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DONALD DEXTER VAN SLYKE

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A Biographical Memoir by

A. BAIRD HASTINGS

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Arnold L. van Slyke

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BY A. BAIRD HASTINGS

DONALD DEXTER VAN SLYKE died on May 4, 1971, after a long and productive career that spanned three generations of biochemists and physicians. He left behind not only a bibliography of 317 journal publications and 5 books, but also more than 100 persons who had worked with him and distinguished themselves in biochemistry and academic medicine. To all who knew him, he was affectionately known as Van, and as Van I shall refer to him in this synoptic account of his life.

Van was born in Pike, New York, a small rural community, and he received his early education in the elementary schools and high school of Geneva, New York. His father was the distinguished chemist Lucius L. Van Slyke, who received his Ph.D. at the University of Michigan in 1882 and was on its staff at the time Van was born, on March 29, 1883. His mother, Lucy Dexter Van Slyke, died two years later. In 1890, L. L. Van Slyke became Chief Agricultural Chemist of the New York Agricultural Experiment Station, a post that he held until his retirement, in 1929. Van and his father and his father's profession were closely intertwined as Van was growing up, which doubtless made chemistry a natural choice of study for him, though for a time he leaned toward architecture. Van had no chemistry courses in high school, but he used to credit his English teacher, Miss Florence Parker, with the lucidity that later characterized all his scientific publications.

Van spent his first college year at Hobart College in Geneva, where he took his first course in chemistry. Since the college had but one chemistry course, he transferred to the University of Michigan, from which he received a B.A. degree in 1905 and a Ph.D. in chemistry in 1907. He once stated: "The chief reason I went there was that Moses Gomberg was there. If there was any outstanding American organic chemist, it was he." In addition to courses in organic, physical, and analytical chemistry, Van also took bacteriology and plant physiology as minor subjects. His doctoral thesis, published with Gomberg in the *Journal of the American Chemical Society* in 1907, was entitled: "The Action of Molecular Silver, of Silver Sulfate and Chloride, and of Sulfuric Acid upon Halogenated Derivatives of Triphenyl-Carbinol Chloride." This occurred shortly after Gomberg's exciting discovery in 1900 of the free radical triphenylmethyl. Van has delightfully reminisced about his days when he was working in Gomberg's laboratory. One day he needed a two-liter bottle that had once contained metallic sodium under anhydrous ether. Thinking the pieces of sodium in the bottom had long since reacted, he dumped them in the sink with running water. "Flashes went off like cannon firecrackers, and when it stopped, Gomberg looked in through his door and said: 'Now, Van Slyke, you know what metallic sodium and water makes'. . . . Those were days when your professor was not at a distance."

After receiving his Ph.D. and marrying Rena Mosher in the same year, Van became an assistant to Phoebus A. Levene at the newly established Rockefeller Institute for Medical Research in New York City. Since this came about somewhat by accident, the circumstances are worth recording. Van had expected to follow in his father's footsteps and become an agricultural chemist. To this end he had taken and passed a civil service examination for a position in the Bureau of Chemistry. He was scheduled to report right after getting his doctor-

ate. But fate took a hand, and at the spring meeting in 1907 of the American Chemical Society, Van's father chanced to sit next to Levene, who was recruiting for his department at the Institute. Luckily for Van and for the Institute, L. L. Van Slyke mentioned the approaching graduation of his son Donald. The upshot was that Van received an invitation from Dr. Simon Flexner, Director of the Rockefeller Institute, to come to New York for an interview. (In those days—and for many years after —Simon Flexner personally interviewed all staff members, no matter how low their rank, before offering them an appointment.) After consultation with his father, Van accepted the offer and thereby began his Rockefeller Institute career as biochemist and clinical chemist that was to last forty-one years—from 1907 to 1948.

THE ROCKEFELLER INSTITUTE, LEVENE PERIOD

The first seven years were spent with Levene, which Van has described as a "wonderful time" working on proteins and amino acids. In 1911, Levene arranged for Van to spend a year in Berlin with Emil Fischer, who was then the leading chemist of the scientific world. He even had the privilege of working with Fischer in his private laboratory. Van was particularly impressed by Fischer's performing all laboratory operations quantitatively —a procedure Van followed throughout his life.

Prior to going to Berlin, Van had published eight papers with Levene and two by himself—one of which concerned his classic nitrous acid method for the quantitative determination of primary aliphatic amino groups. This method, which was in widespread use by chemists and biochemists for many years, depended upon the measurement of the gaseous nitrogen (N_2) evolved by the reaction between alpha amino groups and nitrous acid. It was the first of the many gasometric procedures devised by Van, and made possible the determination of amino acids in small amounts of blood and other biological materials.

Until the development of microbiological and chromatographic procedures, it was the primary method used to study amino acid composition of proteins.

Following his return from Berlin, Van continued his study of amino acid composition of proteins with Levene, and began his studies of protein digestion and metabolism. With his colleague G. M. Meyer, he first demonstrated that amino acids, liberated during digestion in the intestine, are absorbed into the bloodstream, that they are removed by the tissues, and that the liver alone possesses the ability to convert the amino acid nitrogen into urea.

This work led to a study with his assistant, G. E. Cullen, of the enzyme, urease, which decomposes urea to ammonia and carbon dioxide. The quantitative determination of both end products was subsequently the basis of gasometric procedures for measuring urea concentration in blood and urine.

From the study of the kinetics of urease action, Van Slyke and Cullen developed equations that depended upon two reactions: (1) the combination of enzyme and substrate in stoichiometric proportions and (2) the reaction of the combination into the end products. Published in 1914, this formulation, involving two velocity constants, was similar to that arrived at contemporaneously by Michaelis and Menten in Germany in 1913.

Thus were Van Slyke's activities during his first seven postdoctoral years. They centered around the development of better methodology for protein composition and amino acid metabolism. Van was remarkably productive and happy in his work with Levene. As he has stated, work on proteins and amino acids was "his first and enduring love."

HOSPITAL OF THE ROCKEFELLER INSTITUTE PERIOD

Then in 1914 came an opportunity to become the chief chemist of the newly opened Hospital of the Rockefeller Institute, at the invitation of Dr. Rufus Cole, Director of the

Hospital. Van did not decide to make this change lightly. Years later, he recalled, "I was so distrustful of my ability to develop a department of chemistry in the hospital and so reluctant at leaving Levene, that I made Flexner write me a letter saying that if I didn't like it in the hospital I could go back to Levene." But, he continued, "I began to pick up medicine pretty fast and found it fascinating. So I stayed in the Hospital the rest of the time I was at the Rockefeller." That amounted to thirty-four years.

Van once told me that he studied textbooks of physiology and medicine diligently in preparation for his new responsibility. He was fortunate in being able to take Dr. Glenn E. Cullen, his assistant in Levene's laboratory, with him. Cullen, a chemical engineering graduate from the University of Michigan, was mechanically minded, resourceful, and had an outgoing personality. He and Van were a harmonious and effective team that developed the chemical laboratory of the hospital into a facility notable for its contributions to the budding science of biochemistry and to the yet-to-be-born science of clinical chemistry.

Van Slyke also had the good fortune at this time to obtain the services of John Plazin, a young emigré from Latvia, as his personal laboratory assistant. John's ambition was to be the best assistant conceivable for Donald Dexter Van Slyke. This he achieved and maintained until he died forty-seven years later. They worked as one through all those years and their loyalty to and admiration of each other is a tribute to the faithful character of each man. To John, Van was always "Dr. Van Slyke."

Though Van at age thirty entered upon his new responsibilities at the Hospital with some trepidation, he found the clinical staff so helpful and friendly that he experienced little difficulty in making the transition from Levene's laboratory to the clinically oriented environment. After all, under the directorship of Dr. Rufus Cole, the entire Hospital staff was embarking upon a new undertaking in medical research—the intensive study of

disease as a scholarly pursuit—in patients, in animals, and in the laboratory. "Men who were studying disease clinically had the right to go as deeply into its fundamental nature as their training allowed, and in the Rockefeller Institute's Hospital every man who was caring for patients should also be engaged in more fundamental study," wrote Dr. Cole in 1911. Though commonplace today, this was a revolutionary idea at the time.

Van Slyke and Cullen lost no time in applying their sound organic and physical chemical knowledge and technology to the clinical problems under study at the Hospital. The study of diabetes was already under way by Dr. F. M. Allen, the advocate of the "starvation treatment" of diabetics. Though this worked temporarily in some cases, eventual death from acidosis continued to occur. Since acidosis manifested itself in several different chemical ways, and no easy, reliable method for its early detection existed, Van Slyke turned his attention to this problem. Characteristically, he went to the heart of the matter directly. He reasoned that if incomplete oxidation of fatty acids in the body led to the accumulation of acetoacetic and β-hydroxybutyric acids in the blood, then a reaction would result between these acids and the bicarbonate ions that would lead to a lower-than-normal bicarbonate concentration in blood plasma. The problem thus became one of devising an analytical method that would permit the quantitative determination of bicarbonate concentration in small amounts of blood plasma. Again Van turned to a gasometric procedure. He ingeniously devised a volumetric glass apparatus that was easy to use and required less than ten minutes for the determination of the total carbon dioxide in one cubic centimeter of plasma and other aqueous solutions. His original method had an accuracy of about 1 percent.

After the demonstration of the value of using this procedure in the diagnosis and therapy of patients with diabetes and some other disease states, the method was widely adopted in hospital

and research laboratories. It also was soon found to be an excellent apparatus by which to determine blood oxygen concentrations, thus leading to measurements of the percentage saturation of blood hemoglobin with oxygen. This found extensive application in the study of respiratory diseases, such as pneumonia and tuberculosis. It also led to the quantitative study of cyanosis and a monograph on the subject by C. Lundsgaard and Van Slyke.

In all, Van Slyke and his colleagues published twenty-one papers under the general title "Studies of Acidosis," beginning in 1917 and ending in 1934. They included not only chemical manifestations of acidosis, but Van Slyke, in No. 17 of the series (1921), elaborated and expanded the subject to describe in chemical terms the normal and abnormal variations in the acid-base balance of the blood. This was a landmark in understanding acid-base balance pathology and has not been materially improved for fifty years.

Van Slyke and his colleagues, both clinical and chemical, did not confine their interests solely to diabetes and acid-base abnormalities. Van kept work going on proteins and their products of hydrolysis and on better methods for blood chlorides, urea, and ketone bodies in blood and urine. Within seven years after Van moved to the Hospital, he had published a total of fifty-three papers, thirty-three of them coauthored with clinical colleagues. Quantitative clinical chemistry was well on its way at the Hospital, and Van Slyke's contribution to it was well established.

In 1920, Van Slyke and his colleagues undertook a comprehensive investigation of gas and electrolyte equilibria in blood. This was not only a logical outgrowth of the ongoing study of the acid-base balance of the blood, but was also encouraged by Franklin C. McLean at the behest of Prof. L. J. Henderson. McLean and Henderson at Harvard had made preliminary studies of blood as a physico-chemical system, but realized that

Van Slyke and his colleagues at the Rockefeller Hospital had superior techniques and the facilities necessary for such an undertaking. A collaboration thereupon began between the two laboratories, which resulted in rapid progress toward an exact physico-chemical description of the role of hemoglobin in the transport of oxygen and carbon dioxide, of the distribution of diffusible ions and water between erythrocytes and plasma, and of factors such as degree of oxygenation of hemoglobin and hydrogen ion concentration that modified these distributions. Publications from the two laboratories were independent and complementary. It was a happy intellectual collaboration.

A key development in the progress made was Van Slyke's revision of his volumetric gas analysis apparatus into a manometric apparatus. Briefly, this amounted to liberating and isolating the desired gas contained in a known volume of solution, and recording in millimeters of mercury the pressure of that gas at a known fixed volume. The manometric apparatus proved to give results that were from five to ten times more accurate than the volumetric apparatus, and, in addition, made possible the determination of very small concentrations of gas in solution. A series of papers on the CO_2 titration curves of oxy- and deoxyhemoglobin, of oxygenated and reduced whole blood, and of blood subjected to different degrees of oxygenation and on the distribution of diffusible ions in blood resulted.

One of these papers was especially notable. In it were developed equations that predicted the change in distribution of water and diffusible ions between blood plasma and blood cells when there was a change in pH of the oxygenated blood. (This work was done in 1923 at the Peking Union Medical College with F. C. McLean and Hsien Wu.) In a later paper, this was extended to reduced blood as well. A significant contribution of Van Slyke and his colleagues was the application of the Gibbs–Donnan Law to the blood—regarded as a two-phase system, in which one phase (the erythrocytes) contained a high

concentration of nondiffusible negative ions, i.e., those associated with hemoglobin, and cations, which were not freely exchangeable between cells and plasma. By changing the pH through varying the CO_2 tension, the concentration of negative hemoglobin charges changed in a predictable amount. This, in turn, changed the distribution of diffusible anions such as Cl^- and HCO_3^- in order to restore the Gibbs–Donnan equilibrium. Redistribution of water occurred to restore osmotic equilibrium. The experimental results confirmed the predictions of the equations. A total of fifteen papers, under the general title "Studies of Gas and Electrolyte Equilibria in Blood," were published between 1922 and 1928. Van regarded this work as among the best of his scientific output.

As a spin-off from the physico-chemical study of the blood, Van undertook, in 1922, to put the concept of buffer value of weak electrolytes on a mathematically exact basis. By differentiating the mass law equation for weak acids with respect to pH, he arrived at the generalization

$$\beta = \frac{dB}{dpH} = 2.3 \frac{K^1 [H^+] C}{(K^1 + [H^+])^2} + [H^+] + [OH^-],$$

where β = buffer value. This proved to be useful in determining buffer values of mixed, polyvalent, and amphoteric electrolytes, and put the understanding of buffering on a quantitative basis. It was applied in Van's laboratory to the determination of dissociation constants of polyvalent weak acids such as citric acid, whose three acid groups have overlapping dissociation constants.

While this work on blood was going on, Van was preparing to make a detailed and comprehensive study of nephritis and its varied manifestations. In this he had a number of clinical associates, including Dr. Alma Hiller, who was in charge of his clinical chemical laboratory (1918–1948). (After Cullen left in

1921, the basic chemical work of Van's laboratory was successively supervised by A. B. Hastings, 1921–1926; J. Sendroy, Jr., 1926–1937; D. A. MacFadyen, 1937–1940; and R. M. Archibald, 1940–1946.)

Van always had a number of problems under investigation at the same time at the Institute, but he never hurried to publish the results. It was customary for him to put each paper through several drafts and revisions.

Van had a great capacity to concentrate intensely and effectively on the problem at hand, and at the same time keep track of several research problems going on in the laboratory. This is why the publications in any one year often covered a wide range of subjects. For example, during 1928 Van and eight of his associates published twelve papers: one on a gasometric method for sugar determination in blood and urine, another on a new method for hemoglobin determination, three on factors affecting urea excretion in health and disease, and seven additional entries in the series "Studies of Gas and Electrolyte Equilibria in Blood." One of these, "The Solubility of Carbon Dioxide at 38° in Water, Salt Solution, Serum, and Blood Cells," was notable in that the first measurements on the subject were made in 1922, six years prior to publication. Each year the results would be written up for publication and each year Van would say: "We'll take another look at this in the fall, to make sure we can't improve on the accuracy." This was repeated annually until it met Van's standards. It was typical of his publications that one could count on their data and results without question.

The period of preoccupation with the study of blood as a physico-chemical system was followed by intensive study of nephritis, undertaken with a number of clinical colleagues. They followed and minutely documented the life history of the disease through its various stages in patients. This resulted in 1930 in a detailed publication by Van Slyke and nine colleagues

of a monograph in *Medicine* entitled "Observation on the Courses of Different Types of Bright's Disease, and on the Resultant Changes in Renal Anatomy." It was a landmark in that it related the changes occurring at different stages of renal deterioration to the quantitative changes taking place in kidney function.

With his laboratory associates, he continued for many years to study the kidney in health and disease, with particular attention to its metabolism and its ability to excrete waste products, particularly urea. Though in subsequent years, improved techniques for evaluating kidney function have appeared, the work of the Van Slyke laboratory stands as a pioneering model for the clinical study of this excretory organ.

During this period, Van Slyke and R. M. Archibald identified glutamine as the source of urinary ammonia. During World War II, Van and his colleagues documented the effect of shock on renal function and, with R. A. Phillips, developed a simple method, based on specific gravity, suitable for use in the field, for determining red blood cell concentration in whole blood and protein concentration in blood plasma. In postwar years, this method, in Phillips's hands, proved of incalculable value in detecting the severity of, and in following the results of therapy in, cholera.

Also, it was during this period of the 1940s that Jordi Folch joined Van Slyke's laboratory and the manometric apparatus was adapted for the determination of carbon in organic compounds. This led to the detailed study of plasma lipids and in 1948 to the identification by Folch of the important phospholipid, phosphatidyl serine.

Over 100 of Van's 300 publications were devoted to methodology. Most were new methods; some were devoted to improvements he had made in earlier descriptions—either to increase accuracy or to reduce the size of the sample of blood or other material required for analysis. The importance of Van

Slyke's contribution to clinical chemical methodology cannot be overestimated. His gasometric procedures alone accounted for about two dozen of the methods that were applicable to compounds of biological and clinical significance, but they were always devised to answer a physiological or clinical question. These included the blood organic constituents (carbohydrates, fats, proteins, amino acids, urea, nonprotein nitrogen, and phospholipids) and the inorganic constituents (total cations, calcium, chlorides, phosphate, and the gases carbon dioxide, carbon monoxide, and nitrogen). It was said that a Van Slyke manometric apparatus was almost all the special equipment needed to perform most of the clinical chemical analyses customarily performed prior to the introduction of photocolorimeters and spectrophotometers for such determinations.

Though colorimetric procedures were available, they required the development of a color that was often not specific for the substances being measured. Hence, the chemical reaction quantitatively yielding a gas from the specific substance that could be isolated and measured had certain advantages.

VAN SLYKE AND QUANTITATIVE CLINICAL CHEMISTRY

The progress made in the medical sciences in genetics, immunology, endocrinology, and antibiotics during the second half of the twentieth century obscures at times the progress that was made in basic and necessary biochemical knowledge during the first half. Methods capable of giving accurate quantitative chemical information on biological material had to be painstakingly devised; basic questions on chemical behavior and metabolism had to be answered; and, finally, those factors that adversely modified the normal chemical reactions in the body so that abnormal conditions arise that we characterize as disease states had to be identified.

At the beginning of the century, biochemistry was in its infancy, and quantitative clinical chemistry did not exist as

such. It was given to a few individuals professionally trained as chemists, who found themselves engaged in the study of disease in association with clinicians to change the course of the practice of medicine. Donald Van Slyke was one of these chemists.

In 1901, the year before Van Slyke received his Ph.D. from the University of Michigan, the new medical buildings of Harvard University were dedicated. President Charles Eliot, originally a chemist, stated at the dedication, "There is an increasing need of men who have a working knowledge of several sciences which were formerly treated as distinct and whose best representatives in medical schools labored apart, each in his own field. The most promising medical research of our day makes use of biological, chemical and physical science combined. Physiology advances by making applications of the principles, the methods and the implements of all three sciences. Bacteriology and biological chemistry go hand in hand in serving pathology and the public health."

Beginning in 1906 and for the next sixty-five years, it almost seemed as if Donald Van Slyke planned and conducted his activities with these goals in mind. Viewed in retrospect, he combined in one scientific lifetime (1) basic contributions to the chemistry of body constituents and their chemical behavior in the body, (2) a chemical understanding of physiological functions of certain organ systems (notably the respiratory and renal), and (3) how such information could be exploited in the understanding and treatment of disease. That outstanding additions to knowledge in all three categories were possible was in large measure due to his sound and broadly based chemical preparation, his ingenuity in devising means of accurate measurements of chemical constituents, and the opportunity given him at the Hospital of the Rockefeller Institute to study disease in company with physicians.

Since Van Slyke's scientific life was spent at the Rockefeller Institute for Medical Research from 1907 through 1948 (thirty-

five of the years at the Hospital of the Rockefeller Institute), followed by twenty-two years in the Medical Department of the Brookhaven National Laboratory, it covers rather uniquely the evolution of biochemistry and notably quantitative clinical chemistry. During the period 1921–1926, while I was his assistant, the problems under investigation in his laboratory included the development of methods; the study of blood as a physicochemical system and its relation to respiratory diseases; the study of proteins and amino acids and their metabolism; his early work with Dr. Alma Hiller on what ultimately proved to be the new amino acid hydroxylysine; and, finally, in collaboration with clinical colleagues, a definitive study of various types of nephritis. Meantime, while all these different problems were under way, he found time to work collaboratively with Dr. John P. Peters of Yale on the classic, two-volume *Quantitative Clinical Chemistry*. At the time it was published in 1931, it contained practically all that could be stated with confidence about those aspects of disease that could be and had been studied by chemical means. It was widely accepted throughout the medical world as the "Bible" of quantitative clinical chemistry, and to this day some of the chapters have not become outdated.

It is of interest to recall how this collaboration came about. In 1922, John P. Peters, who had just gone to Yale from Van Slyke's laboratory as an Associate Professor of Medicine, was asked by a publisher to write a modest handbook for clinicians describing useful chemical methods and discussing their application to clinical problems. It was originally to be called "Quantitative Chemistry in Clinical Medicine." He soon found that it was going to be a bigger job than he could handle alone and asked Van Slyke to join him in writing it. Van agreed, and the two men proceeded to draw up an outline and divide up the writing of the first drafts of the chapters between them. They also agreed to exchange each chapter until it met the satisfaction of both. This may have improved the accuracy and

completeness of the chapters, but it delayed publication of the book until 1931. Each chapter turned out to be a monograph, and the book had grown to two volumes. One volume, *Interpretations,* dealing only with the physiological and clinical significance of those substances for which quantitative methods were available, contained 1,200 pages and twenty-one chapters. The second, entitled *Methods,* consisted of about 1,000 pages describing in detail those methods that had been proven accurate and useful. Somewhere along the line, the title was shortened to *Quantitative Clinical Chemistry.* It must have met a need, because the first edition sold out rather quickly here and abroad and the publishers soon asked the authors to prepare a second edition. Though they tried, medical research was progressing faster than they could keep up—at least to both their satisfactions. The upshot was that a second edition was never completed.

Though their collaboration was a fortunate one, it was difficult because Van was accustomed, as a chemist, to be content with nothing less than proven accuracy, whereas Peters was used to being confronted constantly with disease manifestations in patients—no two of which were the same. This made it difficult to satisfy both of them at the same time on any one subject. However, the first edition was well worth doing and remains a classic in the subject.

BROOKHAVEN PERIOD (1948–1971)

The year 1948 proved to be a fateful one for Donald Van Slyke. Rena, his wife for forty years and mother of his daughter, Elsa, and son, Karl Keller, had died the year before, and he had reached the Rockefeller retirement age of sixty-five. Though vigorous physically, he was lonely and depressed mentally.

At this juncture, he accepted the position of Deputy Director of Biology and Medicine at the newly formed Brookhaven National Laboratory and met Else von Bardenfleth Brock,

whom he married. The challenge of his new responsibilities cured his depression, and the understanding companionship of Else banished his loneliness. Van thereby entered upon the second position he was to hold in his lifetime with the vigor and enthusiasm that had characterized his forty-one years at the Rockefeller Institute. Van retained the title of Deputy Director only long enough to ensure the appointment of able chairmen in the departments of biology and of medicine and then renewed his life in the laboratory with John Plazin, his lifetime assistant, who had accompanied him from the Institute. Though previously inexperienced with the use of isotopes, he and John were soon at home with them and in 1951, with Robert Steele, published a much-improved method for the determination of ^{14}C.

During the course of the next few years, Van devised a micro version of the manometric apparatus and adapted his various gasometric procedures to it. As a result, determinations that had previously required one milliliter samples now required samples only one-tenth as large, with no loss in accuracy. These micro methods were published as a monograph by Van Slyke and Plazin in 1961, with typical Van Slyke attention to accuracy, clarity, and essential detail.

With his Brookhaven colleagues, Van continued his study of nephritis and nephrosis, of metabolism, and of improved methodology in evaluating acid-base balance clinically.

Among his last papers published from the Hospital of the Rockefeller Institute in 1949 were two on pH determination, with J. R. Weisiger and his son, K. K. Van Slyke, as coauthors. Since his first paper, in 1906, had been with his father, Lucius L. Van Slyke, this must have given him special satisfaction.

From 1951 to 1956, Van served part-time as counselor to Eli Lilly Research Grants. In this capacity, he had the responsibility of identifying promising investigators and making recommendations for their support in the basic medical sciences. He

carried out this responsibility with his customary conscientious and deliberate care. He would visit the laboratories of the investigators here and abroad and keep meticulous notes of his observations, following which he reported his recommendation to the Lilly Research Grants office. In all, his recommendations resulted in the distribution of about $400,000 over the five-year period, which aided many young investigators to get on with their research at a time when seed money was in short supply.

At the end of this venture, he again took up his full-time laboratory life as a Research Biochemist in the Department of Medicine of the Brookhaven National Laboratory, a position he held for the rest of his life.

HYDROXYLYSINE

In the course of his analysis of proteins at the Rockefeller Institute, Van encountered a discrepancy between the amount of colorimetrically determined histidine in a gelatin hydrolysate and that calculated from arginine and nonamino–nitrogen determinations. This observation led in 1921, after Van had attempted to isolate the substance, to publication in the *Proceedings of the National Academy of Sciences* of a paper entitled "An Unidentified Base among the Hydrolytic Products of Gelatin." Finally, in 1938, Van Slyke, Hiller, Dillon, and MacFadyen announced that the "unidentified base" was the new amino acid, hydroxylysine. Its synthesis had to wait another twelve years, being simultaneously achieved by Weisiger in Van Slyke's laboratory and by Sheehan and Bolholfer at MIT. Thus, the requirements for acceptance of a new amino acid were met at last. Van continued to study its biosynthesis and its role in collagen throughout his Brookhaven period. It would have given him great satisfaction had he lived to see the importance it plays today in providing linkage with mucopolysaccharides in plasma membranes.

Thus, Van takes his place with his early teacher, Emil Fischer, as one who discovered a highly important amino acid.

VAN SLYKE AND CHINA

Shortly following the dedication in 1921 of the Peking Union Medical College (P.U.M.C.), Van Slyke spent several months in 1922–1923 in Peking as a Visiting Professor of Biochemistry. Although he became deeply engaged in the laboratory with professors F. C. McLean and Hsien Wu in studies of blood equilibria, he found time to learn much about Chinese history, culture, and people and returned a profound admirer of China and the Chinese. From these early impressions he never deviated.

As early as 1937, he joined with other former P.U.M.C. faculty to provide medical aid to the Chinese people. In 1938, when the American Bureau for Medical Aid to China was formed, Van Slyke was elected a Director; and, in 1941, he became its President, a post he held throughout World War II. He became Honorary President in 1947, and continued to serve actively on the Board of Directors until a few months before his death.

In 1961, he spent two months at Taipei, Taiwan, as a visiting investigator at the Navy's Cholera Research Laboratory, known as NAMRU–2. He was thus able to renew his friendship with former P.U.M.C. faculty who had migrated with Chiang Kai-Shek to Taiwan. They had formed the National Defense Medical College (N.D.M.C.), which Van assisted in various ways while he was there.

In appreciation of his services to the Chinese people, Van received two decorations from the Republic of China: in 1939, the Order of the Jade, and in 1947, the Order of the Brilliant Star. These were among the most treasured of his possessions, and he never relinquished his faith that the Chinese people

will eventually triumph with a national life worthy of their culture, ability, and aspirations.

VAN SLYKE, THE PERSON

Van Slyke served as Managing Editor of the *Journal of Biological Chemistry* from 1914 to 1925, an activity to which he devoted many hours of close personal attention. During his editorship, the *Journal* flourished, and the high standards for clarity of presentation, convincing data, and justifiable conclusions were set that continue to characterize this publication.

He worked and reworked each publication from his laboratory until he could think of no way to improve it, either through experiment or through rewriting. His papers describing new methods were models of clarity and exactness. Nothing was left to the imagination, so that it was said, "If you follow Van Slyke's directions to the letter, your results will have the accuracy he predicts."

As far as I am aware, he never had to correct the data or retract the conclusions contained in his publications. Subsequent advances in technique and knowledge have in some instances led to his work being superseded, but it was nevertheless correct for the time it was published.

Van's usual unadorned use of the English language could be felicitous when he thought it appropriate. As an example, I quote from his Harvey Lecture of 1916, "The Present Significance of the Amino Acids in Physiology and Pathology":

"It is a pleasure, as well as a duty, to acknowledge my indebtedness to Dr. Levene, for six years my chief at the Rockefeller Institute. The work detailed this evening is a direct outgrowth of Levene's own researches on the proteins, was carried out with the constant inspiration of his enthusiasm, and help of his counsel, and of his generosity in making available every facility which the laboratory afforded, even at times to the

delay of his own immediate work, the ultimate sacrifice that can be taken from a spirit such as his."

Van presented at all times a serious mien to the world of science. Only his family and close friends were aware that he was an irresistible punster. As far as I know this frivolous indulgence never found its way into print.

Once, however, he allowed expression to his subsurface humor in a footnote to be found on page 276 of *Quantitative Clinical Chemistry,* Volume 2, *Methods.* It is in the chapter describing the manometric gas apparatus. It reads:

"The closed manometer really owes its origin to our laboratory comrade of many years, Glenn E. Cullen. The numerous genuflexions required during a day's work in reading the low lying zero points of the open tube told heavily on Cullen's jovial proportions, and the laboratory felt so much the loss of his usual contagious spirits, that the more humane closed tube had to be devised."

Van loved to play tennis, which he did up to within a few months of his final illness. Not that he was a master of sparkling strokes, but rather that he accurately and persistently returned almost any ball with which his opponent challenged him. He won points, games, and sets by untiring consistency and precision. He played tennis in much the same way as he attacked and conquered laboratory problems.

As was said on the occasion of his 80th birthday celebration, "Van plays science the way he plays tennis: he senses where the ball (or the problem) is going to be before it gets there, he gets to the ball directly with no lost motion, he never takes both feet off the ground, and when he hits the ball, it is with a firm, straight, and accurately aimed blow. Most exasperating of all, he uses no fancy strokes—but just keeps putting it back until he wins the point. He wins lots of sets, and he solves lots of problems."

In the course of preparing to write this memoir, I encoun-

tered in my files a handwritten memorandum written during the summer of 1926. My five years with Van at the Rockefeller Institute were over, and my new life at the University of Chicago had not yet started. I include it here to help recapture the appearance and personality of the then forty-three-year-old Donald Van Slyke at the height of his scientific productivity.

A Retrospective Log

August 13, 1926

From October first nineteen hundred and twenty-one until June twentieth nineteen hundred and twenty-six I was engaged as one of the staff of the Hospital of the Rockefeller Institute for Medical Research.

The man responsible for my initial appointment, for my mental and scientific growth while there, and my advancement to an opportunity of greater responsibility, was Donald Dexter Van Slyke. His is such an extraordinary scientific personality that I feel impelled to chronicle my impressions of him.

Physically, he immediately attracts your attention and admiration. Short, stocky but well proportioned, his well-formed head, now sparsely covered with graying hair, sits solidly upon square shoulders. In his profile you see expressed his decisiveness. A strong mouth and chin with straight high forehead denote the man. He speaks with crispness and decision yet unkind words never pass his lips.

I've never interviewed him—I could not. But suppose I had—what would the result be like?

Were I to be announced to him on the phone, he would be waiting for me in front of the elevator on the seventh floor of the hospital. Of what other man of equal prominence could that be said? Yet I have seen him do it many, many times during these precious five years with him. Nor does he limit this courtesy to his peers. It is always so, even for the youngest tyro.

Through a little vestibule, I should enter his office, a small room, about 12′ × 12′, and be seated in a straight chair beside his desk. The office appearance merits a few words. A flat top desk sets in the center at an angle so that light falls over his left shoulder as he writes. Along one wall is an open bookcase with volumes he is using now for reference, his own collected reprints and many folders of work in various stages of completion for publication. On top of the bookcase are framed photographs, perhaps twenty. They are some of the men who have worked with him. To catalogue them would take me far afield but a cursory glance shows strong, clean-visaged, intelligent men and today they fill chairs of medicine, of chemistry, of physiology, or are in successful practice. They are all successes. Nor are they confined to America. Danes and Englishmen are among them. The wall back of me—the one Dr. Van Slyke faces—has a group of older faces. There is Emil Fischer with whom Van worked in Berlin, Moses Gomberg of the University of Michigan under whom he took his doctorate degree, P. A. Levene with whom he first worked when he came to the Rockefeller Institute in 1908. Below these are Lawrence J. Henderson of Harvard, who together with Van Slyke has advanced physiology most in this decade, and William Mansfield Clark of the Hygienic Laboratory in Washington (later to head physiological chemistry at Hopkins from 1927 to 1952) whose career had paralleled Van's in success if not in clinical relevance and international recognition. These then are the faces which Van sees when he lifts those steady and penetrating eyes of his from the work on his desk.

In the forty-five years that followed the writing of the above, Van did not change in any important way. It might be said that he did not age significantly until after his terminal disease was discovered.

Even then, he retained a scientific interest in the course of

his condition as late as March 28, 1971, the day before his 88th birthday. As I sat chatting with him, he quoted to me the course that his plasma proteins were taking, as if he were discussing one of his Institute patients under investigation. Though fully aware of the ultimate outcome, there was no evidence that he had any changes to make in the present or past.

Van is survived by a daughter, Elsa Van Slyke, born in 1912, a son, Karl Keller Van Slyke, M.D., born in 1915, and by his second wife, Else Bardenfleth Van Slyke. In spite of Van's lifelong preoccupation with his laboratory research, he was an attentive and companionable father and a thoughtful and affectionate husband. His home was a happy and hospitable haven to his friends and colleagues throughout his life.

Van's contributions to science and to medicine were nationally and internationally recognized and honored by medals, awards, honorary degrees, and memberships in professional societies here and abroad. He accepted them all humbly and gratefully as tributes to his colleagues quite as much as to himself. These honors are itemized at the end of this memoir.

VAN SLYKE'S LEGACY

Donald Van Slyke will long be remembered for his legacy to the following:

To Biochemistry and Physiology:

Exact and accurate methods for the determination of constituents of biological material.

Sound physico-chemical interpretations of the role of hemoglobin in the transport of O_2 and CO_2 by the blood and of the distribution of water and anions between plasma and erythrocytes.

The role of the liver in amino acid metabolism.

The role of the kidney in urea excretion and ammonia formation.

The mathematical definition of buffer value in terms of hydrogen ion concentration, dissociation constants, and buffer concentrations.

A new and important amino acid, hydroxylysine.

To Medicine:

His development to useful maturity of quantitative clinical chemistry through identifying clinical questions capable of chemical attack and devising the methods necessary to answer the questions.

Publication in 1931 with the late John P. Peters of the classic two-volume collection of existing chemical knowledge relevant to disease, entitled *Quantitative Clinical Chemistry.*

The clarification of the subject "acidosis" and the meaning of other acid-base balance abnormalities.

A thoroughly documented description of nephritis as it progresses through its various stages.

A large number of Doctors of Medicine, trained in the chemical approach to clinical investigation, who became leaders in academic medicine.

To his friends and colleagues Van has left the memories of his kindness and evenness of temper, his directness of approach to problems, his ability to avoid distractions that were irrelevant to his objective, his economy of words in speech and publications, his penchant for exactness, clarity, and completeness, and his thoughtfulness in his relations with others.

Altogether, Donald Van Slyke was a prolific scientist, a pioneer in bringing quantitative clinical chemistry to the service of medicine, humble, unselfish, considerate, magnanimous, and rigid only in his adherence to the truth.

Those of us who worked with him loved him, and those who knew him only through his works admired and respected him.

Though the light that was Donald Dexter Van Slyke in life

has gone out, the glow that has illumined so much of chemistry and medicine and so many of those who worked with him shines on.

IN PREPARING this memoir, the author has consulted most of Van Slyke's publications, the transcript of an Oral History prepared by Dr. Peter D. Olch in 1969 and on file at the National Library of Medicine, and correspondence between Van Slyke and the author extending over a fifty-year period.

HONORS AND DISTINCTIONS

HONORARY DOCTOR OF SCIENCE DEGREES

Yale University, 1925
University of Michigan, 1935
Northwestern University, 1940
University of Chicago, 1941
University of London, 1951
Rockefeller University, 1966

HONORARY DOCTOR OF MEDICINE DEGREES

University of Oslo, 1938
University of Amsterdam, 1962
University of Ulm, 1970

MEDALS AND AWARDS

Charles Mickle Fellowship, University of Toronto, "to the member of the medical profession who has done most during the preceding ten years to advance sound knowledge of a practical kind in medical art or science," 1936

Phillip A. Conne Medal, Chemists' Club of New York, for contributions to clinical chemistry, 1936

Willard Gibbs Medal, Chicago Section of the American Chemical Society, for contributions to chemistry, 1939

Order of the Jade, Republic of China, 1939

Kober Medal, Association of American Physicians, for "distinguished research in preventive medicine," 1942

Order of the Brilliant Star, Republic of China, for "meritorious service to the Chinese people," 1947

Fisher Award in Analytical Chemistry, American Chemical Society, 1953

John Phillips Memorial Award, American College of Physicians, for "achievement in internal medicine," 1954

First Van Slyke Award in Clinical Chemistry, American Association of Clinical Chemists, 1957

First Scientific Achievement Award, American Medical Association, 1962

Ames Award, American Association of Clinical Chemistry, 1964

National Medal of Science, USA, 1965

Elliott Cresson Award, Franklin Society of Philadelphia, 1965
Medal of the New York Academy of Medicine, 1966

AMERICAN MEMBERSHIPS

National Academy of Sciences, 1921
American Philosophical Society, 1938
American Society of Biological Chemists (President, 1920–1922)
Harvey Society (President, 1927–1928)
American Bureau for Medical Aid to China (President, 1940–1947)
American Academy of Arts and Sciences
Rudolf Virchow Medical Society in the City of New York
American College of Cardiology (Honorary Member)
American Chemical Society
New York Academy of Medicine
Association of American Physicians
American Association of Clinical Chemistry
Society of Experimental Biology and Medicine

FOREIGN MEMBERSHIPS (HONORARY)

Società di Biologia Chimica, 1928
Deutsche Akademie der Naturforscher, 1932
Società Lombarda di Medicina, 1935
Academy of Science of India, 1935
Society of Biological Chemists of India, 1936
Royal Society of Sciences of Upsala, 1942
Danish Society for Internal Medicine, 1952
Société de Pathologie Rénale, 1952
Società Italiana di Biologia Sperimentale, 1953
Association of Clinical Biochemists, Britain, 1953
Royal Society of Medicine, Britain, 1958
Academia Nazionale dei Lincei, Italy, 1962
Danish Academy, 1956

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KEY TO ABBREVIATIONS

Abderhalden Hanb. biol. Arbeitsmethod. Abt.———Teil = Abderhalden Handbuch der biologischen Arbeitsmethoden Abteilung———Teil
Am. J. Dis. Child. = American Journal of Diseases of Children
Am. J. Physiol. = American Journal of Physiology
Ann. N.Y. Acad. Sci. = Annals of the New York Academy of Sciences
Arch. Intern. Med. = Archives of Internal Medicine
Ber. Dtsch. Chem. Ges. = Berichte der Deutschen Chemischen Gesellschaft
Biochem. Z. = Biochemische Zeitschrift
Biomed. Newsl. = Biomedical Newsletter
Clin. Chem. = Clinical Chemistry
Clin. Chim. Acta. = Clinica Chimica Acta
Fed. Proc. = Federation Proceedings
J. Am. Chem. Soc. = Journal of the American Chemical Society
J. Am. Med. Assoc. = Journal of the American Medical Association
J. Biol. Chem. = Journal of Biological Chemistry
J. Clin. Invest. = Journal of Clinical Investigation
J. Exp. Med. = Journal of Experimental Medicine
Mod. Med. = Modern Medicine
Proc. Natl. Acad. Sci. USA = Proceedings of the National Academy of Sciences of the United States of America
Proc. Soc. Exp. Biol. Med. = Proceedings of the Society for Experimental Biology and Medicine
Trans. Assoc. Am. Physicians = Transactions of the Association of American Physicians

1906

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1907

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1909

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1910

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