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ALFRED NEWTON RICHARDS

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A Biographical Memoir by

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ALFRED NEWTON RICHARDS was born in Stamford, New York, on March 22, 1876, the youngest of three sons of Rev. Leonard E. and Mary Elizabeth (Burbank) Richards. His father was in the fourth generation of a line of Ohio farmers, the first of whom (Godfrey Richards) came to America from the Rhenish Palatinate about 1740. Leonard E. Richards apparently was the first of the line to leave the farm for the university. He worked his way through Ohio Wesleyan University and Union Theological Seminary and was pastor of the First Presbyterian Church in Stamford from 1864 until his death in 1903.

Mary Elizabeth Burbank was the daughter of Rev. Caleb Burbank and Delpha Harris (Burbank), both descendants of emigrants from England to New England prior to 1640. Her father was a graduate of Dartmouth College and Andover Theological Seminary and her maternal grandfather (Luther Harris) was a member of the faculty of Providence College, which subsequently became Brown University. She herself graduated from Granville Female Seminary (subsequently incorporated into Dennison College) and taught school in Norwalk, Ohio, prior to her marriage. During this period she lived in the home of Rev. Alfred Newton, who is still remembered as one of the most beloved and influential men ever to live in Norwalk. His daughter Martha was the future Mrs. Leonard Richards' best friend, and memories of those days evidently impelled the latter to choose the name Alfred Newton for her third son.

The father of the three Richards boys was reserved and strict, the religious training severe, the life austere. The family's income during most of the Stamford period was less than $1000 a year, but they kept a cow for milk and butter and they depended on their own large garden for vegetables. In his notes on this period, Dr. Richards wrote: "We were poor, but like Eisenhower's folks were not aware of it. On his small salary my father and mother managed to save enough to help three sons through college and when father died, he left enough to keep my mother in her home in Stamford entirely independent of help from her sons."

Except for brief periods, such as the arrival of a new baby, there was no domestic help. Mrs. Richards did all the housework (cooking, baking, washing, ironing, cleaning), taught in Sunday school, played the organ and conducted the choir in the church, and was deeply involved in community affairs, especially in those which concerned the school and church. She loved music and learning and did much more than her husband to advance the education of their three sons.

Alfred Newton Richards learned to read at home before he was five years old, and at the age of six he proceeded to the Stamford Seminary and Union Free School, an institution established largely as the result of his father's effort and influence. He went through all the grades and graduated in 1892 as valedictorian of his class, a distinction which (according to his notes), "considering the competition, doesn't mean much."

His brother James at that time was a student at Yale, and although Alfred Newton at age sixteen was not deemed ready for college, he went to New Haven in June 1892 to take preliminary entrance examinations. In two and a half days he took eighteen examinations and succeeded in passing six. A year later he returned to take the twelve examinations he missed previously and a few others he had not been permitted to take in 1892. He did well enough to be assigned to the "first division" and in the autumn of 1893 he was admitted to the class of 1897 of Yale College.

According to his notes, he enjoyed most of the subjects and did well enough to escape any conditions, but not quite well enough to be chosen for Phi Beta Kappa, which was an intense disappointment to his mother. Like all his contemporaries in Yale College, he was not permitted to elect science courses until the third year, when he began chemistry (inorganic and organic) and physics. He was fascinated by the laboratory exercises in chemistry and did some special work that enabled him to graduate in June 1897 with honors in chemistry, which pleased his parents. He did poorly in physics, partly because he discontinued mathematics after the second year, to his subsequent regret.

The great experience of his college years at Yale—and indeed the turning point of his career—was a course in physiological chemistry given by R. H. Chittenden in the Sheffield Scientific School, which then was completely separate from the college. This course was intended primarily for seniors in the college who planned to study medicine, and at the time young Richards regarded himself as one of these. Shortly before his graduation, however, his father let him know that he could expect no further financial assistance and was now on his own.

Chittenden at that time was the leading authority in America on the new science of physiological chemistry. Trained in the rigid requirements of contemporary German laboratories, he was a stickler for accuracy and thoroughness and his laboratory was so operated as to create an ambition for perfection. He also took a personal interest in his students, and so it was natural for him one day in the spring of 1897 to ask young

Richards what he intended to do after graduation. When Richards replied that his original plan to study medicine had to be abandoned for lack of funds, Chittenden offered him a fellowship for a year of graduate study in physiological chemistry in the Sheffield Scientific School. The fellowship covered only tuition, but Richards worked in a summer hotel to raise a little money, got a job waiting on tables in a students' boardinghouse in New Haven to provide room and board, and with a little extra help from his father managed to finance the year 1897-1898 in Chittenden's laboratory.

During this year young Richards was assigned a series of tasks having to do with quantitative chemical methods and he learned that, if he took enough pains, he could do things on his own and do them well. The great experience, however, was a study of the starch-digesting power of human saliva (his own) under different circumstances. This work brought him into close association with Chittenden, whose impressions, judging from the outcome, must have been favorable. It also led to a joint paper in Volume 1 of the new *American Journal of Physiology*, a fact that places Richards among the pioneers of American physiology.

During the spring of 1898 Chittenden was invited to undertake the reorganization of the Department of Medical Chemistry in the College of Physicians and Surgeons of Columbia University in New York. He accepted, subject to the understanding that he would spend only one day a week in New York, when he would lecture to the medical students and consult with the permanent staff. The members of this staff were to be selected from his laboratory at Yale, and Richards was invited to be one of them, at the princely salary of $800, which was far more than he had been accustomed to spend.

So in September of 1898 he began a ten-year association with the old College of Physicians and Surgeons on West 59th Street in New York. During the first six of these years he was an assistant and tutor in physiological chemistry, while for the last four he was an instructor in pharmacology. At first his only connection with the teaching of physiological chemistry was to attend to the preparations for the laboratory exercises of the medical students, to circulate among them in the laboratory to answer questions, and to help whenever occasion arose. He was also permitted to enroll in the Graduate School of Columbia Univeristy as a candidate for the Ph.D. degree, with a major in physiological chemistry and minors in physiology and bacteriology. When he got his Ph.D. in 1901, he was the first ever to receive this degree from the Department of Physiological Chemistry at Columbia. His thesis was on "The Composition of Yellow Elastic Connective Tissue," a topic selected by W. J. Gies, his supervisor at Columbia. It represented a great deal of work and provided a valuable experience in quantitative chemical methodology but, after publication in Volume 7 of the *American Journal of Physiology*, it had no further influence on his career.

A course in bacteriology under Philip Hanson Hiss was a different story. Hiss was interested at the time in the development of differential culture media, in which certain microorganisms would grow while others would not. He called on Richards to provide him with glycogen, which the young biochemist isolated from scallops. Then he asked for a carbohydrate that would yield only levulose on hydrolysis and Richards, having learned from the literature that inulin should meet this requirement, provided him in 1901 with pure inulin separated from Dahlia bulbs. Some thirty years later, when Richards was looking for a diffusible polysaccharide which would not be digested in the blood or in the lumen of the frog's kidney, he thought of inulin, tried it, and (with Westfall and Bott) began to study the renal clearance of inulin in dogs at least a year before the same procedure was attempted by others.

Richards' work with Hiss attracted the attention of

T. Mitchell Prudden and Christian A. Herter, prominent members of the Columbia faculty who in 1901 were about to become trustees of the nascent Rockefeller Institute for Medical Research. The result was a Rockefeller scholarship which enabled Richards to spend the next year working with Herter in the Laboratory of Physiological Chemistry at Columbia on a problem related to the glycosuric effects of adrenaline locally applied to the pancreas of the dog.

Thus in the autumn of 1901 young Richards' career took another turn. The new work was much more interesting than what he had been doing. He got along well with Christian Herter, a man of independent means in whose home he made the acquaintance of such men as Emmett Holt, Park, Jacques Loeb, Ostwald, Ehrlich, Meyer, and numerous musicians, artists, and writers who were Herter's friends. In 1902 he first met George B. Wallace, who had just come to New York from Cushny's Department of Pharmacology at Michigan to introduce pharmacology as an experimental science in the Bellevue Medical School. Richards and Wallace took to one another from the start and soon were sharing a room in a boardinghouse on 46th Street. Until his death in 1949, Wallace was Richards' closest friend.

In 1903 Herter accepted an invitation to become Professor of Pharmacology and Therapeutics at Columbia. He persuaded Richards to accept an instructorship in the new department and assigned him the job of organizing a laboratory course in pharmacology corresponding with the one recently introduced by Wallace at Bellevue. Neither Herter nor Richards pretended to know anything about pharmacology, and so they were given a year's leave of absence in which to prepare for their new assignments. Wallace joined Richards in a trip to Strassburg in June 1903, where they hoped to learn how to organize a student laboratory course in pharmacology from Oswald Schmeideberg, whose laboratory then was the mecca for those seeking preparation for careers in this new science. They were disappointed to find only uninspired lectures and rather pedestrian research "Arbeiten," but Richards relieved the tedium of Schmiedeberg's laboratory by spending the afternoons in the chemical laboratory of Franz Hofmeister, whom he found as interesting and stimulating as Schmiedeberg was the reverse.

In the early autumn of 1903 Richards returned to New York without having learned more pharmacology than he could have gleaned from Schmiedeberg's book, and with no progress in the job of preparing a laboratory course in pharmacology for the following year. Herter was spending the entire year learning pharmacology from Ehrlich in Frankfurt and Meyer in Marburg and was not available for advice or assistance. Richards therefore turned to his friend George Wallace and got his permission to assist in the student laboratory exercises in pharmacology at Bellevue. Thus he learned to carry out a number of relatively simple student experiments. This experience, together with studying textbooks and reading some of the literature, constituted his formal training for a career in pharmacology.

Later in the academic year President Nicholas Murray Butler of Columbia wrote Richards that an increase in admission requirements for the Law School would lessen the University's income to an extent that would make it impossible to go through with the plans for a new Department of Pharmacology. By this time Richards had already resigned from the Department of Physiological Chemistry and was faced with the need to justify a promised salary in pharmacology. On Wallace's advice, he sought and got the permission of John G. Curtis, head of the Department of Physiology at Columbia, to use the newly equipped student Laboratory of Physiology for an elective course in pharmacology for twenty-four students.

President Butler and Herter approved the plan, which Richards proceeded to carry out.

An interlude of this period began with an encounter in 1903 between Richards and John Howland, who was beginning a distinguished career in pediatrics as assistant to L. Emmett Holt. Howland was trying to improve the treatment of a child suffering from cyclical vomiting by searching the urine for substances other than acetone and acetoacetic acid, which had recently been reported to be present. Howland's obvious inexperience in chemistry led Richards to offer his assistance and between them they soon demonstrated the presence in the urine of large amounts of indican (indoxyl sulfuric acid) in addition to ketone bodies. The latter were then regarded as evidence of decreased oxidations in the liver, while the former was known to be an oxidation product of indole, a product of intestinal putrefaction. These considerations led Richards to propose that cyclic vomiting in children might be related to failure of the liver to oxidize indole, a substance that can cause muscular twitchings and convulsions in animals, and to design animal experiments to test the proposition.

The idea was to investigate the influence of interference with oxidations (by means of cyanide) on the toxicity of indole. Preliminary experiments on frogs and guinea pigs indicated that the effects of indole can be prolonged by simultaneous injections of nonlethal doses of cyanide. When similar experiments were made in dogs, an unexpected chronic posioning ensued, characterized by spasticity of muscles, vomiting, and blindness. This lasted several days and was invariably followed by death.

These findings were judged important enough to warrant a report by Howland at the meeting of the American Pediatric Society in June 1904. Unfortunately, Howland's first child was born the night before the meeting and the Society's regulations precluded presentation of the paper by Richards, who was not a member. He was, however, permitted to join in the discussion after the report was read by a member of the Society. Thus he had his first encounter with David Edsall, who was greatly interested in the findings and apparently also impressed by the young chemist-pharmacologist who was instrumental in obtaining them.

Richards and Howland then extended their experiments to include other means of inhibiting oxidations in the liver, and thus they came to a series of observations with chloroform, whose ability to produce acute yellow atrophy of the liver had recently been reported. They spent considerable time on a study of the late effects of chloroform on the liver, including urinalyses and tissue studies. By this time (1908) Richards had accepted an appointment in Chicago and he and Howland decided to compile a report on their indole work. Before doing this Richards characteristically insisted that they repeat the earlier experiments, to be certain that the results could be duplicated by anybody who cared to make the effort. To their horror, they were unable to reproduce the delayed fatal poisoning by cyanide and indole. After many unsuccessful attempts to find the reason for the discrepancy, they finally decided not to attempt a definitive report and the results of this effort were never published.

Nevertheless, the four years of joint effort with Howland were far from wasted. The work on delayed chloroform poisoning led to a publication that attracted considerable attention. Richards' concurrent elective course in pharmacology for medical students entailed a continuing challenge to increase his skill in methods that might be useful in investigations of drug actions, and among these methods perfusion techniques were prominent. The Langendorff procedure for maintaining the functions of the perfused mammalian heart had recently been used to study the actions of chloroform on the mechanical and metabolic functions of the heart, and the possibility of using a corresponding procedure to elucidate the effects of chloroform and other drugs on the liver gave rise to a plan for the perfusion pump which was eventually to determine the course of his career. His connection with the study on chronic indole poisoning as a possible cause of cyclic vomiting in children attracted the attention of David Edsall, who as Professor of Therapeutics at the University of Pennsylvania was instrumental in getting Richards to come to that institution six years later. Richards' association with Howland gave him his first direct contact with clinical problems and was the start of a plan for a collaborative clinical and laboratory activity which eventually became a program in clinical pharmacology, the first of its kind in the country if not in the world. The paper on chloroform poisoning led George Whipple to use this procedure in experiments which began the researches that eventually brought him the Nobel Prize. John Howland got an apprenticeship in quantitative chemical methodology which stood him in good stead in the studies of metabolic diseases in children which subsequently made him famous.

Meanwhile, as Instructor in Pharmacology, Richards was continuing the elective course in pharmacology in the Laboratory of Physiology. This course must have been successful because, in the spring of 1907, the dean of the Columbia Medical School asked Richards to make it a part of the regular course for second-year medical students. There being almost no money available for such purposes, Richards agreed to equip a laboratory for twenty-four students for $500. After a visit to inspect Cushny's laboratory at Ann Arbor, he designed and arranged for the building of six animal tables and some cabinets in his home town, where carpenter work was cheap. These articles were shipped knocked down to New York, where they were assembled by Richards and a retired locomotive engineer, who was hired as diener. Animal holders were purchased from the Department of Physiology, kymographs from the Harvard Apparatus Company, and Richards himself made mercury manometers and sphygmomanometers. Through such improvisations he got the laboratory going on less than $500.

At the end of the first year of this arrangement (i.e., spring, 1908) Richards was offered an assistant professorship of physiological chemistry in the University of Missouri and the professorship of pharmacology at Northwestern University. At first he refused both offers because he was so interested in what he was then doing that he did not want to leave New York. However, he had recently become engaged to Lillian Woody, and when these two tried to foretell when they might be married on what he was likely to earn in New York, they decided to accept the offer from Northwestern. So in August 1908, he and Wallace broke up their partnership in the flat they had shared for six years and he moved to Chicago.

During the ten years he spent in New York (1898-1908) Richards saw and participated in an unparalleled series of events in medical education and research which marked the emergence of the modern pattern, and of himself as one of its most promising young advocates. The decade began with the appearance of his first scientific publication in Volume 1 of the *American Journal of Physiology,* the first of several new periodicals to appear in rapid succession as manifestations of the growing interest in research in the medical sciences in the United States. This paper had to do with the digestion of starch by saliva and its appearance in the new physiological journal places it in the period preceding the separation of the chemical approach to physiology into a distinct scientific discipline, biochemistry. Actually he was soon to play an active part in this separation, and his next contributions to the physiological literature would be along lines other than chemical.

Richards was one of the first scholars of the Rockefeller Institute for Medical Research, which began its distinguished career in 1901. As a Rockefeller Scholar he was working with

Christian Herter in 1904 when the latter was invited by John J. Abel to join in founding a new *Journal of Biological Chemistry*. Abel, who at that time was in charge of both pharmacology and physiological chemistry at Johns Hopkins, had recently been instrumental in establishing the *Journal of Experimental Medicine*. Abel and Herter became joint editors of the new *Journal of Biological Chemistry* and Richards was invited to serve as assistant editor, which involved responsibility for proofreading, preparation of manuscripts for the printers, and business transactions with the publishers. The first number appeared late in 1905 and the journal, now in its 246th volume, has become one of the most important scientific publications in the world. It is noteworthy that, on his retirement as managing editor in 1914, Richards received letters of appreciation from contributors who gratefully recalled instances in which the meticulous, conscientious young managing editor had pointed out errors or misstatements in texts or tables before publication.

The spirit of the times is evident in the ability of John Abel, head of the Department of Pharmacology in the recently organized Johns Hopkins Medical School, not only to direct the Department of Physiological Chemistry as well as his own, but also to bring about the establishment of two of the most influential American scientific journals. As a matter of fact, in 1909 the same man proceeded to establish a third—the *Journal of Pharmacology and Experimental Therapeutics*—but by this time Richards was in Chicago and had nothing to do with the new undertaking. These events were concurrent with the establishment of the American Society of Biological Chemists (1906) and the American Society for Pharmacology and Experimental Therapeutics (1908), as offshoots of the American Physiological Society, which had been in existence since 1887. The next development was the coalescence of these three societies into the Federation of American Societies for Experimental Biology, which took place in Philadelphia in 1913, three years after Richards had moved to that city.

Meanwhile the dynamic new spirit which underlay these events was transforming the medical scene in New York. Its impact was first apparent in the Bellevue School, and the development of major importance to Richards was the coming of George Wallace from Cushny's Department of Pharmacology at Michigan in 1902 to set up the first teaching department in the science of pharmacology in the New York area. The Rockefeller Institute then was under construction and in 1904 Simon Flexner arrived as its director, bringing with him Opie and Noguchi. Meltzer, Levene, and others soon were drawn into the new enterprise. Two new societies which began as strictly local organizations but have grown to have much more than local significance—the Society for Experimental Biology and Medicine, and the Harvey Society—were founded in New York in 1904 and 1905 respectively. The list of research men involved in these developments includes Chittenden, Gies, Prudden, Herter, Lusk, Dunham, Hiss, Wallace, Shaffer, Flexner, Meltzer, Jacques Loeb, Opie, and Noguchi. In his notes, Richards has this to say: "I had the privilege of intimate association—on a somewhat junior basis—with all these people, and became saturated with their ideals. What I accomplished by way of lastingly useful scientific research was negligible but what I got by way of spiritual stimulation was beyond price."

Richards left for Chicago on August 1, 1908, to prepare the laboratory for the opening of classes in September. Pharmacology previously had been combined with physiology at Northwestern and Richards' appointment was intended to give greater recognition to pharmacology, which then was being projected into new prominence by the work of Dale on the actions of natural and synthetic sympathomimetic amines and by that of Ehrlich on the synthesis of arsenical chemotherapeutic agents. Richards was expected to conduct laboratory exercises for classes of about 150 medical students in materia medica and pharmacy, as well as in experimental pharmacology. There was one large room, half of which was equipped with chemical benches and lockers. The other half was vacant except for the professor's desk, which was railed off in one corner. The chemical desks were well made but badly scarred and the energetic new professor, accustomed to smooth chemical black-tops, immediately set to work (with one ignorant and inadequate diener) to remove the unsightly old finish and replace it with a shiny new one. This was accomplished in time for the first semester and the new appearance of the laboratory elicited favorable comments from faculty, students, and visitors, one of whom was Richards' former teacher Chittenden.

Richards had had no instruction or experience in materia medica and pharmacy, but he went about the new task with characteristic energy and dedication and he quickly won the cooperation, respect, and eventually the admiration of the students. For the course in experimental pharmacology in the second semester he prepared much the same laboratory exercises as those he had learned from Wallace. He had the part-time assistance of one third-year medical student and one diener. The class had to be handled in six sections, which meant a student laboratory exercise every day of the week except Sunday. He gave two lectures and conducted two conferences a week. He also managed to keep up with the managing editorship of the *Journal of Biological Chemistry*. On December 26, 1908, he was married to Lillian Woody and set up housekeeping in an apartment on Michigan Avenue.

Research was out of the question except during the summer, when he attempted to learn if acquired tolerance to alcohol would make the heart of an animal resistant to the depressant effects of the drug. The results were inconclusive, but the experience in overcoming the vagaries of the isolated mammalian heart preparation helped to make this experiment one of the memorable events of medical students in his laboratory.

The second year in Chicago was much like the first. During its course he was invited by David Edsall, Professor of Therapeutics at the University of Pennsylvania, to come to that institution to reorganize the Department of Pharmacology. Pennsylvania—the oldest medical school in North America—was at last becoming aware of the ferment that Richards had already experienced in New York and a group of young faculty members was engaged in an attempt to introduce some of the new research attitudes, which had not yet had much impact in Philadelphia. Their immediate program involved the installation of Edsall as Professor of Medicine, his friend Alonzo Engelbert Taylor as Professor of Physiological Chemistry, Howard Ricketts as Professor of Pathology, Richard M. Pearce in a newly endowed chair of research medicine, and Richards as Professor of Pharmacology.

Except for the appointment of Ricketts (who died in the summer of 1910) this program was carried out, and Richards came to Pennsylvania in the autumn of 1910 as one of a small group of devotees of the then new research approach to the teaching and practice of medicine. They were brought there through the efforts of a small but influential minority of the faculty and they were confronted with the hostility of a majority who were satisfied with things as they were. Edsall, the senior member of the group and the one from whom most was expected, stayed one year in this new post and then resigned to go on to a distinguished career at Harvard. Taylor soon left to join his fellow Californian, Herbert Hoover, in relief activities during World War I and transferred his vigor and talents to nutritional economics at the national and international level. Pearce secured support from the Rockefeller Foundation and practically withdrew from university activities. Only Richards, the youngest and most inconspicuous of the group, and the only one without medical training in an institution with a long tradition of clinical excellence, stayed on to win local, national, and international fame for himself, his laboratory, and his adopted university.

The first year in Philadelphia was very difficult. Pharmacology had been allotted considerable space in a new Medical Laboratories Building opened in 1906, but the student courses that had been given followed the traditional materia medica approach and had established a reputation for being uninteresting and unimportant. Richards set to work to make over the laboratory so as to permit mammalian pharmacological experiments by the students, which had not been attempted previously at Pennsylvania. He also insisted that his course should be given to the second-year students rather than the third, as had been the custom. The change meant giving the course twice during 1910-1911, and this was done. He had two assistants to help in the laboratory and run the student conferences, but neither had had any previous experience with the type of course Richards wished to give and he had to begin by doing everything himself.

To complicate matters further, Christian Herter died in December 1910 and the editorship of the *Journal of Biological Chemistry* had to be reallocated. The business and editorial offices were immediately transferred to Richards' laboratory and he became in effect managing editor, with a secretary and an editorial assistant. This arrangement continued until 1914, by which time the enterprise had come to occupy so much of his time that he had to choose between it and serious research. He gave up the *Journal.* The new editor was Donald Van Slyke and the offices were moved to the Rockefeller Institute in New York.

The year 1910-1911 was the nadir of his career at Pennsylvania. During this time his new-type course in pharmacology began to arouse interest, respect, and eventually admiration in the students, who were having their first experience with the modesty, self-criticism, and objectivity of a true scientist. In 1911 he was joined by Oscar H. Plant, who had been teaching pharmacology at the University of Texas. Plant soon proved able and willing to take over the tasks of preparing and conducting the student laboratory exercises, but Richards continued to give all the lectures and to participate in the student experiments. This, with his editorial duties, left no time for research.

As a matter of fact the research program that eventually brought him distinction developed naturally from his unremitting efforts to improve his teaching, perfection of which dominated his existence then and for years to come. The first of a series of pertinent events came in June 1913, when he was approached by a member of the graduating class at Pennsylvania who had found Richards' course in pharmacology so interesting that he wanted more experience in this field before he went to Johns Hopkins to spend a year with Howell in physiology. His name was Cecil K. Drinker and his academic record in the medical school at Pennsylvania marked him as one of the most brilliant students ever enrolled there. After considering several possible research projects, Richards and Drinker decided to undertake construction of the perfusion pump whose general design had been developing in Richards' mind ever since his work with Howland on chloroform poisoning of the liver. It turned out to be a fortunate choice because Drinker had considerable skill in working with metals. The result was a device by which mammalian organs could be perfused with blood in patterns so close to the normal as to permit useful physiological studies in tissues isolated from the body. The functional adequacy of the pump was demonstrated before Drinker left for Baltimore in the autumn of 1913. Drinker went on to achieve distinction in his own right, but he also happened to be the first of a considerable number of medical graduates who came under Richards' influence at early stages in their careers and who contributed to the reputation of his laboratory either directly or through protégés recommended to him. Drinker's greatest contribution to Richards' subsequent rise to prominence actually was his recommendation to two recent graduates of the Harvard Medical School—Joseph T. Wearn and Arthur M. Walker—that they spend a year studying pharmacology at Pennsylvania before settling down to careers in academic medicine. These two men subsequently played preponderant roles in the research projects from which Richards' fame was derived.

Drinker left for Baltimore before the new perfusion pump could be used for more than validation studies. After discussing the matter with Plant, Richards decided in 1913 to utilize the pump to settle once and for all the question of how caffeine causes diuresis. At that time the physiology of urine formation was locked in controversy between the protagonists of the filtration-reabsorption theory of Ludwig and the secretion theory of Heidenhain. Neither side had been able to devise a crucial experiment and Richards therefore was compelled year after year to give the medical students the two alternatives, while refraining from expressing a conviction of his own. The new pump would make it possible to maintain a constant flow of blood through the kidney irrespective of changes in the resistance of the renal blood vessels. Increased urine from caffeine under these circumstances would be evidence favoring stimulation of secretory activity while absence of effect would argue for the filtration-reabsorption concept.

The experimental difficulties turned out to be unexpectedly great. This was long before the discovery of heparin and the only nontoxic anticoagulant available for viviperfusion experiments was hirudin (leech head extract), which was very difficult to obtain after the outbreak of World War I in July 1914. Finally Richards and Plant completed a small series of experiments in which caffeine was found to increase urine formation by the mammalian kidney perfused with a constant volume of blood and diuresis was associated with fall rather than rise in renal arterial pressure. These findings were favorable to the Heidenhain secretion theory and irreconcilable with the Ludwig filtration-reabsorption concept as then formulated. Richards was unwilling to let the matter rest there, but further work had to be postponed until World War I had ended.

Shortly after America became involved in World War I, Richards was invited to join Henry Dale in a study, under the auspices of the British Medical Research Committee, on the cause of wound shock. One result was a definitive investigation of the actions of histamine, which led to a publication that is one of the classics of medical literature. One of the novel conclusions was that the capillaries are not entirely passive, but have considerable capacity for intrinsic control. This idea had immense influence on Richards' subsequent work on kidney function.

In July 1918 Richards was commissioned a major in the U.S. Sanitary Corps and given the assignment of setting up a field laboratory for the study of problems of chemical warfare at Chaumont, France. He went to France early in September and was at Chaumont when the armistice ended the war in November 1918. Shortly thereafter he returned to Philadelphia to resume his professional duties, from which he had been granted leave of absence by the university authorities, and was given an honorable discharge from the U.S. Army in Washington in December 1918.

He plunged immediately into the teaching program, which was arousing greater and greater admiration as time went on. He and Plant also resumed the kidney perfusion experiments they had begun five years previously.

This time the plan was to maintain constant the quality and quantity of blood flowing through a rabbit kidney while raising the renal arterial pressure by several different procedures. These procedures included partial obstruction of the renal vein, stimulation of the splanchnic nerve, and introduction of minimal vasoconstrictor doses of adrenaline. The common result was diuresis, a finding that was regarded as cogent support for the Ludwig filtration-reabsorption concept of urine formation.

These experiments were demonstrated to a number of visiting scientists, one of whom suggested that a concomitant record of kidney volume by an oncometer might provide useful information. When this was done, it was found that while adrenaline in more than minimal dosage caused rise in renal arterial pressure, fall in kidney volume, and anuria, the smallest effective amounts cause rise in arterial pressure, together with increase in kidney volume and diuresis. In corresponding perfusions of the leg, any dose of adrenaline that raised the perfusion pressure caused a pure decrease in limb volume.

These findings suggested to Richards that the paradoxical behavior of the renal circulation following minimal vasoconstrictor doses of adrenaline might be related to the presence of glomerular capillaries intercalated between afferent and efferent arterioles. More specifically, if the efferent glomerular arteriole were constricted a little more than the afferent by minimum effective concentrations of adrenaline, the swelling of the kidney could be attributed to increased glomerular volume, the diuresis to increased glomerular filtration pressure. This general idea has become a familiar and important part of modern nephrology, but at that time it was a totally new concept which Richards was unwilling to consider further without direct experimental proof or disproof. It was against this background that the experiments that made him and his laboratory famous came to pass.

In 1919 Richards' budget was increased enough to enable him to take on a new instructor, whose accession increased the number of his scientific staff by 50 percent, that is, from two to three.

It was my good fortune to be chosen to fill this new vacancy. As a second-year medical student at Pennsylvania, I had taken the course in pharmacology which he and Plant gave and my recollections caused me to want further experience with such work. I remembered that in pharmacology the equipment always worked and the experiments almost always succeeded; when they did not, the laboratory reports came back with painstaking and informative explanations and discussions. I did not realize, until I joined the department, the enormous effort that underlay this smooth performance. Richards set an exhausting pace of attention to detail and rehearsal to the point of perfection. He used to say that the major function of a teaching department was to teach, and that the First Law of Thermodynamics applied as much to teaching as to research, which I took to mean that one got out of teaching precisely what one put into it. I was continuously challenged to try to live up to the standards of excellence he set for himself.

He regarded research in his department as a privilege rather than a right or duty, and he encouraged us recent medical graduates to develop our own projects while trying to blend them into the teaching program as far as possible. I later found that this procedure served the dual purpose of giving the students the benefit of the most recent local advances and of maintaining a peak level of interest of the teaching staff in their assignments. He sought to gain, hold, and deserve a reputation for keeping his teaching program up to date, and in this he succeeded. At the time, this was a novel approach, and the success that was soon to crown his career was, in my opinion, due more to his emphasis on excellence in teaching than to any other single factor.

When I joined Richards' department in the autumn of 1919, he and Plant were finishing the pump perfusion experiments on the kidney that led to the hypothesis that adrenaline, in minimum effective dosage, constricts the efferent glomerular arterioles relatively more than the afferent. Richards did not attempt at the time to elaborate the intellectually stimulating implications of this hypothesis as others have done since, but set himself the task of finding experimental evidence that would prove or disprove it. We all were busily studying Cushny's recent monograph, *The Secretion of the Urine,* and while so doing one of us came upon an inconspicuous account of recent experiments by Ghiron, who claimed to have watched the kidney of a mouse under the microscope while the glomeruli emerged as small dark globules after intravenous injections of dyes. Urged by Richards to try this for ourselves, we were unable to confirm Ghiron's observations, whereupon Richards suggested that the flat kidney of the frog might be more favorable than the globular organ of the mouse. This turned out to be the case and so during 1919-1920 I spent most of my free time watching the circulation on the surface of the frog's kidney under the low-power microscope.

The original purpose was to see if the glomeruli actually increased in volume under the influence of minute doses of adrenaline, but we forgot all about this in our entrancement over hitherto unknown events in the renal circulation, including intermittence of blood flow in different glomeruli and changes in the pattern of flow in individual loops of single glomeruli. The equipment was improvised, my experience nearly nonexistent, and I wound up with a good deal of eyestrain from uneven reflection of intense light from the surface of the frog's kidney. Therefore I was glad to withdraw from this project the next year when Joseph Wearn came from

Harvard to spend two years with Richards. By this time the departmental budget had been increased enough to provide a new instructor to help me in another project.

Wearn quickly improved the technique for microscopic observation of the circulation on the surface of the frog's kidney, but his greatest contribution was his suggestion that fluid might be directly withdrawn from the glomerular space for chemical analysis. At a meeting in Philadelphia in December 1920, he and Richards saw a demonstration by Robert Chambers of a new micromanipulating technique, and Richards, thinking of his urgent desire to demonstrate swelling of the glomerulus by the action of adrenaline on the efferent arteriole, proposed that the Chambers technique be used to inject a minute dose of adrenaline through the glomerular capsule while observing the area under the microscope. Wearn thereupon made the countersuggestion that if this could be done without damaging glomerular structures, the same technique might be used to withdraw fluid directly from the glomerular space for chemical analysis.

The result was one of those simple, direct, unambiguous experiments that researchers dream of but seldom attain. Glomerular fluid was readily collected in volume sufficient for qualitative tests for chloride (by silver nitrate) and sugar (by Benedict's solution) and both tests were positive. Bladder urine, simultaneously collected, gave negative reactions to both. Obviously these normal constituents of the blood were present in the glomerular fluid but were reabsorbed between the glomerulus and the bladder. The result was the first direct and unambiguous evidence of tubular reabsorption, which suggests (though it does not prove) glomerular filtration.

These experiments were reported and demonstrated at the annual meeting of the American Physiological Society in New Haven in December 1921, where they shared the spotlight with the first public announcement of the successful isolation of insulin. Richards' interpretation of his findings as evidence in support of the filtration-reabsorption concept of kidney function in general was challenged on the ground that evidence from the primitive kidney of the frog is not necessarily applicable to the behavior of the more complex mammalian kidney. To this criticism he replied that he and his colleagues had tried to make corresponding observations on the kidneys of mammals but had been unsuccessful. Since the kidney of the frog clearly subserves functions analogous to, if not identical with, those subserved by a mammalian kidney, they had decided that it was better to make the observations on the frog than not to make them at all. This rebuttal won an ovation the like of which I have never seen before or since. I do not know how extemporaneous his discussion was on that occasion but if it was prepared it was done with characteristic foresight, intelligence, and effectiveness.

The final answer to this particular objection was not obtained until nearly twenty years later, when Richards' senior assistant Arthur Walker, assisted by Jean Oliver and Phyllis Bott, succeeded in the incredibly difficult task of collecting and analyzing fluid from the glomeruli and various tubular levels of the kidneys of rats, guinea pigs, and opossums. The findings confirmed those on amphibia in all essential respects.

Before this occurred, however, a number of other important events took place. In 1921 the University increased his budget to enable him to begin a long-planned program in clinical pharmacology. Thus he was able to add to his staff recent medical graduates who, after a few years of full-time participation in the teaching and research activities of the Department of Pharmacology, went on to junior positions in the clinical services of the University Hospital. They continued to participate in the teaching and research programs in pharmacology and they organized and conducted a course in clinical pharmacology for the third-year students. This undertaking was highly successful, largely because it began by attracting such men as Isaac Starr, Joseph Hayman, Hugh Montgomery, Kendall Elsom, Osler Abbott, John Barnwell, and Arthur Walker. Starr, Hayman, Barnwell, and Walker joined Wearn and Richards in the kidney research project, which now went from the qualitative to the quantitative stage.

This step, which eventually involved quantitative determinations of the amounts of different urinary constituents in volumes of fluid of the order of one cubic millimeter or less, was made possible by Richards' observation of the remarkable accuracy with which his eye could distinguish small differences in the colors of fluids contained in glass tubes 0.5 mm. in diameter. By ingenious and painstaking modifications of existing chemical methods, he and his colleagues succeeded in making quantitative measurements of the content of eleven separate urinary components (glucose, chloride, urea, uric acid, creatinine, ammonia, alkali, phosphates, sulphates, total molecular concentration, and protein) in fluid samples collected from the glomerular spaces and from various levels of the corresponding renal tubules. The studies were first made on frogs, then on snakes and salamanders (necturi), and eventually on mammals. Corresponding methods also were developed for various foreign substances (dyestuffs, sucrose, xylose, inulin).

The major conclusion from all these efforts was that the renal excretion of substances normally found in the body involves separation from the glomerular capillaries of large amounts of an ultrafiltrate of blood plasma. Everything normally found in the urine was shown to be present in the glomerular fluid, and in concentrations essentially the same as in the blood plasma. In their course down the tubule the different components of the glomerular filtrate are reabsorbed into the blood stream at different sites and to different degrees ranging from complete (glucose) through nearly complete (water, alkali) to little or not at all (nitrogenous wastes and polysaccharides such as sucrose and inulin). Foreign substances (such as phenol red) can be secreted by the walls of the tubule into the fluid in the lumen, but this was not seen with any normal constituents of the urine and Richards resisted the claims of others that active secretion plays an important part in normal kidney function. He conceded its occurrence in fish with aglomerular kidneys or with foreign substances, and he himself provided a simple, direct, and conclusive demonstration of tubular secretion of a synthetic dye by immersing the freshly excised kidneys of frogs in a very dilute solution of phenol red. In about thirty minutes red streaks were seen in the kidneys and he proved these to be due to dye concentrated in the tubular lumina by injecting fluid under pressure through the ureter. This caused the streaks to be transformed into small spheres, representing the glomeruli with which the tubules were connected. Low concentrations of cyanide prevented the phenomenon, indicating an energy-coupled mechanism. Small amounts of mercuric chloride (a notorious kidney poison) acted like cyanide.

This particular observation gave rise to a study which proved that the decreased renal excretion of water and solutes, the most dangerous effect of mercury in the body, is due to interference by mercury with the selective functions of the renal tubular epithelium. As a result, the entire glomerular filtrate diffuses back into the peritubular circulation without regard to the body's requirements and death ensues from retention of water and waste products that normally would have been held back in the tubules for excretion in the urine. These findings, which were accepted as illuminating the events of "lower nephron nephrosis" in general, increased further the already considerable influence of the contributions of Richards' laboratory on advances in clinical medicine.

By 1924 Richards had become one of the most influential members of the Pennsylvania medical faculty. The process was aided by a close personal friendship, based on mutual respect and admiration, between Richards and William Pepper, who, soon after he became dean of the Medical School in 1912, learned to turn to the self-effacing young Professor of Pharmacology for advice on administrative problems and policies. It was a period of rapid acceptance and growing support of medical research at Pennsylvania, which was being led out of its former lethargy by the gentle, wise leadership of the new dean. Major steps were the appointments in 1921 of Henry C. Bazett (an associate of J. S. Haldane at Oxford) as head of the Department of Physiology, in 1922 of D. Wright Wilson (of Yale and Johns Hopkins) as head of the Department of Physiological Chemistry, and in 1926 of Eliot R. Clark (of Johns Hopkins) as head of the Department of Anatomy. Funds were raised for a new Anatomy-Chemistry wing for the Medical Laboratories and for the first time adequate modern quarters became available for research and teaching in these disciplines.

In 1925 Richards and his friend William Pepper were given honorary degrees (Sc.D.) by the University of Pennsylvania. For Richards, this was the first of thirteen such honors. The next year (1926-1927) he was granted sabbatical leave to accept an invitation from Henry Dale (now Sir Henry) to join in an exploration of the depressor (vasodilator) action of adrenaline. During part of this year he joined his former colleague Cecil Drinker in Krogh's Laboratory of Physiology in Copenhagen, where exciting investigations were being made of the functions of capillaries. While there he performed the simple experiments that proved beyond question the secretion of phenol red by the tubules of the excised kidney of the frog. Later in the year he made a similar experiment on slices of rabbit kidney in Dale's laboratory in London and got a similar result.

In 1927 Richards was elected to membership in the National Academy of Sciences, of which he was to become President twenty years later. By 1927 Arthur Walker was developing into a tower of strength in the kidney research project and was leading a group of able, eager, and devoted young assistants in quantitative chemical studies on fluid collected at various parts of the nephrons of frogs, snakes, and necturi. Reports of these studies were beginning to attract world-wide attention. The teaching program continued to appeal to the medical students and recent graduates were turning in increasing numbers to Richards' department for an experience in research and teaching in a basic medical science before settling down to a clinical career. This was before the development of specific residency training programs and medical graduates had great elasticity in the use of the years between the internship and the final selection of a career. Such young men contributed enormously to Richards' research and teaching programs and further raised the esteem in which his department was held.

In 1931 a new and relatively small private research foundation, the Commonwealth Fund, began a ten-year program of substantial financial support for Richards' kidney research projects. Simultaneously, new quarters were made available by the moving of the Department of Research Medicine from the Medical Laboratories Building to a newly opened Maloney Clinic Wing of the University Hospital. Richards was assigned the vacated space, which his new support enabled him to modernize. Thus he had adequate quarters and funding for the first time in his life. He delegated responsibility for the teaching program to me and proceeded to concentrate on the kidney research enterprise.

The years 1931-1939 were the Golden Age of his research career. Arthur Walker was the leader of a small permanent staff (Walker, Barnwell, Westfall, Bott, Kempton) who were supplemented by a succession of able young men from all over the world. The list includes Howard Florey, Leonard Bayliss, André Simonart, Charles Hudson, James Hendrix, Thomas Findley, James Bordley, John Brown, Frank Queen, Earl Wood, Hubert Royster, Julius Comroe, Eugene Landis, and Robert Dripps, as well as the earlier accessions (Starr, Hayman, Montgomery, Mendenhall, Livingston, Elsom, and Abbott). Not all of these spent all their time on the kidney research project, but there were frequent contacts and discussions, and affection for Richards was a compelling bond.

By 1932 the new enterprise was in full operation and the techniques became more and more sophisticated. Richards had a personal hand in all the activities, but a large share of credit must be given to Walker's doggedness, dexterity, and devotion. A major new development was a procedure for introducing a substance at one level of a kidney tubule and recovering it from another. One of the most pressing questions had to do with the location and extent of the absorption of water by the tubular walls. To obtain pertinent evidence Richards sought a harmless substance which would not diffuse through the tubular walls when so introduced. Such a substance, injected in known concentration into one part of a tubule, could be withdrawn from a lower segment, and any change in its concentration would be a measure of the transport of water into or out of the tubule. He tried dilute starch paste and found, to his surprise, that it underwent partial digestion during its stay in the tubule, presumably because of the presence of starch-splitting enzymes. Casting about for another polysaccharide that would not be digested, he recalled his experience with inulin in Hiss's laboratory at Columbia thirty years previously. He procured a sample of pure inulin from the Bureau of Standards in Washington, tried it, and found it exactly what he wanted.

Further work with inulin showed that it was filtered by the glomeruli, was not reabsorbed in the tubules, was not altered by kidney tissue, was not excreted in the urine of the toadfish (which has no glomeruli), but was rapidly eliminated in the urine of the dog after intravenous injection. Thereupon Richards conceived the idea that inulin might be used to measure the rate of glomerular filtration in mammals and perhaps in man. Accordingly in June 1933 he (with Westfall and Bott) undertook a series of comparisons of the renal excretion of inulin and creatinine (which is filtered by the glomeruli and not reabsorbed by the tubules) and in 1934 a corresponding study was made with xylose. The results indicated that inulin behaves like creatinine in the dog and can be used to measure glomerular filtration, whereas xylose is less satisfactory. This was the extent of the use of inulin to measure glomerular filtration in Richards' laboratory. The subsequent clinical applications came from Homer Smith's group, who apparently conceived the same idea at about the same time and developed it quite independently.

Richards now was world-famous and honors came to him correspondingly. His initial Sc.D. from Pennsylvania (1925) was followed by the same degree from Western Reserve (1931), Yale (1933), Harvard (1940), Columbia (1942), Williams (1943), Princeton (1946), New York University (1955) and finally, in 1960, from the Rockefeller University, sixty years after he received for the support of his youthful research the first grant to be made by what was then the newly created Rockefeller Institute for Medical Research. He received an LL.D. from Edinburgh in 1935 and from Johns Hopkins in 1949, an honorary M.D. from Pennsylvania in 1932 and Louvain in 1949. He was awarded the Gerhard Medal by the Philadelphia Pathological Society in 1932, the Kober Medal by the Association of American Physicians in 1933, the Keyes Medal by the American Association of Genito-Urinary Surgeons in 1933, the Gold Medal of the New York Academy of Medicine in 1936, the Lasker Award in 1946, and the Kovalenko Medal of the National Academy of Sciences in 1953. In 1938 he was invited to give the Croonian Lecture for the Royal Society of London and in 1942 he was elected a foreign member in that Society. In 1934 he received the John Scott Medal of the City of Philadelphia and in 1937 he was given the annual Philadelphia Bok Award. He was awarded the Medal for Merit of the U.S. government in 1946 and was made an Honorary Commander of the Order of the British Empire (C.B.E.) in 1948.

Meanwhile he became increasingly involved in administrative duties at Pennsylvania, and his influence progressed as Pennsylvania developed into a leader in medical research. In 1939 he was appointed Vice President in Charge of Medical Affairs, a position which he held until his retirement for reasons of age in 1948. His predecessor—Alfred Stengel, Professor of Medicine at Pennsylvania—had been able to secure funds to construct a new addition to the medical facilities of the University Hospital and to support the staffing and equipping in it of the Johnson Foundation for Medical Physics, the Cox Institute for Metabolic Research, and a new Laboratory of Research Medicine. Richards worked with characteristic diligence and effectiveness to perform a similar service for the surgical end of the hospital and he succeeded to the extent of a new Agnew-Dulles Wing dedicated largely to research.

The new duties forced him to curtail drastically his participation in the kidney research project, which now entered what proved to be a final phase of work (led by Walker) on the mammalian kidney. Early in 1941 Richards was invited to come to Washington as chairman of the new Committee on Medical Research of the Office of Scientific Research and Development, an organization intended to enlist the cooperation of American scientists in World War II. He was given leave of absence from Pennsylvania and began his new duties on July 15, 1941. He proceeded to divide his time between Philadelphia and Washington until December 31, 1946, when the Washington organization was abolished and he resumed full-time service at Pennsylvania. In the summer of 1941 Walker finished the work under way in Richards' kidney research project and subsequently joined Richards in Washington as an executive assistant. The quarters occupied by the kidney research group were turned over to a new project in aviation medicine, of which the Department of Pharmacology was the center, and were never used again for the original purpose.

From mid-July 1941 until the end of 1946, Richards spent the major portion of his time and energy in Washington, but he usually managed to find a day or two in each week for vice presidential activities at Pennsylvania. One of the most important of these turned out to be the organization of a new Department of Anesthesiology under Robert Dripps. This was a joint undertaking of Pharmacology (whose staff Dripps joined in 1938) and Surgery (of which I. S. Ravdin had recently become the head), but it was consummated by Richards' personal efforts. Dripps's department has gone on to add new distinction to the University of Pennsylvania and to provide another enduring memorial to Richards' term as Vice President in Charge of Medical Affairs.

In his Washington career Richards displayed the same qualities that had won him respect, admiration, and devotion in all his previous endeavors, and with the same result. Under his personal guidance, his Committee on Medical Research secured the cooperation of American medical science in a variety of major research enterprises of vital importance to the war effort. Owing to the foresight of Richards and his associates, the organization was fully functioning when the

Japanese attacked Pearl Harbor and actual war-directed work got under way with much less than the usual delay. The activities involved practically all facets of medical science, clinical and laboratory, and they enlisted the cooperation of academic, governmental, and industrial institutions. Those activities to which major attention was devoted included aviation medicine, trauma, burns, blood substitutes, tropical diseases, bacterial chemotherapy, shock, aerial transport of wounded, and protection against chemical and biological weapons. A comprehensive program on antimalarial drugs, originally undertaken because of interruption of the supply of quinine, led to the development of synthetic drugs far superior to quinine in the prevention and treatment of malaria. The blood substitute program made possible the saving of many lives that would otherwise have been lost. In aviation medicine there were great improvements in protective equipment and a number of advances in fundamental science which paved the way for the postwar developments of the Space Age. Perhaps the greatest immediate contribution to human welfare was the development of penicillin from a laboratory curiosity to a practical therapeutic agent.

In this development Richards played a key role. His own version of it appears in his last scientific publication (1964). Written with characteristic self-deprecation, the paper makes no mention of his personal contribution to the decision to concentrate attention on the production of penicillin by natural fermentation rather than by synthesis. However, I clearly remember his telling me, shortly after Howard Florey came to the United States in the summer of 1941 to start the entire series of events, of the difficult decision between natural production by fermentation (which then was so inefficient as to preclude any but a token supply of penicillin) and laboratory synthesis (which had never been accomplished but which expert chemists then regarded as quite feasible). True to his lifelong adherence to the principle of going from the known to the unknown one step at a time, he used his influence in favor of natural production, which was known to have been successful, though so inefficient that as much as 2,000 liters of culture medium had to be processed to treat a single case of sepsis.

This turned out to be an inspired decision. Within two years, improvements in the culture medium and the selection and development of more productive strains of the mold increased the yield of penicillin from one unit to 900 units per milliliter of culture medium. In 1943 production in deep vats was begun and by June 1944 there was enough penicillin from American and British sources to treat the casualties of the Normandy invasion. At the time of the Japanese surrender in August 1945, production in the United States had risen to 650 billion units per month. By this time British and American chemists had succeeded in synthesizing minute amounts of authentic penicillin, but the cost of producing 100,000 units by natural fermentation already was less than the cost of the labor and material required to put it into an ampoule, and there was no prospect of economic advantage from synthesis. The same situation still prevails.

The activities of Richards' Committee on Medical Research were gradually terminated during 1946 and the organization was abolished at the end of that year. He returned to his post as Vice President in Charge of Medical Affairs at Pennsylvania and served in this capacity until June 1948, when he retired and became Emeritus Professor of Pharmacology. His senior associate in the kidney research project, Arthur Walker, did not return to Philadelphia and Richards made no attempt to resume the project. During these last years of his active career he received three more honorary degrees in addition to the Medal for Merit of the U.S. government and the Order of the British Empire.

In 1947 Richards was elected President of the National Academy of Sciences. For the duties of that high office he was well qualified by his previous service as chairman of the Committee on Medical Research of the OSRD. During the war years, he had worked in the house of the Academy and had there gained a broad understanding of how the Academy and its Research Council could further science and the national welfare through close relations with many sections of the federal government.

The chairman of the National Research Council during his presidency was Detlev Bronk, his friend and Pennsylvania colleague of many years. To him Richards gave strong support, encouragement, and freedom in the development of the Council as scientific adviser to the government and to private foundations. During his presidency of the Academy his wise counsel and sound judgment were widely sought by congressional committees and executive agencies.

Under his vigorous leadership the scope and significance of the Academy's Research Council quickly grew. As it did so, and as he envisioned an ever-growing role for science in government and universities, Richards modestly decided to retire in favor of a younger man. That he did in 1950. In 1948 he was appointed to membership in the Medical Section of the First Hoover Commission on the Organization of the Executive Branch of the U.S. government and was active in this enterprise until March 1948. During the same year he became a member of the Board of Directors of Merck and Company, to whom he had already been a consultant for some twenty years. This relationship was a major source of satisfaction in the final stage of his career. The nature of the relation is indicated by his selection to serve as chairman of the Scientific Committee of the Board of Directors during the 1953-1955 period. From 1948 until his death he also was an Associate Trustee of the University of Pennsylvania.

Final honors were the presentation of the Abraham Flexner Award of the Association of American Medical Colleges in 1959, for outstanding service in the teaching of medical students, and the naming after him in 1960 of a new medical research building attached to the Medical Laboratories which had been his scientific home for the preceding fifty years. His remarks on that occasion are recorded in *Medical Affairs,* a publication of the Pennsylvania Medical School, in the summer of 1960. They include a revealing summary of his attitude toward life in general and toward the University of Pennsylvania in particular. His words were as follows:

"Any name that is carved into a permanent structure of this, the oldest and, as we choose to think, the most illustrious school of medicine in this country, acquires an incomparable distinction. It still seems incredibly unreal that the name which is being thus recognized today should be the one my parents gave to me and I can expect that the rest of my days will be periodically beset with alternating periods of elation, doubt, and disbelief—never, I am sure, without humility.

"This latest indebtedness to the University of Pennsylvania about to be incurred today is the culmination of a long series of blessings which have come through my half-century of associations here. It seems not only appropriate but obligatory that I recite those which have meant most to me."

He went on to enumerate the generous arrangements which Provost C. C. Harrison made for the start of his career at Pennsylvania in 1910; the leaves of absence granted him by Provosts Edgar F. Smith in 1917 and Charles Penniman in 1926 to enable him to work with British physiologists; the addition to his budget in 1921 of funds which made it possible to add young physicians to his staff and thus to develop a program in clinical pharmacology; the authorization to accept the support of the Commonwealth Fund for the years 1931-1941; a leave of absence for five years beginning in 1941 to accept a presidential appointment for war work in the Committee of Medical Research; the privileges of a laboratory and equipment which enabled him to do what he most wanted to do, with small administrative duties; a dean, Dr. William Pepper, who for thirty-two years gave him friendship, encouragement, and the help of ripe wisdom and calm judgment; and younger associates through whose independent intelligence and skill important progress was made.

He acknowledged the generous financial contributions of the U.S. Public Health Service to the construction of the building that now bears his name, and to the support of the investigators working in it. Then he had this to say:

"We are proud that our investigators have the quality which warrants the confidence and support of the granting agencies and their expert advisors. We do not now fear the old imagined threat of federal control. But ready access to abundant research funds is associated with subtle temptations not easy to recognize and resist.

"Those are the temptations to ask for more than is needed or justified; to overestimate the influence of volume of results perhaps at the expense of quality; to delegate too much of the work to assistants or technicians and thus for the investigator to be deprived of opportunity of seeing the chance breaks which nature so frequently yields. There is also the temptation to shape the plan of a research to suit what are believed to be the aims of the granting agency or to the peculiarities of the expert advisors; the temptation to forget that a reasonable degree of austerity is a wholesome stimulant; that excessively elaborate equipment can convert the investigator into a technologist and may obstruct his direct vision of the living system which he studies and of its beauties; that discoveries are usually made not by teams, but by an individual, lonely and tormented by a passion to break through the blank wall which stands in the way of his understanding."

This, his last public utterance, seems to me to contain an appropriate *apologia pro vita sua.*

His last years were clouded by the slow advance of an inoperable neoplasm, and by the tragic death of his son and only child in an airplane crash in November 1962. Death came to him from a respiratory infection on March 24, 1966, two days after his ninetieth birthday.

In the preceding pages I have attempted to present an impersonal account of the career of Alfred Newton Richards. The information on the period prior to 1919 (when my own association with him began) is derived for the most part from copious notes left by him for the benefit of his biographer, a circumstance that bespeaks the sympathetic consideration for others that was one of his outstanding traits. For the rest, I have depended principally on my own memory, supplemented by his own notes and publications and by comments from other former colleagues and friends. The bare facts leave little doubt that this was one of the most distinguished and important medical scientists of his generation. Having been associated with him as student and colleague for fifty years, I am quite certain that that is how he would want his biography to end. I am equally certain, however, that the importance of this man depended more on the impact of his personality on his contemporaries than on his scientific achievements, great as these were. Actually the two were so interwoven that a meaningful evaluation of his career requires an attempt to add the contours of a warm human being to the bare skeleton of his accomplishments. Therefore I venture to append a brief account of the part played by his personal traits, as I knew them.

His career seems to have been determined by a series of apparently coincidental openings of doors whose existence must have been previously unknown to him. The coincidences were too numerous and too uniformly fortunate to be entirely accidental, and those who had the good fortune of working with him will have no difficulty in discerning the imprint of the character traits that attracted and held us to him. The most important of these were complete honesty (coupled with an extraordinary capacity for making himself the most severe critic of his own thoughts and actions), an all-pervading striving toward perfection in everything he undertook (coupled with a surprising degree of physical stamina and a great willingness to draw upon it), high intelligence (along with an abhorrence of pretentiousness and egotism), unselfishness, deep concern for others, a constant search for simple, direct approaches and for evidence that will speak for itself, and a rare, gentle sense of humor.

It is reasonable to suppose that most if not all of these qualities must have been as evident to Chittenden, Hiss, Prudden, Herter, Wallace, Howland, Edsall, and others who opened doors for him at critical periods in the formative stages of his career as they were subsequently to William Pepper, Cecil Drinker, scores of the colleagues and thousands of students at Pennsylvania, Sir Henry Dale and others in England, Vannevar Bush in the OSRD, the Research Council and membership of the National Academy of Sciences, the trustees of the University of Pennsylvania and of the Rockefeller Foundation, the directors of Merck and Company, the faculties of the thirteen universities who gave honorary degrees to him, and the various organizations that presented him with medals and other awards.

He led by example rather than precept and he asked of his associates nothing that he was not ready and able to do himself. When demands on his time and energy came to exceed the possibilities of effective personal participation he did not attempt to maintain a tenuous involvement in all the current activities, but withdrew completely from some of them and confined his efforts to a residue in which personal participation was still possible. Those who came to his department expecting to have the experience of working with him had one reason to be grateful for this policy. Those to whom complete responsibility for some of the department's activities was delegated had another. The common denominator was a great and growing affection to add to the respect and admiration this man already had engendered. His genuine concern for students and colleagues and his legendary sense of humor were additional reasons for strong emotional attachments.

Such considerations do not appear in the record of his career but they were of tremendous importance in generating and maintaining the reputation which attracted to him the younger associates who contributed greatly to his success. In the critical period before his research made him famous his teaching program for medical students was the source of attraction. From firsthand experience I know the incessant search for improvement and the enormous expenditure of physical and mental effort that underlay the favorable reaction of the students. He used to say that the sole reason for the existence of a teaching department in a medical school is to teach medical students, that research is a privilege and not an inalienable right. Thirty years before the project method of medical education became popular in America he used to encourage his younger associates to incorporate their current research activities into the student laboratory program, and we did as much of this as our limited resources would permit. Eventually I realized that in so doing we were simultaneously maximizing the interest of the students (by letting them in on the formative stages of the solution of problems) and that of the younger staff members (by giving them responsibility for demonstrating the importance of their own brain-children). This interplay was a major part of the attraction of his laboratory for medical graduates.

In the account of his career I have tried to show how his success in research was directly due to his unremitting search for improvement in his teaching. Those of his associates who went on to teach medical students followed his example, with similar results. My own efforts along those lines underlay the discovery of ephedrine (which resulted from the injection of a crude extract of an unknown Chinese drug in the course of a practice experiment in preparation for a student exercise) as well as my interest in respiratory control and the cerebral circulation (which was part of a lifelong search for an explanation of the effects of morphine on respiration).

His unremitting efforts to improve his teaching of medical students were largely responsible for his rise from obscurity to international fame at Pennsylvania. He came there largely because the University had decided to follow the current trend toward the physiological approach to pharmacology and Richards had already organized and conducted successful student courses at Columbia and Northwestern. His recent contributions to the understanding of delayed chloroform poisoning, together with his services as assistant editor of the *Journal of Biological Chemistry* and the favorable reports on his teaching of medical students, must have marked him as one of the outstanding young pharmacologists of his day. It is noteworthy that he began his career as a biochemist and was led to become a pharmacologist by a series of coincidences involving his introduction by Hiss to Prudden and by Prudden to Herter, shortly before Herter undertook to organize a department of pharmacology at Columbia. The arrival of George Wallace and the strong friendship and admiration that soon developed between Richards and Wallace represented another coincidence. So did the establishment of the *Journal of Biological Chemistry* with Herter as editor while Richards was working with him.

But it was the unbroken record of superior performance of teaching duties that made possible the events that brought him fame. In his subsequent career at Washington he made an entirely new set of admirers and friends and from conversations with some of these I know that the same character traits were responsible. The performance was repeated in his relations with Merck and Company after his retirement.

Thus from the start of his career to its close his impact on his environment went from obscurity through uncertainty to interest, admiration, and affection. Many anecdotes attest to his wisdom and personal charm. Those of us who knew him well will always remember the infectious grin and chuckle that characterized his moments of relaxation as well as the example of modesty, self-criticism, and search for perfection that he set us. Some of his character traits may have been derived from his parents and teachers, but some were all his own. It was a unique combination.

BIBLIOGRAPHY

KEY TO ABBREVIATIONS

Am. J. Med. Sci. = American Journal of Medical Sciences
Am. J. Physiol. = American Journal of Physiology
J. Biol. Chem. = Journal of Biological Chemistry
J. Pharmacol. Exp. Therap. = Journal of Pharmacology and Experimental Therapeutics
J. Physiol. = Journal of Physiology
Penn. Gaz. = Pennsylvania Gazette
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