Krogh's in Copenhagen. "This was his old laboratory, an old house—machine

shop and 'diener's' quarters on the ground floor, laboratory on the second floor, and Krogh's living arrangements on the top floor. There were no cupboards in the laboratory and one could roam around and see all the apparatus Krogh had made and used on high shelves. Krogh used to say that if one could theorize and reason correctly for five or ten minutes in physiology without doing an experiment, one was very lucky."

He returned to Baltimore greatly invigorated and no longer worried about his lack of training. The secretion problem occupied and stimulated him. The Physiology Department at Hopkins under Marshall was small and appears to have taken social as well as midday nourishment from Abel's pharmacology group. Like Abel, Marshall gave relatively little time or energy to medical school teaching. Their idea of curricular reform was probably to move toward the smallest number of class hours possible; at one time Abel was running about eighty hours for the entire course. Both men made their influence felt by force of character and example in subtle ways. In those far-off and very active days, Marshall appeared intense and somewhat remote to his colleagues; he is said to have changed little between 1925 and 1955. He enjoyed reading, and in younger days, walking, but had no hobbies. He liked good company in small doses and looked forward to lunches and dinners at the Hamilton Street Club in downtown Baltimore with a small and select group of lawyers, writers, businessmen, and Hopkins professors. He was something of an ascetic; the life of an English don would have been eminently suitable for him.

His physical presence matched his cast of mind. Tall, thin, handsome, well-groomed, and formal, with a strident voice bearing the accent of Charleston, he was uninhibited in giving opinions or criticism of scientific peers. He was famous for his (well-placed) profanity, but this too was selective and

emphatic. Three old-fashioned staples were used with such skill (damn, hell, and bastard) that he never needed or even hinted at the sexual expletives. He had the social graces of his "caste," but no social ambitions or "snobbery." He was a very private person and would not share personal or family adversities.

As he grew older, his photophobia and intermittent claudication worsened, so he did not enjoy the outdoors. As we shall see, his scientific world expanded, but his private intellectual world continued to be less than that of the usual academic. In the 1920s and after he seemed to revert to the isolated ways of his boyhood. He had little interest in literature, art, religion, music, sports, or philosophy; thus he remained at a distance from most of us. The key was science, and to realize that despite his austere and (to some) frightening presence, he was fundamentally kind, supportive, and optimistic about himself and his close colleagues.

In 1932 Abel retired and Marshall was appointed to his chair, which was renamed Pharmacology and Experimental Therapeutics. There were several reasons for this rather unusual academic shift; dominant were the desire "to be the old man's successor," and the feeling, strong in Marshall at age forty-three, that his destiny lay closer to chemistry than to physiology.

There followed an unusual time, for at the peak of his intellectual power and prestige Marshall idled, waiting for chance or observation to point to the future. He was finished with the kidney; secretion was proved and accepted by all, and it interested him no longer. In this time of waiting, he did make an important observation in a different area from all his other major work: that in respiratory depression anoxia provides a major ventilatory drive mediated through the sino-aortic mechanism (Section III). This had the mark of

Marshall's contributions—a fundamental discovery and a firm base for human medicine.

Marshall held his chair until his retirement in 1955. During the twenty-three years of his tenure, he passed through three separate phases of research, which are considered below (Sections IV–VI). In the first, the sulfonamides, he became a principal actor at the dawn of chemotherapy and achieved world renown. His multiphasic and powerful training was brought to bear on the chemical, physiological, and pathological aspects of the subject. He was fortunate—or prescient—in having talented and dedicated young colleagues in medical pharmacology (Windsor Cutting and Kendall Emerson), bacteriology (Harold White), chemistry (Calvin Bratton), and chemotherapy (John Litchfield). These men, with Morris Rosenfeld, were the nucleus of an advanced teaching and training department, responsibilities that were not forgotten even though the guiding passion was research. For thirty-five years he sat on the Advisory Board of the Johns Hopkins Medical School and fought, among other things, for freedom in curricular matters, free time for students, departmental autonomy, and the highest standards for faculty selection. He was one of the first to realize the importance of clinical pharmacology and began to train men in this area as far back as 1936. While he recognized that such men must be good doctors, he was convinced that they must also be able to take their place as scientists in the pharmacology departments; this is now the pattern of this "new" field. He believed that basic pharmacologists should also have medical training; after World War II he sought and received private funds for a program to create pharmacologists by "training medical men in chemistry, or training chemists in medicine." Each man's three-to-six-year program fit individual requirements; the products of the plan are now nearing

the ends of their careers in university, governmental, or industrial pharmacology.

It was characteristic of Marshall that no matter how passionately he felt about a subject, when he dropped it, he never looked back. This was his pattern with the study of renal secretion, sulfonamides, malaria, and cinchoninic acids. He scorned some of his followers who were "looking for the second decimal place," but some of those added depth to what he began. It freed him from the intellectual torments that Homer Smith suffered as he followed and classified the twisting trails of renal physiology decade after decade.

Marshall retired in 1955, and in the next decade served a variety of useful functions. He became an industrial consultant and an advisor to the National Cancer Institute. For four years he spent a month each year teaching at the new University of Florida College of Medicine. He continued to radiate the same intangible love for his subject and hope for its future that was the legacy of Abel's lunch table, and reached back to Schmiedeberg and Buchheim. Each year he gave several lectures on the kidney[4] and on chemotherapy using an historical perspective and a spare, clear delivery. It pleased him to say that he had known all the significant men in renal physiology after Heidenhain. There was no other formal teaching, but a string of pleasant days, given to consideration of ideas, observation of experiments, and pronouncements—often spiced with his well-adjusted profanity—in the direction of poseurs and incompetents. He became interested in the teaching program and in several of the medical students and kept his appointment until he could see "my first class graduate."

There was a most significant part of Marshall's life that was all but concealed from his colleagues in Baltimore and

[4] Reprinted in *The Physiologist*, 9, no. 4 (Nov. 1966).

his confreres in Washington. This was his role at the Mount Desert Island Biological Laboratory, at Salsbury Cove, Maine, where he summered for forty years. After he completed his renal work in the early 1930s, he stopped working at the laboratory, but at his home, looking over the western aspect of Frenchman's Bay, he read, wrote, talked to friends, and gathered energy and enthusiasm for the fall ahead. He followed the work in the laboratory with his usual attention to detail and provided an astonishing amount and quality of guidance for generations of investigators. It often seemed that most of the ongoing work in the laboratory had been presaged, at least qualitatively, by his thinking in those rich, early years. Sometimes these early observations were in his memory, sometimes in his notes, and surprisingly often in the literature; this last to the profound discomfort of the hapless investigator who had rushed off to Maine without a session in the library. Marshall was a somewhat different man in Maine than in Baltimore. At Hopkins, he persisted in the old fashion of calling departmental colleagues and students by their last names, and he kept aloof from their family affairs, except for one fine party each year in his home. In Maine, he slipped naturally into first names and showed true affection and interest for the younger men, as well as their wives and children. He and Mrs. Marshall were favorites at parties, and gatherings at their home were greatly enjoyed.

Although administration was a distant second to research in his life, Marshall could be most effective when required. This was evident in his directorship of both departments in Baltimore and at two occasions in Maine: the first during the reestablishment of the laboratory after World War II (along with Homer Smith and Roy Forster) and the second when he was president of the laboratory from 1960 to 1964. In these roles he appeared ruthlessly efficient, as if he realized so well how these tasks ranked compared with science.

Marshall's character was perhaps susceptible to (using a favorite word of his) more clean-cut analysis than most, for he possessed absolute integrity. In the light of this undiluted quality, his occasional (or frequent, depending on the company) lapses from the amenities should have surprised or disturbed no one. He was profoundly loyal to all the men who had ever worked with him. He was the antithesis of the organization man. Self-reliance was the key; he was an Emerson-like hero. In a certain cast of the stern face, he even resembled the Concord philosopher. Marshall stayed in his laboratory and worked; he shunned all the ordinary apparatus of success. Some of these came to him anyway; he was president of the Pharmacology Society in 1942 and was editor of its journal from 1932 until 1937. He was a member of the American Philosophical Society and the American Association of Physicians and received the LL.D. from the College of Charleston in 1941. Astonishingly, in view of all that he pioneered and accomplished, he won no prize, received no awards or special honors. Was this related to his utter independence, his forthright manner, his lack of political ambition, his disregard for compromise, his avoidance of commitment to a single field?

Such a man will not come again, for the times that produced him have vanished. He was a bridge between the nineteenth and twentieth centuries for science, medicine, manners, the South, Johns Hopkins, and Maine. The pharmacologists now training for the twenty-first century might turn to his scientific life and principles as guides to their future.

I. UREA AND EARLY KIDNEY STUDIES

When Marshall was in Abderhalden's laboratory in 1912, he became interested in enzymes and decided to work on urease, entirely as an academic exercise. Back in Baltimore

he got some soybeans from an Italian market on Gay Street, and was amazed at the ease and quantitative specificity with which the extracts decomposed urea. He knew

> [T]hat C.S. Hudson had used the enzyme invertase to determine cane sugar, and I was suddenly struck with the idea that urease could be used to determine urea and that the procedure would be extremely simple. That evening I left the laboratory with L.G. Rowntree and walked with him across Monument Street to the old Johns Hopkins Club. I asked Rowntree if there were any need for a simple, quick method of determining urea in urine, blood and body fluids. He said he was at the time very much interested in determining urea in blood, but the known methods were very difficult, cumbersome and time consuming (Folin's micromethods had just been published and had not come into general use). I told Rowntree I had a very simple method or at least could devise one in a few weeks. He replied that if I did that I could have a Chair in Physiological Chemistry in a very few years.
>
> This conversation with Rowntree was a sufficient stimulus to make me go at the matter with great enthusiasm. I believe I talked to Walter Jones about the matter, but he was not at all interested. In a week or 10 days the job was done and my first publication from the Medical School was being prepared. I recall that during this exciting week, I never left the laboratory until 1:00 to 3:00 a.m. It was quite worthwhile to be on the mountaintop for a short time.
>
> One of the greatest compliments I have ever had was paid me by Otto Folin at our first meeting. It was at the Philadelphia meeting of the Biochemical Society (Christmas 1913). When I was introduced to Folin, he said that when he had read my paper on the determination of urea by using urease, he thought it was perfect rot. He continued and said that he had tried my method and it was o.k., and he wanted to congratulate me. This from Folin!—only a few months after my first paper on Physiological Chemistry had been published.

Using this method, Marshall and Davis studied the distribution of urea in tissues and found that it was distributed evenly and rapidly, except for fat. They also measured its renal clearance. This was a signpost to much later work in kidney physiology and the pharmacology of sulfanilamide.

Two other significant studies were done in this decade, the first on the

[I]nfluence of the adrenals on the kidney. In it is stated, "The excretion of some substance by the adrenals which is necessary for normal kidney function, and the consequent interrelationship of the two glands serves as a very probable explanation of the results which are presented in this paper. Should it be found possible to prevent the renal changes in animals deprived of their adrenals by injection of adrenal extracts, it would support this hypothesis." About fifteen years later, others found it possible to prevent renal changes by injection of adrenal cortical hormone or extract. I recall clearly that in the first draft of this paper the adrenal cortex was implicated, but in revisions a more cautious statement was made.

Another series of observations resulted from my interest of the effect of the adrenals on the kidney. These were done with Kolls during the years 1915–1917. Essentially the important observation was that unilateral section of splanchnic nerve (or unilateral denervation at the renal pedicle) resulted in *anesthetized* dogs in the excretion of a much greater amount of water, chloride, bicarbonate, urea, sulfate and phosphate, but of the same amount of creatinine and phenol red by the denervated kidney as compared to the normal. In addition, compression of the renal artery could bring about a decrease of water and chloride with no change in the excretion of creatinine. The conclusion arrived at was that the changes were caused by vasodilation of renal vessels and increased blood flow to the kidney after section and that secretory action could not be attributed to the renal nerves. Some years later, others found that unilateral nerve section in the *unanesthetized* dog produced no change in the excretion of water or chloride. The interpretation then was that renal vessels were not normally in tone, but were put in tone under anesthesia. About a third of a century after our experiments on nerve section, I reconsidered the evidence. It seems that the above explanation cannot be correct as no change in the creatinine means no change in glomerular filtration rate and no change in phenol red, no change in renal blood flow. Others have now confirmed this by unilateral nerve section in anesthetized dogs. It looks as if the nerves are actually secretory in the sense of influencing reabsorption by the tubule—but why only in anesthetized and not unanesthetized animals? I have been puzzling for years to see how to attack this problem anew.

II. RENAL SECRETION

Marshall came to this work from the urea-adrenal-kidney-renal nerve progression described above. Additionally and significantly, his friend Rowntree had twelve years earlier introduced phenol red as a test for renal function—50 percent of the dose was eliminated in the first hour. But since filtration rates were not known (until Rehberg, 1926), it was not apparent to anyone (except perhaps Marshall) that the phenol red data implied a second process.

The epoch-making paper with Vickers in 1923 contained two simple observations. Following intravenous injection in the dog:

- Phenol red was concentrated in the kidney to 12 × that of plasma.
- The amount in the urine was greater than drug (unbound) filtered, even assuming that all the plasma was filtered, and using a very high value for renal blood flow—300 ml/min, a "safe maximum."

The authors concluded that "the problem would appear to be definitely settled, and satisfactory evidence would seem to exist that . . . filtration, reabsorption and secretion all play a role in the elimination of urine."

But it was not so easy—new ideas *are* dangerous and threatening. For one reason or another, these experiments were attacked by Cushny, Starling, A. N. Richards,[5] Rehberg, Oliver, and Ekehorn. If Marshall had any supporters (Homer Smith?), they are not in the record. A 1930 paper by Richards and Walker (*Journal of Biological Chemistry,* 87:479) records

[5] "Alfred Newton Richards," in *Biographical Memoirs of the National Academy of Sciences,* vol. 42 (New York: Columbia University Press for the National Academy of Sciences, 1971), pp. 271–318.

"an experiment technically one of the best," in which the ratio of phenol red in frog glomerular urine/plasma was 16. The astonishing comment follows: "It is impossible however to accept the result." There is no reference to Marshall in the paper.

His further work with Crane in 1924 supported secretion, but more interesting events lay ahead. In his wide reading, Marshall came across the fact that certain fish lack glomeruli; even better, his friend Alan Chesney (later dean and historian of Hopkins) told him that one of these, the goosefish (*Lophius piscatorius*), lived in the waters off Maine. Another, the toadfish (*Opsanus tau*), lived in the nearby Chesapeake.

Accordingly, Marshall went to Maine, and at the Mount Desert Island Biological Laboratory, with his student Allan Grafflin (later to become professor of anatomy at Hopkins), showed that phenol red was excreted in the goosefish without a glomerulus, along with many other low-molecular-weight substances, sugars excluded. He later found the same for the toadfish. The fight was nearing its close; the comparative method had paid off. But not before the redoubtable Richards cried out—after Marshall's paper at the XIII Physiological Congress in Boston—"he found the one beast in the world that will support his theories."

In 1931 Marshall wrote his final paper on the subject, bringing the 1923–1924 work into focus with new experiments in which glomerular filtration was measured. The supporting data from fish were cited and, most importantly (then and for the historians), there are three pages of rebuttal to his opponents of the past decade, the names a roll call of the renal establishment.

He finished this era with a masterly review (1934) of the comparative physiology of the kidney. Data on anatomy, physiology, and evolution were synthesized to show the un-

questioned power of the comparative approach, a view that was to be vindicated and amplified over the next fifty years.

III. INTERLUDE: RESPIRATORY AND CARDIAC PHYSIOLOGY AND PHARMACOLOGY, 1932–1936

We hear best in Marshall's words an account of the rather unusual transition, when he walked upstairs from one Hopkins department to another and began a new academic life at age forty-five.

> In 1932 when I transferred from the Chair of Physiology to the Chair of Pharmacology and Experimental Therapeutics, the main problem which had interested me for more than a decade in regard to renal physiology—active secretion by the convoluted tubule—was settled. It was answered in the affirmative due mainly to the investigations of myself and coworkers. A great number of problems were now apparent and waiting for solution in regard to renal excretion. These were, however, mainly a quantitative study of the qualitative framework which had been established in the past quarter of a century. I deliberately decided not to engage on them, but to seek a new field of research. Some time was spent in 1932–33, in reorganizing the laboratory course in pharmacology. This led to an interest in respiratory stimulants which lasted until the fall of 1936. One important outcome of this work was the rediscovery of the depression of respiration by oxygen and an analysis of its mechanism.

Like so much else of Marshall's work, this study had direct clinical significance; it is a prime rule in accident rooms not to give oxygen to patients depressed with morphine, barbiturates, or allied drugs. With Rosenfeld he showed that oxygen removed the sino-aortic respiratory drive, which had recently been discovered by Heymans. In a typical vein, Marshall invokes the comparative method by recognizing that when the mammal is threatened with anoxemia, "it may adapt itself . . . to a primitive type of respiratory control (the sino-aortic rather than central) which is normal for lower vertebrates."

His interest in respiration was coupled to an exercise in physical chemistry in the work (again with Rosenfeld) on cyanohydrin equilibria. The goal was to take advantage of the widely varying rates of reactions between CN^- and aldehydes or ketones to find a compound to detoxify HCN, and also one that would slowly release CN^- as a nontoxic respiratory stimulant.

Belonging intellectually to this period, but done earlier, was the first measurement of cardiac output in an unanesthetized laboratory animal, using the Fick principle. His colleague Grollman extended this work and applied it to man, using acetylene rebreathing.

These papers made considerable advances in their several fields. They show breadth, economy of style, attention to important issues, and high technical competence in both physiology and chemistry. None of this work was done by technicians, and the entire budget of the Physiology Department was about $10,000 per year! Federal grants, of course, were unknown.

IV. CHEMOTHERAPY, 1936–1941

Looking back in 1952, Marshall wrote:

> It was amusing to be a free lance—no field of work—waiting for some accidental observation to point out a promising lead. . . . Then around 1936, I began to read of streptozon (Prontosil) and how it cured human cases of streptococcal and staphylococcal septicemia. Would that my friend Charles Hooper, Research Director of Winthrop (Metz or Bayer it was called) had not died a year or so before of pneumonia, which the new drug could have cured! Hooper used to come down two or three times a year and tell me of the new things cooking at the I. G. at Elberfeld, but always said, "That's what the German Johnnies say, I can't vouch for it. Do you want some of this new drug?" He would have brought Prontosil to me at least two years before I became interested in it.
>
> In St. Louis in 1919–1920, I had become interested in the chemotherapy of bacterial infections. Nothing came of this interest except an unpub-

lished address before the St. Louis Section of the American Chemical Society. When successful bacterial chemotherapy arrived, I was ready for it; partly, I think on account of my meditation in St. Louis eighteen years before—and, I think some of my best contributions with my able collaborators have been in this field.

As I can see it, our significant contributions to bacterial chemotherapy were as follows. A simple, accurate and specific method was devised for the determination of sulfonamides in blood and tissues. Using this method, a quantitative study of the absorption, excretion, distribution and degradation of sulfanilamide was completed. These results had the effect of devising a rational basis of dosage—an initial loading dose and then a maintenance dose every four hours day and night. Soon dosage of the sulfonamides was based on blood concentrations rather than on number of grams administered by mouth. Quantitative methods were devised for studying the effectiveness of the sulfonamides on experimental bacterial infections in mice.

As a result of our fundamental studies in bacterial chemotherapy, two new sulfonamide drugs were introduced by us into clinical use. In each instance, this has not only been the introduction of a new drug but of a new principle in bacterial chemotherapy which would be applicable to many other drugs. The chemical and pharmacological properties of the sodium salt of sulfapyridine were first described in a publication from my laboratory. This compound was introduced clinically for intravenous use and was the precursor of the use of sodium salts of other sulfonamides. Sulfanilylguanidine (sulfaguanidine) was prepared here. It had the unique properties of being fairly soluble in water, poorly absorbed from the gastrointestinal tract and highly active against various bacteria *in vitro*. This suggested that this drug or one having similar properties might prove useful in the treatment of bacterial infections confined to the intestinal tract, and not exhibit any toxicity on account of poor absorption. Both of these drugs were useful after their introduction; although, now utilizing the same principles, better ones have been found. Sulfaguanidine was sent to the Near East in 1941. Hamilton Fairley was much impressed by it. In "Medicine in Jungle Warfare" (Proc. Roy. Soc. Med., *38*:195, 1945) he states that it was the considered opinion of many officers in the Australian Medical Corps that sulfaguanidine saved Port Moresby from the Japanese.

This description modestly recalls the facts, but not the excitement, triumphs, and significance of these five years.

Marshall and his collaborators were the architects of quantitative chemotherapy, and showed the direct line from laboratory to clinic. These observations and measurements were extraordinarily solid and precise and are still useful. Accurate chemistry was dominant in this thinking, and the standard was applied to bacteriological and pathological measurements. The blood level concept and practice were born here, along with the idea of drug distribution and decay. It is extraordinary how Marshall's work on urea—a quarter century earlier—prepared him for sulfanilamide.

The discovery of compounds more active and less toxic than sulfanilamide was anticipated by the quantitative data showing that cure of septicemia in mice was accomplished at different blood levels, depending on drug structures: sulfadiazine was sixty-four times as active as sulfanilamide in vitro, and eleven times in vivo. These techniques and conclusions had a profound effect on development of sulfonamides in the drug industry. Even the incidental findings, such as that sulfanilamide caused an alkaline urine and metabolic acidosis, were important. This was on the road to discovery of the carbonic anhydrase inhibitors.

V. MALARIA, 1941–1946

World War II brought sulfonamide research to an end in Marshall's laboratory. Malaria was "the number one medical problem of the war" and attacked through a complex arrangement under the Emergency Management Act and the Office of Scientific Research and Development (OSRD), whose medical arm was the Committee on Medical Research (CMR). This interlocked with advisory committees of the National Research Council and the National Academy of Sciences. But it all worked!

The CMR was headed by A. Newton Richards, the distin-

guished professor of pharmacology at the University of Pennsylvania, and Marshall's great antagonist in the battle about renal secretion. There is every evidence that they worked beautifully together in the war years. The National Research Council held an organizing conference through their Division of Medical Sciences in July 1941, at which the following occurred: "After extensive discussion of possible lines of research, various reports were requested. Of those submitted, that of Dr. E. K. Marshall, Jr., foreshadowed what was to become the principal line of work. Special researches were immediately begun by several of the conferees."

Thus it transpired that Marshall became a prime mover in the government malaria program, which expanded enormously in the years to come and involved universities, industries, and exchange of information with our allies. Committees, panels, and conferences in Washington multiplied to an astonishing degree, covering the territory from basic parasitology to biochemistry to clinical medicine. They were headed by the most eminent (often also the best) men in the field. Baltimore became a secondary hub of the vast enterprise with the establishment of the Survey of Anti-Malarial Drugs, headed by Dr. Frederick Wiselogle.

This office arranged the testing of 13,000 substances received from hundreds of sources, and codified their activity over a four-year period. The work was accomplished by a devoted staff; there was no computer. Marshall was a consultant to this unit also, which was about 200 feet from the Pharmacology Department. Investigators who thought they (or their drugs, which came to the same thing) had been slighted in the program referred toughly to "the high command in Baltimore."

But unlike most of his colleagues at these councils in the two cities, Marshall also had a very busy laboratory run-

ning, in which chemicals were screened for their activity in the avian malarias. New methods of analyses were worked out; structure-action relations were analyzed; distribution of drugs in the body was measured. He was unsparing of himself and his younger colleagues; it was a crucial wartime effort, seven days a week with no holidays.

Rigorous quantification of the experimental avian infections was badly needed. Marshall was often at odds with the parasitologists; on some he vented ire laced with his usual expletives. Typically the chemists were his allies and friends. He relied heavily on Kenneth Blanchard, a polymath in all branches of chemistry who was to join Marshall's department after the war. It was all exciting and full of high idealism, but scientifically frustrating. Marshall did not like the idea of bird malaria—it represented not only an alien class but organisms alien to human malaria. But it was, at the time, the best they could do. Marshall's close scientific friend, James A. Shannon (later the enormously successful director of the National Institutes of Health as it became a major force in world research) was head of the Research Group at Goldwater Hospital in New York. These two had also an earlier bond, renal physiology. This curious link of topics was also common to the younger colleagues in the program: Berliner, Taggart, and Earle. It was Shannon, along with Alf Alving at the University of Chicago, who defined the role of the 4-amino and 8-amino quinolines in the human malarias. These men, along with Robert Loeb, Lowell Coggeshall, Leon Schmidt, and many others, were dedicated to the closest attention to data obtained from the laboratory and human volunteers—it was a triumph of true cooperation. It was frustrating that there was no time to work out the many problems that arose almost daily. Yet scientific issues were not ignored, and one of great theoretical and practical importance emerged and captured Marshall's imagination. Should drugs be given to maintain a

constant blood concentration in infectious disease? Marshall, having introduced this concept for the antibacterial sulfonamides, was nevertheless convinced that this did not apply to the quinolines in malaria, which had a different pattern of distribution and mechanism of action. It was typical that he was flexible, realistic, and outspoken in such an argument.

The situation was indeed critical. Supplies of quinine were cut off, and atabrine (quinacrine) turned the skin yellow and was the target of many unfounded rumors, typical of wartime, so the troops would not take it. Furthermore, it did not seem to be working well until the Shannon group showed that a loading dose was essential—an early triumph of what is now rather elaborately called pharmacokinetics. This surely reflected Marshall's principle of a loading dose for sulfonamides, now curiously forgotten in the use of antiinfective agents. Thus quinacrine was found superior to quinine and became the most important single contribution to the control of malaria in the Pacific War.

Meanwhile, the search for new agents continued. The discovery of chloroquine was a major accomplishment, resulting from study of some 200 4-aminoquinolines. This class suppresses *vivax* malaria and is a radical cure for *falciparum* malaria. A main goal of the program was to find a radical cure for *vivax* malaria, which was made particularly difficult by lack of basic knowledge about the exoerythrocytic cycle in man, and lack of a proper model in birds. Nevertheless, following an early German lead, intensive screening and pharmacology was done on several hundred 8-aminoquinolines, leading to the discovery of primaquine, still the chief drug for cure of this disease.

In April 1946 at a Symposium in Wartime Pharmacology at the Federation of American Societies for Experimental Biology, Marshall said farewell to this vexing and exciting period. It was about his average time for a subject, no matter

how passionately pursued. He dropped malaria and never looked back.

VI. THE LAST DECADE: METHODS, CINCHONINIC ACIDS, ETHANOL

In the fall of 1946 the past had been cleared away, and Marshall at fifty-seven faced fresh problems with new vigor. He was interested in rational dosage schedules for chemotherapeutic agents, and still rather enraged that his dictum of constant blood levels for sulfonamides unthinkingly had been transferred to the antimalarials and to penicillin. He thought (but Jim Shannon did not agree) that he had demolished the malaria argument, and now with Gordon Zubrod he turned to penicillin and showed that a moderate dose interval does not weaken the effect, and that cure is a function of total dose. This was related to its lytic or bacteriocidal action and still guides use of the drug. Marshall's heart was still in chemistry; he would have loved to develop an analytical method for penicillin, but failed. He did succeed with streptomycin, however, and went on to a full-dress study of its pharmacology.

In the course of using a selection of cinchoninic acids as fluorescent ligands for antibiotics, Marshall noticed their anti-diuretic effect. (I had come to his laboratory in 1946 as a medical student and trainee: graciously he had allowed me two years to study and finish work of my own on arsenic and antimony left over from war work on tropical diseases.) He now asked me to find if the cinchoninic acids worked through the posterior pituitary or directly on the kidney. To his great disappointment (since no drug of the latter type was known), it was the former. Nevertheless, it introduced us to the hypothalamus and then the anterior pituitary; it was the dawn of their relations in the work of Geoffrey Harris of London. Now came a shared excitement, still felt a third of a century

later; some of the cinchoninic acids synthesized by Blanchard (a clean-cut structure-action relation was found) stimulated the pituitary–adrenal system! It was also the year of ACTH (adrenocorticotropic hormone) and we had (possibly) a new drug for the rheumatoid and other connective tissue diseases.

Once again, it was as if Marshall had been waiting for this, and he sprang into action, mobilizing his clinical associates and students. He and I took an unusual step—a train trip out to Chicago—to attend the first ACTH conference. But the clinical trials of 3-OH-2-phenylcinchoninic acid were disappointing: there was some beneficial effect, but also enough toxicity to end the study. Marshall had no further interest in the theoretical aspect. He left it to his plodding student to section the hypothalamus of the rats (under the tutelage of David Bodian) with pituitary lesions and to guess that these drugs might be working at the level of the paraventricular nuclei.

In the last years, Marshall's luck and judgment continued to hold. He continued with talented and devoted young colleagues as he had for forty years, particularly Albert Owens, who was also his physician. He still selected important and unsolved problems. Marshall was always intrigued by ethanol; he now showed that the classical zero-order kinetics of decay from blood following the usual size dose changes to first order when the dose is small or at the tail-end of the curve. In the first case the systems for drug metabolism are saturated; in the second they are not. Finally, as a result of his own hospitalization and taking of chloral hydrate, he became interested in its metabolism, neglected since its introduction as the first synthetic drug 100 years before. The chief findings were that a very large fraction is oxidized to trichloracetate; the smaller amount reduced to trichlorethanol is responsible for the narcotic effect. Trichlorethanol and ethanol

share common oxidative pathways, to aldehyde and acid. The data suggested that trichlorethanol itself is a more potent and reliable hypnotic than chloral hydrate; it is now marketed as trichlofos sodium, the salt of the phosphate ester of trichlorethanol.

In this last (1955) work, we find again the inspiring characteristic of Marshall's work since 1912: the synthesis of the basic sciences in the service of medicine.

I THANK Drs. Robert W. Berliner and C. Gordon Zubrod for their review of this memoir, particularly their help with the malaria story. I am grateful to Dr. J. Wendell Burger for some personal insights into Dr. Marshall's character. The passages quoted in the text are from Dr. Marshall's manuscript memoir, written at various times between 1942 and 1955.

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