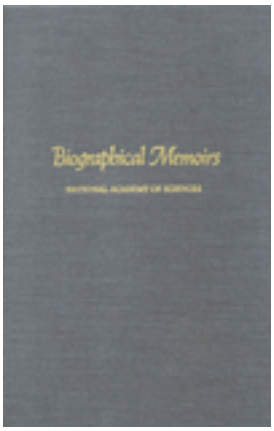

Biographical Memoirs V.63

Office of the Home Secretary, National Academy of Sciences

ISBN: 0-309-58595-3, 546 pages, 6 x 9, (1994)

Biographical Memoirs

NATIONAL ACADEMY OF SCIENCES

NATIONAL ACADEMY OF SCIENCES
OF THE UNITED STATES OF AMERICA

Biographical Memoirs: Volume 63

NATIONAL ACADEMY PRESS
WASHINGTON, D.C. 1994

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INTERNATIONAL STANDARD BOOK NUMBER 0-309-04976-8

LIBRARY OF CONGRESS CATALOG CARD NUMBER 5-26629

Available from
NATIONAL ACADEMY PRESS
2101 CONSTITUTION AVENUE, N.W.
WASHINGTON, D.C. 20418

PRINTED IN THE UNITED STATES OF AMERICA

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PREFACE

On March 3, 1863, Abraham Lincoln signed the Act of Incorporation that brought the National Academy of Sciences into being. In accordance with that original charter, the Academy is a private, honorary organization of scientists, elected for outstanding contributions to knowledge, who can be called upon to advise the federal government. As an institution the Academy's goal is to work toward increasing scientific knowledge and to further the use of that knowledge for the general good.

The *Biographical Memoirs*, begun in 1877, are a series of volumes containing the life histories and selected bibliographies of deceased members of the Academy. Colleagues familiar with the discipline and the subject's work prepare the essays. These volumes, then, contain a record of the life and work of our most distinguished leaders in the sciences, as witnessed and interpreted by their colleagues and peers. They form a biographical history of science in America—an important part of our nation's contribution to the intellectual heritage of the world.

PETER H. RAVEN
Home Secretary

Biographical Memoirs

VOLUME 63

THOMAS ADDIS

July 27, 1881–June 4, 1949

BY KEVIN V. LEMLEY AND LINUS PAULING

THOMAS ADDIS was one of the early physician members of the National Academy of Sciences. As a physician-scientist, he had a distinctively quantitative and rigorous approach to clinical problems. His name is firmly connected to the study of kidney function and structure-function correlation and to the diagnosis and dietary treatment of the class of kidney disorders once collectively known as Bright's disease. During his life he developed a national and international reputation as a result of his research and his success in treating patients. His approach to diagnosis and treatment, however, never came into widespread clinical use and fell into almost total disuse in the United States soon after his death. The application of dietary therapy in renal disease is currently enjoying a considerable renaissance, and Addis's work is being rediscovered and appreciated once more for its rigor and clarity.

[Statement by L.P., a friend and former patient of Tom Addis: Forty years ago I agreed to write the biographical memoir of Tom Addis. His widow, however, asked me not to include any mention of his political beliefs and activities. She said that she and her two children would not permit such mention, partly because of their fear for their own safety. This was at the start of the McCarthy period. I

felt that a biographical memoir that did not mention this important aspect of Tom Addis's life should not be published, and I deferred writing the memoir. Now, after the death of Mrs. Addis, I feel free to publish the memoir, in the writing of which I have had the great benefit of collaboration with Dr. K. V. Lemley.]

Tom Addis was born in Edinburgh, Scotland, on July 27, 1881. His mother was Cornelia Beers Campbell. His father, Thomas Chalmer Addis, was a Presbyterian minister. Addis was raised in a religious and rather ascetic environment with a great emphasis on moral values. In his youth he carried a bible in his pocket and was quite conversant about its contents. Decades after his naturalization as a U.S. citizen in 1917, he still considered his native Scotland and Edinburgh as "the most beautiful country and the most lovely town in the world." Addis was graduated from Watson's College in Edinburgh in 1900 and received the M.B.Ch.B. degree in 1905 from the Faculty of Medicine of the University of Edinburgh. Following three more years of hospital training in Edinburgh, Gloucester, and Bristol (including a year working and living in slums), he received the M.D. degree and was elected to membership in the Royal College of Physicians (Edinburgh). Two years of postdoctoral research in Berlin and Heidelberg followed (1909–11) as a Carnegie scholar and fellow. Addis returned to Scotland as registrar at Leith Hospital (Edinburgh) in 1911.

Later in 1911 Addis accepted an appointment as chief of the Clinical Laboratory of the Department of Medicine of the newly organized Stanford University School of Medicine in San Francisco (the medical school moved to its current location on the Palo Alto campus in 1959). The new medical school dean, Dr. Ray Lyman Wilbur, brought Addis to Stanford on the recommendation of Sir Clifford Allbutt of the University of Cambridge, an event Wilbur

later remembered as "among the more fortunate things which I did as a young dean of a young medical school."

In 1913 Addis married Elesa Bolton Partridge, with whom he eventually had two daughters, Elesa and Jean. Mrs. Addis was a trained nurse and later a nurse-dietician in Addis's renal clinic at Stanford. Addis was promoted to associate professor of medicine in 1913.

He served as a captain in the U.S. Army Medical Corps during World War I (1917–19) at Camp Lewis, Washington, as part of a medical contingent drawn from Stanford Medical School. Earlier, before the United States formally entered the war, Addis had come under the threat of prosecution by the U.S. Attorney's office in San Francisco, probably for violation of the neutrality laws (he was then still a British citizen). He benefited from the intervention of Dr. Wilbur, who was on leave from the medical school while working in the office of Herbert Hoover, President Wilson's wartime food administrator.

Addis became professor of medicine in 1920 and served in that capacity until becoming professor emeritus in 1946. He also ran the Clinic for Renal Diseases at Stanford from 1921. He served as consultant to the surgeon general during World War II (1942–45), working on artificial substitutes for blood plasma with support from the Office of Scientific Research and Development (OSRD). After retirement, Addis continued to work in his laboratory at Stanford until the summer of 1948, when he moved to Los Angeles to continue his research, working with Dr. Jessie Marmorston in Harry Goldblatt's Institute for Medical Research at Cedars of Lebanon Hospital.[1]

Addis died at the age of sixty-seven at Cedars of Lebanon Hospital on June 4, 1949, in septic shock following surgery to remove a kidney infarcted as a result of thromboembolic disease.

Addis published over 130 scientific and clinical papers as well as two important books, *The Renal Lesion in Bright's Disease* (1931, 4), with J. R. Oliver, and *Glomerular Nephritis: Diagnosis and Treatment* (1948). He received the following prizes and lectureships: a Carnegie research fellowship, the Gibbs Prize, and in 1942 the Cullen Prize (awarded by the Royal College of Physicians of Edinburgh for the "greatest benefit done to practical medicine in the previous four years"); he delivered the Harvey Lecture in 1928 and the Thayer Lectures in 1931 and was visiting fellow at the Rockefeller Institute in 1928. Addis was a member of the Association of American Physicians, the American Physiological Society, the Society for Experimental Biology and Medicine, the American Society for Clinical Investigation (president in 1930), and the National Academy of Sciences from 1944. He was also a fellow of the Royal College of Physicians (Edinburgh) and the American College of Physicians.

Addis's students, colleagues, and co-workers over the years included Ray Lyman Wilbur, C. K. Watanabe, George D. Barnett, Jean R. Oliver, A. E. Shevky, M. C. Shevky, Marjorie G. Foster, Douglas R. Drury, B. A. Flyers, Leona Bayer, Lois L. MacKay, Eaton M. MacKay, Lee J. Poo, William Lew, David A. Karnofsky, Evalyn Barrett, Florence Walter, Horace Gray, David A. Rytand, Arthur L. Bloomfield, Richard W. Lippman, Jessie Marmorston, Leland J. Rather, Edward C. Persike, Eloise Jameson, Belding Scribner, Marcus A. Krupp, William Dock, B. O. Raulston, and Roy Cohn.

ADDIS'S EARLY LABORATORY WORK (1909-19)

Addis's early work was concerned with several different clinical problems. As with his later work, it was characterized by a high degree of methodological sophistication and a critical attitude toward current practice. His pragmatism

and concern with practical clinical applications are also apparent throughout. His earliest work (part of it conducted during a Carnegie research fellowship in Germany) concerned blood coagulation. He showed convincingly that, contrary to earlier claims, oral administration of either citric acid or calcium lactate had no effect on blood coagulation in patients with a variety of diseases, both hemorrhagic and thrombotic. These studies used Addis's modification of a standard coagulation assay (McGowan's method), a modification that he validated by daily triplicate determinations of his own coagulation time over fifty days. He also contributed investigations into the pathogenesis of hereditary hemophilia, suggesting that the disease is due to a defect in the conversion of prothrombin to thrombin, rather than in the activity of the thrombin itself or (as was believed by Sahli and others) a cellular defect.[2]

After moving to Stanford, Addis conducted spectroscopic analyses with Wilbur of the hemoglobin breakdown products (bile pigments) in hemolytic disease states such as pernicious anemia. He also published several studies on diabetes mellitus, including an analysis of the different clinical methods for estimating the degree of acidosis (this was just before the advent of insulin therapy), a critique of the conventional preparation of the diabetic patient for surgery (which he held to be "a pure hypothesis, unsupported by any experimental work") together with a proposal for better perioperative management, and an approach to the early diagnosis of diabetes mellitus in patients incidentally found to have glycosuria. The latter was based on a graded increase in the "strain" imposed on the glucose-utilizing tissues by increasing daily glucose loads, an early form of glucose tolerance test in which glycosuria rather than blood sugar was measured, and an approach similar to that which he later employed in studying kidney function.[3]

Several studies were carried out during Addis's service in the Army Medical Corps during World War I. Measurements of blood pressure and pulse rates in recruits were used to construct tables of normal values for these parameters under conditions of basal and normal activity, exercise, and changes in position.

UREA EXCRETION AND THE AMOUNT OF FUNCTIONING RENAL TISSUE (1916-25)

Almost from the time of Richard Bright's first clinical and pathological descriptions in 1827 of the constellation of kidney ailments that so long bore his name, the fact that blood urea levels rise in diseases of the kidney had been known. Because the kidneys are the sole excretory organs for urea (formed in protein catabolism), blood urea concentrations rise whenever renal excretory function is compromised. As early as 1856, Picard recommended the measurement of blood urea as a diagnostic tool. Little more was done with these observations, though, until the turn of the century and the development of analytical procedures (principally by Folin, Wu, Van Slyke, and Marshall) capable of accurately determining urea concentrations in small samples of blood and urine. This ushered in an era of dynamic tests of kidney function using the rate of renal urea excretion and the blood urea concentration.

From 1916 to 1925, Addis and his colleagues produced about thirty publications on the quantitative assessment of renal function through measurement of urea excretion. Two large series concerned renal function in man ("The Rate of Urea Excretion I–VIII") and in the rabbit ("The Regulation of Renal Activity I–XI"). In the human experiments, Addis, his students, and his co-workers were the subjects, supplying the specimens for literally hundreds of blood and urine urea determinations. In all these studies

the goal was a functional assessment of the anatomic state of the normal and diseased kidney: "This would give us what we most need in clinical work—an anatomical foundation for early diagnosis, prognosis, and treatment. For functional studies have in the last resort no fundamental significance unless they are of such a nature that structural inferences may be drawn from them." In this attitude, Addis continued in an intellectual tradition dating back to Richard Bright and René Laennec, two of the pioneers in clinical-pathologic correlation. Bright in particular had sought to understand kidney disease "by reference to Morbid Anatomy" (as he stated it in his famous *Reports on Medical Cases*). Addis saw himself faced with "the problem of the relation between renal function and structure, the problem which Bright set before himself nearly a century ago." Given the very poor level of understanding of kidney physiology at the time, it is not surprising that Addis and many of his contemporaries sought a bedrock of reliable knowledge in the relatively better understood pathology of the kidney.

In the first paper in this series, Addis and Watanabe examined the previous quantitative theory of Ambard and Weill (1912) against their more complete and carefully obtained data and found that although it was qualitatively suggestive, it did not "allow . . . even a rough prediction of the rate of urea excretion" (1916, 1). This motivated a very long paper by Addis (1917) in which he described his own test to assess "the work of the kidney." In it he outlined the characteristics of an ideal substance for testing the secretory (i.e., excretory) function of the kidney: It must be "a true end-product . . . incapable of chemical alternation within the body . . . whose only path of excretion [is] through the kidneys"; its blood concentration should also be susceptible to alteration by systemic administration.[4]

Earlier attempts at a functional assessment of renal

had foundered on the high normal variability of renal excretory function, variability arising largely from the changing excretory needs of the body.[5] Addis and his colleagues were convinced that such high variability was found only in short-term studies of renal function and was due to a changing balance in the factors that normally regulate renal activity. Over twenty-four-hour periods, the forces tended to cancel one another, leading to a greater stability in the measured renal function. The fundamental index of function that Addis and his colleagues settled on was the ratio $U \cdot V/B$, the Addis urea ratio, where U is the urine urea concentration, V is the urine volumetric flow rate, and B is the blood urea concentration. Thus, the product $U \cdot V$ is the urinary excretion rate of urea. The urea ratio was approximately constant in a given individual (and reflected the functioning renal mass), at least for urine flows over about two milliliters/minute, the augmentation limit of Van Slyke.

Many of the later papers in this series were dedicated to describing factors that contribute to the short-term variability in renal excretory function, so that these could be controlled during clinical examinations. Later Addis extended the urine collection period to twenty-four hours and thus overcame much of this variability. The principal factors uncovered were the state of diuresis, diet (particularly caffeine, protein, and amino acids), exercise, and certain hormones (adrenalin and hormones of the posterior pituitary gland).

Among the factors subject to external control was the blood urea concentration B. It was established that the variation in the ratio $U \cdot V/B$ decreases with increasing blood urea concentrations. Addis's interpretation of this finding was that the "strain" of excreting greater amounts of urea would push the kidney to the maximum work of which it was capable.[6] Thus, patients were studied after receiving

an acute oral urea load. Tests of renal function were in addition conducted in a fasting state and during a water diuresis (which Van Slyke had also shown decreases variability). Through such efforts to suppress or stabilize regulatory influences, the coefficient of variation for urea ratios in a single individual in Addis's lab was reduced to 5.1 percent.

Addis conceived of the excretory capability of the kidney as the result of two factors: the total functioning mass of secretory tissue (the relatively constant factor) and the level of renal activity (the variable factor). The influence of renal mass on excretory function was suggested by the observation that the body weights (and hence the kidney weights) of rabbits and men fall in approximately the same proportion as their urea ratios (35:1 and 33:1, respectively). This was also suggested by studies of the urea ratio in animals with reduced functional mass as a result of nephrectomy[7] or graded damage to the kidney in experimental uranium nephritis.[8] Interestingly, Addis and his colleagues did find that the ratio $U \cdot V/B$ somewhat overestimated kidney weight (approximately 17 percent) after compensatory hypertrophy. The discrepancy was rectified in a morphological study by Jean Oliver in which he showed that a disproportionately large amount of renal hypertrophy following uninephrectomy was due to hypertrophy in the proximal convoluted tubules. At that time, renal excretory function was thought to be primarily a secretory process (the importance of glomerular filtration was not yet fully appreciated), and the most effective portion of the nephron for urea secretion was considered to be the convoluted tubule.

The evolution of all kidney studies was considerably advanced by the development of the concept of renal clearance. The first expression of the clearance concept, viz., that the Addis urea ratio expresses the virtual volume of blood freed of urea by the action of the kidney in a unit of

time, was made by Addis in his Harvey Lecture.[9] He acknowledged that this interpretation as a virtual volume was pointed out to him by his colleague G. D. Barnett. On the other hand, Van Slyke and his colleagues at the Rockefeller Institute for Medical Research, who had been doing similar detailed studies on urea excretion for years, were the first to use the word "clearance."[10] Homer Smith later speculated that it "is difficult to judge the importance of words as the vehicles of ideas, but . . . had Barnett or Addis used Van Slyke's happy expression 'cleared' instead of 'freed,' renal physiology might have been significantly catalyzed in 1917 or thereabouts."[11]

The urea excretion ratio was measured by Addis in patients with Bright's disease from about 1920. Further use of the urea clearance as a measure of kidney function was cut short by the introduction of creatinine clearance[12] and eventually inulin clearance[13] as clinical and research markers of glomerular filtration. Although he continued to use the urea ratio as an index of the osmotic work of the kidney, Addis did adopt the creatinine clearance as a functional test, eventually contributing to the development of practical clinical methods for determination of the serum creatinine concentration.[14]

CLINICAL CLASSIFICATION OF BRIGHT'S DISEASE (1922-33)

Richard Bright first described the complex of albuminuria, edema (dropsy), and postmortem gross pathological findings of granular kidneys and an enlarged heart in his famous *Cases* in 1827. Over the next century, Bright's concept was expanded by many investigators. In 1853 Wilks suggested that there were cardiovascular causes of renal disease, and Müller introduced the term "nephrosis" in 1905 to describe chronic renal disease without signs of inflammation. In 1914 Volhard and Fahr divided Bright's

disease into nephrosis, nephritis (inflammatory renal disease), and arteriosclerosis, a classification that provided the basic framework for pathological diagnosis until the proliferation of histopathological entities that followed the widespread introduction of renal biopsy in the 1950s.

Since functional dynamic tests were introduced in the early 1900s, the understanding of Bright's disease began to follow a path that led away from morphology. Addis was concerned with determining the nature and extent of Bright's disease during life (i.e., making a clinical rather than a pathological diagnosis) while retaining the traditional anatomical basis for classifying the disease. He therefore tried to salvage clinical methods that others had rejected as unreliable or uninformative by learning how to reduce the considerable variability inherent in them. Addis, however, considered a functional approach alone to be inadequate. Owing to "the reserve power of the renal tissue," purely functional tests might fail to detect even the 50 percent loss of renal mass after uninephrectomy. At the same time, many of the physicians who favored functional tests rejected examination of urine sediment. Addis felt that this was also due primarily to methodological problems: "A superficial and casual examination of urinary sediments will make anyone feel inclined to agree with the modern view that little is to be gained from such studies." He also felt, however, that the troublesome day-to-day variability in the appearance of the sediment was due to variations in the conditions of the examination and not necessarily to changes in the disease process.

His approach to the clinical classification of Bright's disease was therefore twofold: quantitative examination of the urinary sediment (the Addis count)[15] indicated the nature of the lesion, and the urinary urea clearance (the Addis urea ratio) indicated the extent of the lesion. From

this dual approach, Addis and his colleagues built up a tripartite clinical classification of Bright's disease analogous to that of Volhard and Fahr: hemorrhagic (nephritis), degenerative (nephrosis), and arteriosclerotic Bright's disease. Van Slyke and his colleagues had at the same time also been studying patients with Bright's disease.[16]

Although not entirely satisfactory, this classification was intended to serve as a "local scaffolding" until a better understanding of the etiology of the disease could be attained. The latter was to be accomplished through followup of patients with Bright's disease over years or even decades, including a final clinicopathological correlation in the form of postmortem examination.[17] Much of this early work in the classification of Bright's disease was summarized in a book Addis jointly wrote with the pathologist Jean R. Oliver, *The Renal Lesion in Bright's Disease* (1931, 4), a detailed decade-long examination (with quantitative functional studies and microscopic pathology) of Addis's patients with Bright's disease. "The book had a purpose . . . identical with the purpose of Volhard and Fahr's book."

From studies of the effects of renal ablation and uranium toxicity on renal structure, the concept emerged that the clinical outcome in Bright's disease depended on the balance of processes of tissue destruction and tissue restoration, the latter largely through hypertrophy. The clinician should therefore attempt to impede the former and enhance the latter, where possible. Doing this was not a simple task. High levels of protein ingestion clearly increased the maximum degree of renal hypertrophy (see next section) that followed loss of renal mass, but Fahr and Smadel (1939) soon demonstrated that high-protein diets also increase the rate of renal destruction in rats with Masugi nephritis (now called nephrotoxic serum nephritis).

Along with a classification scheme and a preliminary etiologic

"scaffolding," therefore, an attempt was made to define some form of effective therapy, although the almost total ignorance regarding therapy at this time might have been a "good and sufficient excuse for abstention from all forms of treatment." Experimental and theoretical considerations, however, suggested at least "a plan of action." Since the provisional cause of progression in Bright's disease was "the product of a combination of a disease process and the demand on the damaged organ to do its usual amount of work," a theory of therapeutic "rest" from renal work was advanced. This was certainly not unknown as a therapeutic principle at the time. Addis was undoubtedly familiar with the contemporary practice of thoracoplasty (collapsing and resting the tuberculous lung), as practiced by his friend and colleague, the surgeon Leo Eloesser, and also with the work of Allen[18] and probably of Homans[19] on the destructive effect of "overuse" in the experimentally damaged pancreas. To apply these insights, however, it was first necessary to define what constitutes renal work.

The theory Addis developed proposed that renal work consists of the thermodynamic work of concentrating the urinary solutes, particularly the major urinary solute urea. This hypothesis had the advantage of simplicity—the "reversible" work for a unit volume of urine is proportional to the logarithm of the urine to the blood concentration ratio of the substance being excreted, $W = RT \log (U/B)$.[20] Specifics of the theory changed with increasing understanding of the physiology of the kidney, especially the demonstrations by Rehberg (1926) and Smith and colleagues (1938) of the extremely large volume of glomerular filtrate produced by the kidney (180 liters/day). Thus, the early conception of renal work as urea secretion by the proximal convoluted tubules eventually evolved into the idea of renal work as water extraction from an increasingly concen

trated tubular fluid. The physician could help rest the kidney by decreasing the amount of urea to be excreted with a low-protein diet, by prescribing a liberal water intake (if the circulatory system allowed) to dilute the urea in the urine, and by prescribing enough salt in the diet (after the edema-forming phase of the disease was passed) to raise the urine salt concentration to approximately that of the blood. In the latter case, the work of salt concentration would approach $RT \log(1) = 0$; otherwise, diluting the urine to decrease urea work would actually increase the salt (diluting) work. The thermodynamic concept of renal work, on the other hand, did not lend itself easily to being followed over time, so the idea arose to look at the results of sustained renal work, viz., renal hypertrophy.

The role of dietetic therapy in Bright's disease was repeatedly considered. As in the preceding century, the winds of medical opinion regarding the appropriate amount of protein in the diet of patients with Bright's disease changed direction again during Addis's career. Addis used dietary therapy in treating Bright's disease from the early 1920s. His approach took into account not only the principle of minimization of renal work but also the effect of urinary protein losses,[21] the likelihood that with decreased appetite in renal disease less than the prescribed amount of protein would actually be ingested, vitamin supplementation in light of a restricted food intake, and the special requirements for growth in children (for whom Addis prescribed up to 2 grams/kilogram of body weight per day, almost four times the adult level). In addition, he showed that proteinuria in patients with Bright's disease increases with increasing levels of dietary protein intake, without changes in the serum protein concentration unless dietary protein has been manifestly inadequate.[22] Thus, Addis's success in treating patients with chronic Bright's disease may have

been realized in part because he was the first to recognize the need to individualize dietary therapy in patients, in order to gain the benefits of a low-protein diet without incurring an excessive risk of protein malnutrition.

ORGAN GROWTH AND HYPERTROPHY (1925-49)

As in earlier work on the regulation of renal activity and the rate of urea excretion, much of Addis's work on organ growth and hypertrophy was reported in a large series of papers on factors that determine renal weight. Addis was not an author of all twelve papers in this series. Much of his work on the topic was conducted in collaboration with Eaton and Lois MacKay, William Lew, Lee J. Poo, and Horace Gray.

With the development of the concept of therapeutic rest, a reliable index of renal work was needed. Although the thermodynamic definition of renal work played a major theoretical role, it also had limitations. The idea of organ weight as an indirect measure of organ work was therefore exploited. The use of change in organ weight to reflect work was supported by an analogy with the increase in muscle mass that results from sustained increases in muscle work.

In order to utilize this approach, organ weights had to be normalized for age, sex, and diet, and the relationship between organ weight and body weight (or surface area) had to be established. Weights of different organs under specific "stresses" were examined: hypertrophy of the gastrointestinal tract under conditions of increased dietary bulk (increasing the work of moving material through the tract), changes in the weight of paired organs after removal of one of them, and changes in organ weights following alterations in overall metabolism (thyroidectomy, thyroid hormone administration, pregnancy). In the kidney the ef

fects of age on growth at the time of nephrectomy, protein intake, dietary urea administration, and other factors were studied.

After about 1940, Addis became very critical of the term "compensatory hypertrophy," since its use usually belied a profound ignorance of the nature of the organ function being compensated. "In this endeavor nothing is more likely to still curiosity and initiative than a nomenclature that implies knowledge where only ignorance exists." Even so, growth of the remaining nephrons following partial nephrectomy seemed to Addis to lower the urea work load per gram of remnant nephrons and thus be an adaptive response to an increase in renal work per nephron.

MECHANISMS OF PROTEINURIA (1932-49)

The final major topic that Addis investigated was the relationship between proteinuria and kidney disease. He suggested that pathological proteinuria might be due simply to an intensification of those normal (physiological) processes and factors that cause the appearance of the minimum amounts of protein found in normal urine. He considered mediation of proteinuria through local kidney hemodynamics to be probable.

At the time of his death, much of Addis's research on this topic at Cedars of Lebanon was being conducted in laboratory rats, including studies of protein-overload proteinuria, renin-induced proteinuria and the effects of adrenalectomy, and sex differences in the levels of proteinuria in rats. A number of interesting phenomena were described, but conclusions ready to find expression in clinical practice were not, in the main, achieved. The specific goal of these investigations was to understand the role of proteinuria in the progression from latent to degenerative phases of glomerular nephritis (see below) and, in particular, the

relevance of proteinuria to tubular degeneration, which Addis considered "the central mystery of the disease."

The book *Glomerular Nephritis: Diagnosis and Treatment* (1948, 4) is a synthesis of over thirty years of work by Addis and his co-workers at Stanford's Clinic for Renal Diseases. His colleague Arthur Bloomfield felt that the book would "perhaps interpret the man to his followers better than anything else he has done." To those who had been close to Addis's work over the years, little in the book would be particularly new. Many of its conclusions were based on papers published in the preceding years. However, Addis clearly felt that he had finally accumulated enough data and clinical experience to present a case for the broader clinical adoption of the diagnostic and therapeutic methods he had perfected over decades. "For no matter how well supported by reason and buttressed by fact a new method of treatment may be, there is no sure foundation for clinical action other than clinical experience."

The book has a strongly philosophical tone and thus also serves as a vehicle for an exposition of Addis's philosophy of clinical medicine and scientific research. In addition, Richard W. Lippman has stated that, "The thread of his concern with political philosophy is to be found in all his writing in later years, most notably in the book 'Glomerular Nephritis'." Although perhaps only implicit in its formulation, Addis's political and social philosophy can clearly be recognized in the book, especially in his description of the social organization of work at the clinic. Another remarkable feature of this work is its literary grace and power. It is a masterpiece of both critical reasoning and pathos. Belding Scribner, a former student in Addis's lab and one of the founders of hemodialysis, has said that to this day the syllabus given to the new nephrology fellows in his division starts with the last chapter of Addis's book.

Glomerular Nephritis is largely dedicated to an explication and defense of the principle of rest from osmotic work in the treatment of glomerular nephritis. The concern with glomerular nephritis, rather than Bright's disease, might seem to signal a shift in Addis's interests. In fact, his clinic at Stanford always primarily saw patients with nephritis or with kidney diseases simulating it. This is the reason patients were referred to Addis. In concentrating on glomerular nephritis, Addis had picked one of the most perspicuous causes of Bright's disease. Unlike pyelonephritis (an infection) or vascular diseases, the initial insult (ß-hemolytic streptococcal infection) was invariably of limited duration, and what Addis followed in his patients was the evolution of a pathological process intrinsic to the kidney, the oscillating and tenuous balance of forces of tissue restoration and destruction during the long latent stage of glomerular nephritis. The forces to be examined were the kidney's own. He rejected "the assumption that the disease is a parasite on the body: The laws that govern the maintenance and growth of structure and the operation of the functions of the body are still in effect. The disease has only changed the conditions under which they act."

The book includes sections on methods of laboratory work, the organization of clinical medicine, determining the nature and extent of the lesion in glomerular nephritis, the differential diagnosis of glomerular nephritis from other proteinuric kidney diseases, and the treatment of glomerular nephritis derived from experimental work and touchingly illustrated and interwoven with an extended case history of a single patient, from his diagnosis at age eight to his death from uremia in his early thirties. The chapters on determining the nature and extent of the lesion and on treatment bring together many years of research by Addis

and his colleagues, as well as others, under an analysis at once critical and imaginative.

Without doubt Addis's most original contribution to the treatment of kidney disease was his rest therapy. As he put it, "In dealing with a damaged or diseased organ, we must strive first of all to rest that organ from its work." Addis contrasted rest with "inactivity"—the former includes the very active processes of repair and regeneration. His focus on the work of urea excretion is now considered by most investigators to have been misguided and probably to have contributed to the disaffection of many with his ideas.

Why did Addis believe urea excretion to be the pivotal form of renal work? In rats a high-protein diet and unilateral nephrectomy both cause hypertrophy of the (remaining) renal mass; in fact, the renal growth curves in these two situations are almost identical. It is easy to see the basic stimulus to the remaining kidney after contralateral nephrectomy as an increased excretory workload. Since the most obvious consequence of a high-protein diet for the kidney is also excretion of larger amounts of urea (the final breakdown product of protein in the body and the major urinary solute), it was indeed logical for Addis to at least consider the osmotic excretory work of the kidney as a major factor in causing renal hypertrophy and thus in contributing to renal work.

One of the most revealing traits that we can observe in a human being is how he or she deals with apparent contradictions in his or her world view. Addis was quite aware of inconsistencies in his rest theory, in particular with the importance it assigned to the osmotic work of the kidney. The sophistication of his reasoning in holding to the osmotic theory in spite of these objections has often been overlooked in light of the resounding rejection the theory

itself received at the hands of improved physiological understanding.[23]

Addis was well aware of the large discrepancy between the calculated thermodynamic (urea-concentrating) work of the kidney and values of renal metabolism determined from organ oxygen consumption (after all, the fundamental work was performed by his colleague William Dock).[24] Even allowing for a major component of "friction" (i.e., thermodynamic inefficiency), solute concentration could account for only about 4 percent of total renal metabolic expenditure. Yet he felt that no data spoke "for or against the objection that the energy requirements for osmotic work are so small that they cannot be regarded as effective with respect to any major events within the kidney. The objection itself is based on analogy and arises because of a difficulty in conceiving that a small change in energy relations may sometimes lead to large material results." The above-mentioned similarities between renal growth after nephrectomy and growth on a high-protein diet supported his idea of the "effectiveness" of renal osmotic work.

Two statements that Addis made in *Glomerular Nephritis* may help to explain his willingness to continue to use a hypothesis about which he acknowledged several significant problems.

> We would rather set down in black and white some beginning of a theory, no matter how provisional and faulty, than remain in the silence that surrounds unknown and uncriticized presuppositions. For thought, once expressed, has a way of curing its own errors. What is asked of a hypothesis is not that it should precisely prefigure the mechanism that actually exists. All we require is that it should suggest questions that can be answered by experiment, and that it should emerge in the simplest possible manner and without contradiction from what we do know about the problem.

As always, the acid test for Addis was the implications of theory for clinical practice. The rat experiments were for

him just "secondary, even if necessary, supports. It is true that if they had not vindicated the rest of the hypothesis we should have concluded that we had been misled in the interpretation of our clinical experience. Clinical history is full of such mistakes. But if our clinical experience of many years had not seemed to confirm the theory we should not have ventured to advance it as a basis for the action of others."

[Statement by a former patient, L.P.: "I was Dr. Addis's patient from March 1941 until his death. While on a trip to New York, I was told by Dr. D. D. Van Slyke and Dr. George Burch at the Rockefeller Institute for Medical Research that I was suffering from glomerular nephritis, and was advised to cancel my visit to the Mayo Clinic to give the Mayo Memorial Address for that year, and instead to go to Dr. Addis in San Francisco. My edema was high, over twenty pounds, as was my urinary protein loss, about twenty g per day. I was placed on a salt-free diet, which eliminated the edema in four months, and on a rigorous minimum-protein diet, which I followed for fourteen years. Addis also had me take supplementary vitamins and minerals, drink much water, and rest in bed to the extent that my professional duties permitted. I am now, fifty years later, in quite good health.

I remember that at one time, about 1942, I was with him in his cubicle, talking about the state of my health. We were interrupted by a phone call, which seemed to be about some political activity. He started to discuss it with me, and then interrupted himself to say 'No—pay no attention. Your job is to get well.'

I now realize that Addis's regimen was completely orthomolecular. I received no drugs. My treatment involved only the regulation of the intake of substances normally present in the human body: increased intake of

water, vitamins, and minerals and decreased intake of protein and, for a time, salt, combined with some rest in bed.

I dedicated my 1950 book *College Chemistry* to him with these words: 'To the memory of Dr. Thomas Addis, who in applying science to medicine kept always uppermost his deep sympathy for mankind.' "]

ADDIS, THE MAN

Tom Addis is remembered by his colleagues as a gentle and charismatic man, of broad learning and interests. He was no "ivory tower scientist." His daughter Jean remembered that his knowledge of poetry and economics and music "reached into his work . . . There was no division to all these things."

William Dock considered that "as a medical scientist he was in a class by himself." His approach to clinical problems was logical and incisive but also extremely practical. Although a consummate researcher, Addis was, according to Ray Wilbur, committed "not [to] research just for research's sake, but to [relieving] human suffering." To Arthur Bloomfield his relations with his patients were marked by "deep friendship and concern."

Despite the efforts of Addis and his colleagues, many patients eventually died of renal disease. This was a part of every "kidney man's" experience, before the advent of dialysis and transplantation.[25] Addis found it very difficult to visit his patients when the end was near. But they would not be satisfied with any of his associates, so in the end he would see them and provide what comfort he could. "It is our job to do our best to keep [the patients] on the firing line to the very last gasp. Since our best endeavor amounts to almost nothing we need not take ourselves too seriously. . . . More and more we cease to play even a minor role in the drama. We retreat to the wings to watch the last act of

the tragedy." The respect his patients' families felt for him was such that permission for postmortem examination was usually granted. Many of his wealthier patients and their families contributed financially to his clinic at Stanford.

Addis had eccentricities. Most of his professional correspondence was written by hand, Mrs. Addis typing only the most formal reports. He was rather indifferent toward payment for his services as a doctor, since seeing patients was one of those activities for which he was paid as a university professor. He was also probably the only man in San Francisco to have a charge account on the ferry and cable car lines, because he was so likely to forget his change. The conductors knew that Mrs. Addis would be by periodically to settle accounts. He was as likely to go home wearing his white lab coat as his blue suit coat, and he could announce that he was leaving for New York as casually as though he were just crossing the bay.

Although he rarely, if ever, held formal lectures at the medical school, Addis had a profound influence on many of the students and young physicians working in his clinic. He was instrumental in furthering the careers of several of them. Belding Scribner worked in Addis's lab as a fourth-year medical student. When Scribner left the lab in 1945 for an internship at San Francisco County Hospital, Addis gave him the laboratory's electric pH meter (a valuable piece of equipment in those days) to use on the personal laboratory "cart" that Scribner had put together. Scribner dates his interest in the kidney from his work with Addis, whom he described as a role model. Another of Addis's co-workers, Leona Bayer, decided on a career in medicine after working in his lab.

The renal clinic was run along very democratic lines. All members were involved in virtually all aspects of the experiments, and preexperiment "conferences" saw to it

that everyone understood and viewed the "enterprise as an organic whole." Addis was prepared to learn from, as well as to teach, everyone: "wives, mothers, and sisters, who, with our patients, are our true colleagues with whom we work and from whom we learn." Addis's longtime laboratory assistants, Lee J. Poo and William Lew, would say that they worked "not for but with Dr. Addis."[26] Indeed, both of them appeared often as coauthors on publications with him.

Addis's attitudes toward medicine and science cannot be separated. "[In the beginning] I was all set on measuring things and was trying to be 'scientific.' But anyone who has patients and patience can scarcely help coming at last to see that experiments that don't answer questions about patients are, for the doctor, pretty irrelevant. For the last ten years or so we have not asked any questions from our rats that did not give us at least a hope of getting answers that referred to our patients." Addis's attitude toward his patients dominated his research work, and the Clinic for Renal Diseases at Stanford University held its sessions right in the laboratory, in the midst of experiments ("we can't separate the rats and the patients"). On clinic days the laboratory was a sight to be remembered. It was humming with activity. Patients sat all about, watching with interest the tests, both those that were routine and those that were part of some special research project, being made in front of their eyes. Then, when Dr. Addis saw one of his patients, the information about his or her condition was up to the minute. No distinction was made between clinic (usually nonpaying) and private patients, and each visitor waited in turn to see Dr. Addis. The normal administrative procedures of the hospital were often bypassed for renal patients in view of the frequency of their visits intended simply to follow the course of the disease. In the

first years of the clinic, such follow-up did not directly benefit the patient and was done mainly to improve methods of differential diagnosis.

Although having patients to follow was vital, Addis believed that "Clinical experience is the final arbiter, not the original source of knowledge. Clinical work is not enough. The all-important thing is to start the derivation of first approximation answers to clinical questions through experimental work on animals" (1939, 1). But it could also not stop there. "[T]he doctor is not a [scientific] positivist"; all the studies of renal function are just "means to his end, which is action, not knowledge." He is, in fact, "obliged to be more than scientific": while the scientist is always attempting to generalize his or her understanding, the clinician must individualize his or her understanding to each particular patient.

Although Addis could be found in his laboratory any day of the week during an experiment, life in the barnlike lab retained a pleasant and cultured atmosphere. Addis was a great lover of classical music, and during clinic days some Beethoven or Brahms chamber music might be playing on the phonograph in his office. Traditional teatime was also observed in the renal lab, attended by a variety of colleagues (such as Bloomfield and Dock) as well as laboratory personnel. Topics of discussion during these sessions could be the arts or history (Addis was an admirer of R. G. Collingwood), although through the course of the 1930s the discussions turned increasingly often to political and social problems, such as the international rise of fascism.

Addis was an advocate of the civil rights of blacks, Jews, and the politically oppressed. In 1941 he interceded to try to get a teaching position for his friend Dr. Alfred Mirsky (because, he wrote to a friend, "It is true that it is hard for Jews to get teaching positions"). His political involvement

was well summarized in a memorial address by his Stanford colleague physiology professor Frank W. Weymouth:

> Injustice or oppression in the next street or . . . in any spot inhabited by men was a personal affront to Tom Addis and his name, from its early alphabetical place, was conspicuous on lists of sponsors of scores of organizations fighting for democracy and against fascism . . . and [he] worked on more committees than could reasonably have been expected of so busy a man. A picture comes to mind of his spare frame stretched out in a waiting room chair calculating from current experimental data on his slide rule as he waited with a delegation to present a complaint at the City Hall. . . . Tom Addis was happy to have a hand in bringing to the organization of society some of the logic of science and to further that understanding and to promote that democracy which are the only enduring foundations of human dignity.

Addis had great sympathy with the Republican cause in Spain. Josep Trueta, the noted trauma surgeon and occasional kidney physiologist, once wrote to Addis that he hoped to meet him one day "and talk of so many of the subjects of our common interest, like the kidney & Spain." Addis was for twelve years chairman of the San Francisco chapter of the Spanish Refugee Appeal. This organization, with the Joint Anti-Fascist Refugee Committee, was dedicated to helping political refugees from Franco's Spain, in part by supporting the Varsovia Hospital in Toulouse, France. The hospital was opened during the liberation of southern France during World War II and was run solely for the medical care of Spanish refugees from Franco's fascism. After Addis's death, funds raised by his San Francisco chapter helped to build a new diagnostic laboratory pavilion in the hospital. The pavilion, inaugurated on January 1, 1950, was named for Addis.

Addis was onetime chairman of the San Francisco chapter of Physicians' Forum, a national organization favoring national health insurance. Such activities cost several phy

sician acquaintances of Addis their membership in the medical association. In fact, Addis had been in and out of the American Medical Association throughout his career, resigning (or being expelled) shortly before his death for refusing to make a required $25 contribution to finance an AMA public relations campaign opposing President Truman's plan for national health insurance.

Addis made no secret of his sympathies toward the Soviet Union, at a time when one could be branded a "premature anti-fascist" simply for supporting the Spanish Republicans.[27] Addis came back from a 1935 tour of the Soviet Union enthusiastic about the medical accomplishments of the socialist state (which included experimental human cadaveric kidney transplants as early as 1933). He also supported (at least in discussions at lab teatime) the concept of democratic centralism, which in retrospect played an important role in the development of Stalinism. He seemed to view it as an extension of the same organization of work that operated in his lab. One close colleague described his commitment to the Soviet system as "an act of faith." Left-wing political views and friendships with leftist activists such as Harry Bridges were "generally accepted as part of his eccentricities," according to Leona Bayer, tolerable foibles in such a respected scientist. Even conservative colleagues, such as the neurosurgeon Fred Fender, were among his admirers. There is little consensus among his twenty-eight former colleagues on how much Addis's political views and public stands may have influenced the decision to take away his lab at Stanford. Addis certainly perceived himself as somewhat of a nuisance to the administration at Stanford. He expressed surprise as well as pleasure with the Festschrift in his honor published in the Stanford Medical Bulletin (1948) "because I have spent thirty-five years . . . systematically insulting them because of what I

regard as their extraordinarily antiquated and dangerously stupid political notions."[28]

ADDIS, FORTY YEARS LATER

With increasing use of the renal biopsy and the attendant proliferation of pathological diagnoses, the use of such general categories as Bright's disease decreased during the years after Addis's death. The Addis test (quantitative examination of the urinary sediment) and the urea ratio test soon fell into disuse. Even Addis had accepted the creatinine clearance in the end. The success of steroids in the treatment of nephrotic syndrome and the availability of dialysis and transplantation led to a deemphasis on dietary therapy, at least in the United States. Dietary therapy had always been most widely accepted in chronic renal disease because of its effect on uremic symptoms, not because it prolonged survival. Hence, with dialysis available, protein intake could be liberalized.

In the 1970s the outlines of a new "unification" began to emerge in the understanding of chronic progressive renal insufficiency. Observations of a steady, predictable decline in kidney function once about three-quarters of the functional mass was lost were made by Mitch, Walser, and others. There was also a renewed appreciation of the acute effects of dietary protein loads on kidney filtration rate. In 1982 a hypothetical mechanism was proposed that tied dietary protein intake and compensatory "hyperfunction" itself to progression of a large number of renal diseases, as well as the slow loss of renal function with age.[29] Since that time, interest in the dietary treatment of chronic renal failure has increased enormously in the United States. Interestingly, dietary treatment of near end-stage renal failure had been kept alive in Europe (largely by Carmelo Giordano and Sergio Giovannetti in Italy) from the early 1960s, even

adding the twist of supplementing a very low protein diet with essential amino acids. The most recent studies (1988) suggest a decisive role for glomerular hypertrophy in the pathogenesis of the end-stage kidney.

In 1981 Rytand and Spreiter published a forty-fifty-year follow-up study of patients with orthostatic proteinuria who were first seen by Addis and Rytand.[30]

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We thank Betty Vadeboncoeur for her help.

NOTES

1. There has been some controversy over the circumstances under which Addis eventually left Stanford Medical School. It was standard practice at the time for emeritus faculty at the university to retire from active research or practice, so it was only "through a special dispensation from the University that Dr. Addis [was] permitted to remain on after his retirement," a dispensation largely contingent on private funding of the renal clinic—the university provided probably no more than 10 percent of the clinic's operating funds (from correspondence of Mr. Norman Tyre). Addis, in fact, actually turned down private funding in early 1947 because it was tied to his exclusive use, a condition he felt inappropriate for a group enterprise like the clinic. On the other hand, university president Tressider had arranged for Addis "to continue the use of laboratory facilities as long as he has the productive capacity and the facilities are not urgently needed by the active members of [the] faculty." Although, given his research productivity and scientific stature, it is arguable that Addis was one of the most active members of the faculty, and he eventually had to vacate the clinic space in the summer of 1948 so that it could be converted to a clinical biochemistry laboratory. Addis was determined to carry on his work, at least until a younger investigator could establish himself or herself in the lab ("All our past work is now paying dividends. We can't stop now."). Addis therefore relocated members of his research group to new quarters at Cedars of Lebanon Hospital in 1948.

2. M. M. Wintrobe, *Blood, Pure and Eloquent* (New York: McGraw-Hill, 1980).

3. T. Addis (1917, 9): "It is a generally applicable principle that a defect in function becomes more and more apparent, the greater the strain to which [the organ] is subjected."

4. These criteria closely parallel the characteristics of an ideal marker of glomerular filtration, as enunciated later by Homer Smith. The emphasis on filtration, rather than excretion, arose as advances in renal physiology (e.g., the comparative physiology of glomerular and aglomerular kidneys) clarified the relative roles of the three factors in urinary excretion: glomerular filtration, tubular secretion, and tubular reabsorption. The principal drawback in fact to

using urea excretion to assess renal function is that it is the product of all these processes—filtration, secretion, and reabsorption—and as a composite index has compounded problems of variability.

5. Addis and others rejected Cushny's (1917) view that "blind physical force," unresponsive to regulatory needs of the body, governs kidney function.

6. It has been proposed that more information about renal function capacity could be obtained if creatinine or inulin clearances were determined before and after an acute dietary protein load, allowing assessment of basal function and the renal reserve (J. P. Bosch et al., *American Journal of Medicine* 75[1983]:943).

7. Addis, Meyers, and Oliver (1924).

8. Watanabe, Oliver, and Addis (1918).

9. T. Addis, "The Renal Lesion in Bright's Disease," *Harvey Lecture Series* 23 (1928):222–50. Here he described blood flow through the kidney "as consisting of two portions, a portion that passes through unchanged and another portion from which the urea is completely removed."

10. E. Müller, J. F. MacIntosh, and D. C. Van Slyke, "Studies of Urea Excretion. II. Relationship Between Urine Volume and the Rate of Urea Excretion by Normal Adults," *Journal of Clinical Investigation* 6 (1929):427.

11. H. W. Smith, *The Kidney: Structure and Function In Health and Disease* (New York: Oxford University Press, 1951):66.

12. Rehberg (1926); Jolliffe and Smith (1931).

13. Richards and colleagues (1934); Shannon and Smith (1935).

14. Barrett and Addis (1947); Addis, Barrett, and Menzies (1947, 3).

15. This is quantitative determination from a timed urine collection of the rates of excretion of formed elements (such as red blood cells, white blood cells, and casts) and protein.

16. D. D. Van Slyke, E. Stillman, E. Müller, et al., "Observations on the Courses of Different Types of Bright's Disease, and on the Resultant Changes in Renal Anatomy," *Medicine*, 9 (1930):257–392.

17. Postmortem correlation was complicated by the apparent convergence of the three types of pathological lesions in a given patient over time. Aspects of all three tended to be present by the time of death, unless death occurred accidentally early in the course of the disease.

18. F. M. Allen, *Studies Concerning Glycosuria and Diabetes* (Cambridge University Press, 1913).

19. J. Homans, "A Study of Experimental Diabetes in the Canine and Its Relation to Human Diabetes," *Journal of Medical Research*, 33 (1915):1.

20. J. D. Newburgh, "The Changes Which Alter Renal Osmotic Work," *K. Clin. Invest.*, 22(1943):493–46.

21. David A. Rytand recalls this aspect as unique to Addis's approach.

22. Persike and Addis, *Archives of Internal Medicine*, 81(1948):612.

23. For example, Homer Smith's acid comment: "Physiologically, the work represented by the composition of the final urine is an almost negligible fraction of the work it is known the kidney must do. . . . [It] represents only about one per cent of the probable metabolism of the kidney as calculated from the oxygen consumption. This is not to say that the efficiency of the kidney is only one percent. . . . [It] is the thermodynamic approach . . . that is only one per cent efficient." Smith, however, ignored the reasonable possibility that other free-energy requiring reactions in the kidney may be related to the osmotic work.

24. W. Dock, *American Journal of Physiology*, 106(1933):745.

25. Bright's disease was the fourth most common cause of death in the United States in 1940 (S. J. Peitzman, "Nephrology in the United States from Osler to the Artificial Kidney," *Annals of Internal Medicine* , 105:937–46.

26. "Festschrift for Thomas Addis," *Stanford Medical Bulletin*, 6(February 1948):5.

27. This interesting catch-all concept was an ingenious solution to the problem of distinguishing the early anti-Franco activists—mostly Socialist or Communist—who opposed Franco's and Hitler's fascism already in the 1930s from those whose antifascism was a part of the larger war effort. Addis was in fact named as a Communist during questioning of his colleague Leo Eloesser, who was rather indifferent to such labels and the consequences they carried.

28. Letter to L.P. from Addis, March 26, 1948.

29. B. M. Brenner, T. W. Meyer, T. H. Hostetter, "Dietary Protein Intake and the Progressive Nature of Kidney Disease: The Role of Hemodynamically Mediated Glomerular Injury in the Pathogenesis of Progressive Glomerular Sclerosis in Aging, Renal Abla

tion, and Intrinsic Renal Disease," *New England Journal of Medicine* , 307(1982):652.

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Dietrich Bodenstein

DIETRICH H. F. A. BODENSTEIN:

February 1, 1908–January 5, 1984

BY JAMES MURRAY

THE HALLMARKS OF Dietrich Bodenstein's career were his zest for life, his love of beauty in science, and his enthusiastic encouragement of his younger colleagues. His boundless energy and his uncompromising commitment to scientific truth set him apart from many of his contemporaries. To know Dietrich was to experience a force of nature.

Dietrich Hans Franz Alexander Bodenstein was born in East Prussia on February 1, 1908. He grew up on the family estate at Corwingen, at that time an almost feudal survival of an earlier Europe. During his youth he roamed the forests and fields of the estate with his rifle and insect net in search of natural history specimens for his personal "museum." It was only natural, therefore, that when he entered the University of Konigsberg in 1926 he began his studies with Otto Koehler, the distinguished observer of bird behavior. While still a student he published his first paper on a moth that he had found for the first time in East Prussia.

In 1928 Dietrich moved to the University of Berlin, where he became a research assistant in experimental morphology at the Kaiser Wilhelm Institute for Biology. It was there that he came under the influence of Professor Otto

Mangold, at a time when the most exciting results were forthcoming on the control of development in amphibians. Typically, it was the larger questions and not the experimental material that challenged Dietrich's imagination. Encouraged by Mangold, he began to investigate that most challenging problem, control of molting and metamorphosis in insects. It was a study that was to occupy him to the end of his life. In his last scientific papers, published from 1978 to 1981 on work done while on an Alexander von Humboldt fellowship at the University of Marburg, Dietrich used modern chemical and immunological techniques to confirm his previous deductions on the role of ecdysone in the control of development.

In 1933, however, Dietrich's work at the Kaiser Wilhelm Institute was interrupted by the rise of national socialism in Germany. Warned by Mangold that he might be in political trouble with the Nazis, Dietrich accepted a position as research associate at the Institute of Marine Biology in Rovigno, Italy. From there he moved to a similar post at Stanford University, where he worked from 1934 to 1941. During this time he not only continued his studies on insect hormones but also collaborated with Victor Twitty in experiments on the role of ectodermal structures in the development of amphibia.

Dietrich's growing scientific reputation was recognized with a Guggenheim fellowship, which he held in the Department of Zoology at Columbia from 1941 to 1943. From there he moved briefly to the Connecticut Agricultural Experiment Station in New Haven before settling down as an insect physiologist at the Army Chemical Center at Edgewood, Maryland, a position he held from 1945 to 1958. There he met and married his lifelong companion, Jean Coon Bodenstein.

It was while Dietrich was at Edgewood that a curious lapse in his scientific career was made good. The declining fortunes of his family had prevented him financially from being examined for the doctoral degree, and up until 1953 there had never been a convenient moment to bring Dietrich's formal title into line with his undoubted stature in the scientific community. It was his former mentor Professor Otto Koehler who made the arrangement for Dietrich's doctoral examination to be held at the University of Freiburg in that year. Nothing was skirted in the process. Dietrich presented a bound copy of his publications numbering some fifty-nine items and was duly examined by each member of the professoriat of the faculty of science. To no one's surprise he was duly awarded the degree of doctor of philosophy. Indeed, his election to the National Academy of Sciences followed only five years later, in 1958.

From 1958 to 1960 Dietrich served as embryologist with the Gerontology Branch of the National Heart Institute, based in the Baltimore City hospitals. He then entered the final stage of his career, accepting the Lewis and Clark Professorship and the chairmanship of the Department of Biology at the University of Virginia. He took over a tiny department, badly housed and poorly equipped. On his retirement from the chairmanship in 1973, the department had trebled in size. It was housed in, and indeed beginning to outgrow, a modern, well-equipped laboratory building. Moreover, with his genius for personal relationships, Dietrich had assembled a group of colleagues who shared his enthusiasm for modern biology, especially those aspects of the subject dealing with genetics, biochemistry, and, above all, development.

Dietrich continued actively in research after giving up

the chairmanship in 1973. The culmination of his career was undoubtedly his receipt of an Alexander von Humboldt Award for senior U.S. scientists. It represented for him not only recognition of his long and fruitful scientific career but also in a very real sense his reconciliation with his native Germany. It was typical that Dietrich did not regard the appointment as some sort of ceremonial sinecure but as an opportunity to undertake new and exciting work with younger colleagues who could add different techniques to his research armamentarium.

Dietrich's scientific reputation will ultimately rest on the elegance and incisiveness of his investigations into the control of insect development. From his earliest days at the Kaiser Wilhelm Institute, he recognized the precision with which the events of molting and metamorphosis take place and wondered about the mechanisms by which they are controlled. His first major set of experiments was designed to find out whether the timing of larval molts and the differences between larval and pupal molts were controlled by time-dependent processes within the cells of the skin itself or by signals from some internal source. He reasoned that he could make this distinction by transplanting skin between larvae of different ages. He taught himself the exceedingly difficult techniques for transplanting larval prolegs from older to younger larvae and performed hundreds of successful transplants. He was rewarded with quite clearcut results. The transplants invariably molted in synchrony with the host. Moreover, instead of undergoing a pupal molt, the transplants underwent an extra larval molt, indicating control by blood-borne factors that Dietrich insisted should be considered as hormones.

At that time biochemical methods were not sufficiently well developed for the reliable assay of insect hormones in

physiological concentrations. Therefore, it was necessary to develop biological assays for detecting their origin and action. Dietrich used the imaginal discs of *Drosophila* to assess the function of organs thought to be involved in the production of hormones. He reasoned that there would be very little growth hormone in adult animals so that he might use the body cavity of adults as culture chambers. When he transplanted imaginal discs into the body cavities of adult males, they did indeed remain in good condition, although there was no evidence of growth or development. But when he included several ring glands (the suspected hormone-producing organ) with the transplants, the discs enlarged and eventually formed the appropriate adult structures. On the other hand, transplantation of discs into the body cavities of females resulted in growth of the discs without the addition of ring glands. Dietrich concluded, therefore, that his initial assumption was only partly correct and that females, but not males, actually contain growth hormone in the adult stage.

Dietrich continued his investigation of the role of hormones in molting by using the head segment of an early larva transplanted into the abdomen of an adult fly. By observing the number of hooks on the lower jaw, it was possible for him to establish whether molting had taken place. In these experiments molting occurred only when ring glands were included with the transplant, indicating that both growth and molting were controlled by a single hormone.

The next stage of the investigation was to separate the effects of the two hormones now known to control development, the growth and molting hormone and the juvenile hormone. In order to do this Dietrich had to use a different insect. In *Drosophila* the ring gland is actually a

compound organ containing both the prothoracic gland (the source of growth hormone) and the corpus allatum (the source of juvenile hormone). It has not so far been possible to separate the two parts surgically. Dietrich therefore turned to the cockroach, where these organs are separable. By surgically joining a late larva, which was ready to undergo the pupal molt, with a younger larva containing a corpus allatum, he showed that the older larva was induced to undergo an additional molt. The presence of juvenile hormone therefore maintains the juvenile condition and prevents the formation of the pupa. In the control experiment similar pairs without an active corpus allatum both underwent a pupal molt.

All of these experiments were carried out before the chemical identity of these hormones had been established. They clearly show how good experimental technique and logical reasoning can resolve very complex interactions. Dietrich, however, welcomed the advances in biochemistry that made it possible to test his hypotheses about the action of these hormones. His last major work was a collaboration with Scheller and Karlson while on his Humboldt fellowship. They repeated some of the early experiments with imaginal discs to see whether Dietrich's hypothesis about the different levels of growth hormone in male and female flies could be substantiated with modern techniques. They transplanted leg discs into adult blowflies, with or without the addition of ring glands. After nine days the discs were measured and the initial observations confirmed. In males without ring glands the discs showed almost no growth whatsoever; but in males with ring glands and also in females without them, the discs had doubled in size. Using an antibody against growth hormone and a radioactive label, it was possible to show that the concentration of

hormone in the blood of adult females was seven times that in adult males. Dietrich was characteristically delighted to have his pioneering work so decisively confirmed.

In his retirement Dietrich returned to the interests of his early life. He was presented with an ultraviolet light trap with which he assembled a large collection of the moths of Virginia. Each specimen is a tribute to his "good hands" and his meticulous care in mounting them.

Dietrich's zest for life stayed with him to the end. He survived two heart attacks that would have finished off lesser mortals, returning to the full enjoyment of his science, his azalea garden, and his many friends and colleagues. The third attack was, however, too much even for his indomitable spirit. He died quietly at the University of Virginia Hospital on January 5, 1984, leaving a permanent vacancy in the lives of all who knew him. He is survived by his wife, Jean C. Bodenstein, and by a daughter from a previous marriage.

IN THE PREPARATION OF this memoir, I have relied extensively on a memorial address given by I. R. Konigsberg on January 17, 1984, at the University of Virginia and on conversations with Dietrich's family and colleagues.

HONORS AND DISTINCTIONS

DEGREE

Ph.D., 1953, University of Freiburg

PROFESSIONAL RECORD

1928–33 Assistant in Experimental Morphology, Kaiser Wilhelm Institute, Berlin

1933–34 Research Associate in Marine Biology, Rovigno, Italy

1934–41 Research Associate in Biology, Stanford University

1941–43 Guggenheim Fellow, Columbia University

1944 Assistant Entomologist, Connecticut Agricultural Experiment Station

1945–58 Insect Physiologist, Army Chemical Center, Maryland

1958–60 Embryologist, National Heart Institute, Gerontology Branch, Baltimore City Hospitals

1960–73 Lewis and Clark Professor of Biology and Chairman, Department of Biology, University of Virginia

1973–78 Lewis and Clark Professor of Biology, University of Virginia

1978–84 Professor Emeritus, University of Virginia

PROFESSIONAL SOCIETIES

American Society of Zoologists

Genetics Society of America

American Association of Anatomists

Society for the Study of Development and Growth

American Society of Naturalists

American Society for Cell Biology

American Institute of Biological Sciences

American Association for the Advancement of Science

HONORS

Sigma Xi

Phi Sigma

Honorary Member, Soc. Biol. do Rio Grande do Sul, Brazil, 1952

Member, National Academy of Sciences, 1958

Fellow, American Academy of Arts and Sciences, 1961

Vice-President, Zoology Section, American Association for the Advancement of Science, 1963

Fellow, Society of Fellows, University of Virginia, 1968

Alexander von Humboldt award for Senior U.S. Scientists (West Germany), 1977

POSTDOCTORAL STUDENTS

A. Abdel-Malek
A. R. de la Paz
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MASTER'S STUDENTS

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1962 Hope J. Nerangis
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1937 Beintransplantationen an Lepidopterenraupen. IV. Zur Analyse experimentell erzeugter Bein-Mehrfachbildungen. *Roux' Arch. Entw. Mech.* 136:745–85.

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Walter H. Brattain

WALTER HOUSER BRATTAIN

February 10, 1902–October 13, 1987

BY JOHN BARDEEN

MOST NOTED AS A coinventor of the transistor, Walter H. Brattain, an experimental physicist, spent the bulk of his professional career at the Bell Telephone Laboratories, first on West Street in New York City and later in Murray Hill, New Jersey. For the discovery of the transistor effect, he shared the 1956 Nobel Prize for physics with William B. Shockley and me. His main interests focused on the electrical properties of surfaces and interfaces, first on thermionic cathodes for applications to vacuum tubes and later on semiconductors for applications to diodes and transistors. Toward the end of his career, he became interested in biophysical problems in which electrolytic conduction plays an important role. Brattain was an initial member of the Bell Solid State Department, formed at the end of World War II to exploit the understanding of properties of solids made possible by quantum theory.

For some years before his retirement from Bell, Brattain taught on a part-time basis at his alma mater, Whitman College, and returned there to teach following his retirement. His research at Whitman was mainly on flow of ions through lipid bilayers in collaborations at Whitman and Battelle Northwest Laboratories.

Brattain loved the Northwest, where he had spent his

boyhood. He enjoyed the outdoor life, fishing and hunting, and, as he has said, the more rugged the conditions the better. In autobiographical notes written in 1975, he described his background and early education:

> I was born on February 10, 1902, in Amoy, China, where my father was a teacher in the Ting-Wen Institute for Chinese boys. My parents returned to their native state of Washington in 1903, and that part of my childhood that I can remember was spent in Washington, first in Spokane until I was nine years old and then on a homestead near Tonasket.
>
> My parents, Ross R. and Ottilie Houser Brattain, were both born in the territory of Washington of pioneer stock. My father was born near Farmington and my mother in Colville where she was baptized by Cushing Eells who founded Whitman College in honor of his fellow missionary Marcus Whitman.
>
> My father graduated from Whitman College in 1901. He was first a teacher in Amoy, China, then a stockbroker in Spokane, then a homesteader, cattle rancher and flour miller in Tonasket. His father, William Cullen Brattain, crossed the plains from Iowa to Springfield, Oregon, in 1852, as a boy 16 years old with his father Paul Brattain whose Quaker grandparents Robert Brattain and Mary (Millikan) Brattain were born in Randolph County, North Carolina, 1746 and 1747. My grandfather did some prospecting for gold but spent his life farming. My grandmother, Agnes McCalley Brattain, was born in the Canadian Province of New Brunswick and crossed the plains to Springfield, Oregon, from Chicago in 1859 when she was four years old with her father Andrew McCalley and mother, Christine (Millar) McCalley, both from Scotland.
>
> My mother went first to Whitman College and then to Mills College, California, where she graduated in 1901. Her father, John Houser, came to the West across the plains to San Francisco in 1854 from Stuttgart, Germany. Her mother Marie (Reiniger) Houser, also from Stuttgart, came over later. My grandfather finally settled in Pomeroy, Washington, where he had his own flour mill which still is standing today.
>
> From my ninth year on, the chief family occupations were farming, cattle ranching and flour milling. I rode after cattle in the mountains and carried a rifle when I was 14, and during school vacation I worked alongside my father from this age on.
>
> I first went to Roosevelt grade school in Spokane, then rode horseback five miles to Tonasket to go to grade school. I was promoted a grade

> because of my ability with arithmetic. High school: Queen Anne, Seattle, first year; Tonasket High School, second and third; Moran School, Bainbridge Island, fourth year. Stayed out of school and worked on our cattle ranch for one year between my junior and senior years of high school.

Brattain had a younger brother, R. Robert ("Bob"), also a physicist, who had an outstanding career with the Shell Oil Company, and a sister, Mari, both of whom survived him.

With financial help from an aunt, Walter followed his parents and attended Whitman College. He was stimulated to study physics by an outstanding teacher, Benjamin H. Brown, who had many students who went on to successful careers. His parents had also taken courses under Professor Brown. The physics majors in 1924 in addition to Brattain were Walker Bleakney (professor at Princeton), Vladimir Rojansky (professor at Union and Harvey Mudd colleges), and E. John Workman (president, New Mexico School of Mines), all of whom had distinguished careers. The members of this famous class were known as the "four horsemen of physics."

Bleakney tells an anecdote about Brattain's student days that illustrates the determination in response to a challenge that he showed in later years:

> Once he asked Professor Brown about a problem, the nature of which I can no longer recall, and Brown said we could not solve it because we had not yet studied the necessary tools. But Walter persisted, and Brown said to him, "If you solve it, I will excuse you from the final exam and give you a grade of 90." Of course Walter rose to the challenge and in a few days he did achieve the solution. Brown sheepishly admitted he had made a mistake but lived up to his promise. When the other three of us were slaving over the final exam Walter was gleefully chortling on the sideline. But we had the last laugh. When the final grades came out Walter's was the lowest in the class! You can be sure we did not let him forget that.

Following Whitman, Brattain attended the University of Oregon, where he received an M.S. in physics. He then

went on to the University of Minnesota to do a Ph.D. thesis under John T. Tate on "Efficiency of Excitation by Electron Impact and Anomalous Scattering in Mercury Vapor." He left in the fall of 1928 to take a position at the U.S. National Bureau of Standards, where he spent a year before joining Bell Labs.

When Brattain was a graduate student, the revolution in understanding at the atomic level brought about by quantum theory was under way in Europe. Few physicists in the United States were knowledgeable about quantum theory. In the late twenties, many young American scientists went to Europe to learn about the exciting developments taking place. Brattain was fortunate to be able to study quantum mechanics at Minnesota under John H. Van Vleck, then a young Harvard Ph.D. who was a pioneer in applications of quantum concepts to solids. His course in quantum theory must have been one of the first given in this country. Brattain often mentioned that he was fortunate to be in graduate school at the beginning of the period when scientists no longer *had* to go to Europe to study quantum physics. Another professor Brattain credits with being an important influence was Joseph Valasek, whose interest was in piezo-electricity.

At the Bureau of Standards, Brattain worked in the Radio Division, where he was mainly interested in the development of piezoelectric frequency standards. In 1929 he met Joseph A. Becker, a staff member of Bell Laboratories, at a meeting of the American Physical Society. Becker took a liking to him. It did not take much persuasion to get Brattain to transfer to Bell, the premier industrial laboratory in the country. For more than a decade, Brattain worked closely with Becker on a variety of problems on thermionic emission and on copper oxide rectifiers.

I first met Walter in 1934 through his brother, Bob, who

at that time was a fellow graduate student with me at Princeton. Walter and I had a common interest, since my Ph.D. thesis, under the direction of E. P. Wigner, was on the theory of the work function as derived from the quantum theory of metals. Brattain was then living alone in an apartment in Greenwich Village in New York City and working at the West Street laboratories of Bell.

In the spring of 1935, Brattain married Karen Gilmore. A native of Ohio, Karen received a Ph.D. in physical chemistry from the University of Minnesota. It proved to be a good match, her calm demeanor serving as an antidote to Walter's somewhat volatile temperament. They had one son, William, born in 1943. Unfortunately, Karen died prematurely of cancer in 1957, but lived long enough to accompany Walter to the Nobel ceremonies in Stockholm in December 1956.

In the depression days of the 1930s, Bell had a hiring freeze. No new staff members were added between 1930 and 1936. During much of this time, they worked short hours at reduced pay. Many took advantage of the extra free time to take courses at Columbia or to participate in informal study groups at Bell. There was much interest in learning more about the quantum theory of solids. One of the first hired after the freeze was lifted was William Shockley, a Ph.D. student of John Slater at MIT. He and Foster Nix organized a study group in solid state physics, in which Brattain was an active participant.

Interest in quantum mechanics at Bell was stimulated by the Nobel Prize-winning experiments of C. J. Davisson and L. H. Germer, which showed that electrons have wave properties, as had been suggested by de Broglie and by Schrödinger. Arnold Sommerfeld had given a simplified model of a metal in which it was assumed that the outer electrons become detached from the metal atoms to form a sea of electrons

obeying Fermi-Dirac statistics. The sea of electrons moves in a positive background formed from the metal ions.

Sommerfeld's theory provided a microscopic model from which one could calculate the temperature dependence of thermionic emission in terms of the work function, the energy required to take an electron from the uppermost occupied energy levels of the metal and place it outside one of the crystal faces of the metal. Although Bell Labs did not have any theoretical physicists working on quantum theory, Karl Darrow wrote a series of semipopular articles, many published in the *Bell System Technical Journal*, that helped make the quantum ideas more widely known. One of the first of these articles, published in 1929 in the first issue of *Reviews of Modern Physics*, described Sommerfeld's theory of metals. Sommerfeld made a world tour in 1931 in which he helped spread his ideas. One of his stops was at a summer school at the University of Michigan. Among those attending the lectures was Walter Brattain. He and Becker later did a series of experiments on thermionic emission that helped to give experimental verification of the Sommerfeld theory.

These experiments involved techniques that Brattain used later in experiments that led to the discovery of the transistor effect. Thermionic emissions and emission under the influence of an electric field (field emission) depend on the work function of the surface. Differences in work function between two surfaces are equal to the contact potential difference, the difference in potential outside the two surfaces when there is an electric contact between the two metals. Brattain and Becker found that the difference in work functions as determined from thermionic emission is equal to the difference in contact potentials.

Other experiments they did involved studies of effects of adsorbed atoms on the work function of tungsten. Atoms

that are adsorbed as positive ions tend to decrease the work function and increase the thermionic emission. Brattain and Becker studied the effect of adsorbed thorium as a function of surface coverage and found that the work function is a minimum when the surface is completely covered with one adsorbed layer.

The other major problem that Brattain and Becker worked on during prewar years was to try to understand rectification at the interface between copper and its oxide Cu_2O. The rectification was discovered by L. O. Grondahl and P. H. Geiger in 1927, who found that the ratio of the current between forward and reverse directions could be as large as 4,000. Copper oxide rectifiers were used in the telephone system primarily as a modulator in carrier systems. Making the rectifiers was largely an empirical art—copper was oxidized by heating in air, and an electrode (e.g., aquadag) was painted on the outer surface of the oxide. It was not until the late thirties that an adequate theory of rectification was given by Nevill Mott and Walter Schottky.

One of the last research projects undertaken by Brattain before the war was an investigation of the rate of oxidation of copper at different temperatures using a radioactive copper tracer. He was also a participant in some of the early work on silicon for application to cat's whisker detectors for radar. Since vacuum tubes did not operate at the high frequencies involved, resort was made to the point-contact semiconductor detectors of the early days of radio. The further development of silicon and germanium for radar during the war by the MIT Radiation Laboratory, the University of Pennsylvania, and Purdue University provided essential background for the discovery of the transistor.

Brattain and his family moved to New Jersey when Bell opened up the Murray Hill Laboratories. During the war many of the staff members were involved with military

problems unrelated to their peacetime research interests. Brattain spent two years working on airborne magnetometers for detection of submarines.

In the summer of 1945, as the war was drawing to a close, plans were formulated by Mervin Kelly (then executive vice-president) and others for an interdisciplinary solid state department. The hope was to apply the understanding of solids at the atomic level made possible by quantum theory to develop new materials for components in the telephone system.

The Solid State Division, with Shockley and Stanley O. Morgan as coheads, was an interdisciplinary one consisting of chemists and physicists as well as engineers familiar with the problems of telephone communications. Also included were theorists who had begun to develop an understanding of the properties of solids from the atomic point of view. While most members were long-time Bell employees, most of the theorists were recruited from outside. I joined the division in the fall of 1945, after World War II came to a close.

The initial semiconductor group, one of several in the division, consisted of Walter Brattain and Gerald Pearson, experimental physicists; Robert Gibney, a physical chemist; and Hilbert Moore, an electrical engineer. Initially, because of wartime crowding, I shared an office with Brattain and Pearson and became interested in semiconductors.

A long-term goal was to make an amplifying device with a semiconductor to replace the vacuum tube. The result was the transistor, essentially an electrical valve with three electrodes such that a voltage applied to one can be used to control the current flowing between the other two. There had been considerable development of germanium and silicon as diodes for use as detectors for radar during the war. Being elements, they were easier to purify and their

properties easier to understand than those of compound semiconductors. We decided to concentrate our efforts on these materials, then available in the form of reasonably pure polycrystalline ingots. Shockley had suggested what is now known as a thin-film field-effect transistor, but initial attempts to make such a device had failed.

None of us had worked on semiconductors during the war, so we were eager to learn about the developments that had taken place. With new materials to study and new concepts to help understanding, it was a very exciting time to be involved in semiconductor research. We followed the Bell Labs tradition of forming study groups to learn about what had been accomplished.

Those involved with the research were good friends socially as well as scientific collaborators. The Brattains were active members of a duplicate bridge club. Walter and I were partners in bridge games arranged at Bell Labs. We were also enthusiastic golfers and enjoyed many a match together. When we lived in different places we would try to get in a round of golf when we got together at scientific conferences in this country and abroad.

In an interview given in later years, Brattain recalls:

> I cannot overemphasize the rapport of this group. We would meet together to discuss important steps almost on the moment of an afternoon. We would discuss things freely, one person's remarks suggesting an idea to another. We went to the heart of many things during the existence of this group and always when we got to the place where something had to be done, experimental or theoretical, there was never any question as to who was the appropriate man in the group to do it.

The close collaboration between experimentalists and theorists extended through all stages of the research, from the conception of the experiment to the analysis of the results. Most papers were authored jointly by an experi

mentalist and a theorist. Brattain concentrated on surface and interface phenomena, while Pearson concentrated on current flow in the bulk of a semiconductor.

Early in our studies we learned about the theories of rectification at a contact between a metal and a semiconductor that had been developed by Mott and Schottky. The more complete theories of Schottky and his co-worker E. Spenke, done early in the war, were not available in the West until after the war.

Current in a semiconductor can be carried in two different ways, by conduction electrons, extra electrons that do not fit into the valence bonds, and by holes, places where electrons are missing from the valence bonds. The first is called n-type, from the negative charge of an electron, and the second, p-type. Silicon and germanium are ambipolar; they can be either n-type or p-type, depending on the nature of the impurities present. By thermal excitation or by light (photoconductivity), electrons can be excited from the valence bonds, giving equal numbers of conduction electrons and holes to add to the conductivity. What we discovered in the course of research is that the conductivity can likewise be enhanced by current flow from an appropriate contact, the principle of the bipolar transistor. Both the field-effect and bipolar principles are used in present-day transistors and integrated circuits.

The experiments that led to the discovery of the bipolar principle and to the invention of the point-contact transistor were done in December 1947. The point-contact transistor consists of two metal (cat's whisker) contacts on the upper surface of a small block of germanium that had a large-area, low-resistance contact on the base. Each point contact by itself forms a rectifying contact relative to the base. One, the emitter, is biased in the direction of easy flow; the other, the collector, is biased to a higher voltage

in the reverse direction. A signal applied between emitter and base appears in amplified form between collector and base.

Within less than a month, Shockley suggested the junction transistor in which the entire action takes place within the bulk of a semiconductor rather than at metal-semiconductor contacts. All present-day bipolar transistors are of the junction type. Both field-effect and junction transistors put much greater demands on control of material properties than point-contact transistors. It took almost two years before the first junction transistors were made in the laboratory and several more years before they were put in production. It took more than a decade for materials technology to reach the stage required for field-effect transistors.

An essential step was the growth of large, highly pure single crystals, initiated by Gordon Teal in 1948. It was also necessary to learn how to introduce foreign elements to control the conductivity (n-or p-type) in minute regions of the crystal. The introduction of integrated circuits did not occur until the early 1960s, nearly fifteen years after the initial invention.

The first transistor to be put in production by Bell Labs was the point-contact transistor in a form designed in large part by William G. Pfann in 1948. It was produced and used in the Bell system for approximately a decade. Another early form was the alloy transistor in which alloy junctions are made on opposite faces of a thin slab of germanium.

While the point-contact transistor was relatively easy to make, its operation was difficult to understand in detail. Brattain undertook a series of experiments to help understand how minority carriers (holes in n-type germanium) flow from the emitter point and how minority carriers in

troduced flow to and add to the collector current. The collector point was formed by passing a large current through it so as to alter the characteristics of the germanium in the vicinity in an unknown way. Immediately adjacent to the surface of the germanium there is a thin layer (inversion layer) of p-type conductivity with the charge of the added holes balanced by electrons in bound states at the surface of the germanium. It was learned soon that holes introduced at the emitter could flow in and add to the conductivity of the n-type bulk, as in a junction transistor. These experiments led to a better understanding of how the current-voltage characteristics of the point-contact transistor depend on the parameters involved.

Also important was learning how an inversion layer of opposite conducting type is formed at the free surface of a semiconductor with the charges balanced by electrons in surface states. I collaborated with Brattain in this study for a couple of years after I left Bell to go to the University of Illinois in 1951, and he later worked with C. G. B. Garrett and with P. J. Boddy. He showed that the inversion layer could be varied considerably by surface ambient. This work was important for junction devices where one wants to passivate the surface so as to avoid a harmful inversion layer.

Some of the experiments with Boddy were to study effects of electrolytes adjacent to a semiconductor surface. Brattain became interested in blood clotting when his son, Bill, underwent heart surgery. This led to an interest in electrochemical processes in living matter. Several papers were written in collaboration with Boddy and P. N. Sawyer on vascular prostheses and related problems. He continued these interests after moving to Whitman College, where he collaborated with David R. Frasco of the Chemistry Department at Whitman and with Donald R. Kalkwarf of Battelle Institute at Richmond, Washington. Some of this

work involved flow of potassium ions through lipid bylayers, in which he saw some analogies with flow of electrons through metal-semiconductor rectifying junctions.

Brattain was for many years an active participant in international meetings conducted by the Commission on Semiconductors of the International Union of Pure and Applied Physics. He served on the commission for several years and was the chairman in 1966. As long as he was able, he was a regular attendant at meetings of the National Academy of Sciences. He took great pleasure in attending meetings of Nobel laureates and students at Lindau, West Germany, organized by Count Bernadotte, a descendant of the Swedish royal family. Through his membership on the Defense Science Board, he became a good friend of Senator Henry ("Scoop") Jackson.

Brattain's years at Whitman College were certainly among the happiest of his life. He enjoyed teaching undergraduates. A favorite course was "Physics for Nonscience Majors," one taught earlier by Professor Brown. His marriage to Emma Jane (Kirsch) Miller in May 1958 was a happy one. They both enjoyed travel and music. He played golf regularly at the local country club, and he resumed fishing in rugged surroundings.

A victim of Alzheimer's disease, he spent the last four and a half years of his life at a nursing home in Seattle, where he died on October 13, 1987. Pearson, who had a distinguished career at Stanford following his retirement from Bell, survived Brattain by less than two weeks.

Brattain was elected to the National Academy of Sciences in 1959. In addition to the Nobel Prize, he received the Stuart Ballantine Medal and the John Scott Medal. He was an honorary member of the Swedish Royal Society and of the Institute of Electrical and Electronic Engineers and a fellow of the American Physical Society and of the Ameri

can Academy of Arts and Sciences. He was a recipient of six honorary degrees, including those from his three alma maters. He was elected to the National Inventors Hall of Fame and posthumously to the Information Processing Hall of Fame of INFOMART.

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L E Dickson

LEONARD EUGENE DICKSON

January 22, 1874–January 17, 1954

BY A. A. ALBERT

LEONARD EUGENE DICKSON was born in Independence, Iowa on January 22, 1874. He was a brilliant undergraduate at the University of Texas, receiving his B.S. degree as valedictorian of his class in 1893. He was a chemist with the Texas Biological Survey from 1892–1893. He served as a teaching fellow at the University of Texas, receiving the M.A. degree in 1894. He held a fellowship at the University of Chicago from 1894 to 1896 and was awarded its first Ph.D. in mathematics in 1896. He spent the year 1896–1897 in Leipzig and Paris, was instructor in mathematics at the University of California 1897–1899, associate professor at Texas 1899–1900, assistant professor at Chicago 1900–1907, associate professor 1907–1910, and professor in 1910. He was appointed to the Eliakim Hastings Moore Distinguished Professorship in 1928, and became professor emeritus in 1939. He served as visiting professor at the University of California in 1914, 1918, and 1922.

Professor Dickson was awarded the $1,000 A.A.A.S. Prize

Reprinted from the *Bulletin of the American Mathematical Society*, vol. 61, no. 4, July 1955.

in 1924 for his work on the arithmetics of algebras. He was awarded the Cole Prize of the American Mathematical Society in 1928 for his book *Albegren und Ihre Zahlentheorie*. He served as editor of the Monthly 1902–1908, and the Transactions from 1911 to 1916, and he was president of the American Mathematical Society from 1916–1918. He was elected to membership in the National Academy of Sciences in 1913 and was a member of the American Philosophical Society, the American Academy of Arts and Sciences, and the London Mathematical Society. He was also a foreign member of the Academy of the Institute of France, and an honorary member of the Czechoslovakian Union of Mathematics and Physics. He was awarded the honorary Sc.D. degree by Harvard in 1936 and Princeton in 1941.

Professor Dickson died in Texas on January 17, 1954.

Dickson was one of our most prolific mathematicians. His bibliography (prepared by Mr. Richard Block, a student at the University of Chicago) contains 285 titles. Of these eighteen are books, one a joint book with Miller and Blichfeldt. One of the books is his major three-volume *History of the theory of numbers* which would be a life's work by itself for a more ordinary man.

Dickson was an inspiring teacher. He supervised the doctorate dissertations of at least fifty-five Chicago Ph.D's. He helped his students to get started in research after the Ph.D. and his books had a world-wide influence in stimulating research.

Attention should be called to the attached bibliography. It includes Dickson's books with titles listed in capitals. It does not include Dickson's portion of the report of the Committee on Algebraic Number Theory, nor does it include Dickson's monograph on ruler and compass con

structions which appeared in *Monographs on Modern Mathematics*.

We now pass on to a brief discussion of Dickson's research.

1. *Linear groups*. Dickson's first major research effort was a study of finite linear groups. All but seven of his first forty-three papers were on that subject and this portion of his work led to his famous first book [**44**]. The linear groups which had been investigated by Galois, Jordan, and Serret were all groups over the fields of p elements. Dickson generalized their results to linear groups over an arbitrary finite field. He obtained many new systems of simple groups, and he closed his book with a still valuable summary of the known systems of simple groups.

   Dickson's work on linear groups continued until 1908 and he wrote about forty-four additional papers on the subject. In these later papers he studied the isomorphism of certain simple groups and questions about the existence of certain types of subgroups. He also derived a number of theorems on infinite linear groups.
2. *Finite fields and Chevalley's Theorem*. In [**44**] Dickson gave the first extensive exposition of the theory of finite fields. He applied his deep knowledge of that subject not only to linear groups but to other problems which we shall discuss later. He studied irreducibility questions over a finite field in [*113*], the Galois theory in [*114*], and forms whose values are squares in [*139*]. His knowledge of the role of the non-null form was shown in [*155*]. In [*142*] Dickson made the following statement: "For a finite field it seems to be true that every form of degree m in $m + 1$ variables vanishes for values not all zero in the field." This result was first proved by C. Chevalley in his paper *Démonstration*

d'une hypothèse de M. Artin, Hamb. Abh, vol. 11 [1935) pp. 73-75. At least the conjecture should have been attributed to Dickson who actually proved the theorem for $m = 2, 3$.

3. *Invariants*. Several of Dickson's early papers were concerned with the problems of the algebraic geometry of his time. For example, see [**4**], [**48**], [**54**]. This work led naturally to his study of algebraic invariants and his interest in finite fields to modular invariants. He wrote a basic paper on the latter subject in [**141**], and many other papers on the subject. In these papers he devoted a great deal of space to the details of a number of special cases. His book, [**172**], on the classical theory of algebraic invariants, was published in 1914, the year after the appearance of his colloquium lectures. His amazing productivity is attested to by the fact that he also published his book, [**173**], on linear algebras in 1914.
4. *Algebras*. Dickson played a major role in research on linear algebras. He began with a study of finite division algebras in [**105**], [**115**], [**116**], and [**117**]. In these papers he determined all three and four-dimensional (non-associative) division algebras over a field of characteristic not two, a set of algebras of dimension six, and a method for constructing algebras of dimension mk with a subfield of the dimension m. In [**126**] he related the theory of ternary cubic forms to the theory of three-dimensional division algebras. His last paper on non-associative algebras, [**268**], appeared in 1937 and contained basic results on algebras of degree two.

Reference has already been made to Dickson's first book on linear algebras. In that text he gave a proof of his result that a real Cayley division algebra is actually a division algebra. He presented the Cartan theory of linear associative algebras rather than the Wedderburn theory but

stated the results of the latter theory in his closing chapter without proofs. The present value of this book is enhanced by numerous bibliographical references.

Dickson defined cyclic algebras in a Bulletin abstract of vol. 12 (1905–1906). His paper, [**160**], on the subject did not appear until 1912 where he presented a study of algebras of dimension 16.

Dickson's work on the arithmetics of algebras first appeared in [**204**]. His major work on the subject of arithmetics was presented in [**213**] where he also gave an exposition of the Wedderburn theory. See also [**237**] and [**238**].

The text [**231**] is a German version of [**213**]. However, the new version also contains the results on crossed product algebras which had been published in [**223**], and contains many other items of importance.

5. *Theory of numbers*. Dickson always said that mathematics is the queen of the sciences, and that the theory of numbers is the queen of mathematics. He also stated that he had always wished to work in the theory of numbers and that he wrote his monumental three-volume *History of the theory of numbers* so that he could know all of the work which had been done in the subject. His first paper, [**28**], contained a generalization of the elementary Fermat theorem which arose in connection with finite field theory. He was interested in the existence of perfect numbers and wrote [**166**], and [**167**] on the related topic of abundant numbers. His interest in Fermat's last theorem appears in [**190**], [**136**], [**137**], [**138**], and [**144**]. During 1926–1930 he spent most of his energy on research in the arithmetic theory of quadratic forms, in particular on universal forms.

   Dickson's interest in additive number theory began in 1927 with [**229**]. He wrote many papers on the subject during the remainder of his life. The analytic results of

Vinogradov gave Dickson the hope of proving the so-called ideal Waring theorem. This he did in a long series of papers. His final result is an almost complete verification of the conjecture made by J. A. Euler in 1772. That conjecture stated that every positive integer is a sum of J nth powers where we write $3^n = 2^n q + r$, $J = 2^n > r > 0$, and $J = 2^n + q - 2$ Dickson showed that if $n > 6$ this value is correct unless $q + r + 3 > 2^n$. It is still not known whether or not this last inequality is possible but if it does occur the number $g(n)$ of such nth powers required to represent all integers if $J + f$, or $J + f - 1$, according as $fq + f + q = 2^n$ or $fq + f + q > 2^n$ where f is the greatest integer in $(4/3)^n$.

6. *Miscellaneous*. We close by mentioning Dickson's interest in the theory of matrices which is best illustrated by his text, *Modern algebraic theories*. His geometric work in [**179**], [**181**], [**182**], [**183**], [**184**], [**185**], and [**186**] must also be mentioned, as well as his interesting monograph [**219**] on differential equations from the Lie group standpoint.

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Sterling Emerson

STERLING HOWARD EMERSON

October 29, 1900–May 2, 1988

BY JOHN R. S. FINCHAM

STERLING EMERSON was born in Lincoln, Nebraska, the son of R. A. Emerson, the main pioneer of corn genetics. In 1914 his father was appointed head of the Department of Plant Breeding at Cornell, and the family moved to Ithaca. Sterling himself graduated from Cornell University in 1922. The same year saw his first scientific publication, a long paper in *Genetics* under the names of R. A. and S. H. Emerson on the genetic relationships of andromonoecious mutants in maize. Following graduation he undertook postgraduate work in the field of plant cytology in the University of Michigan under the supervision of Bartlett. He obtained a fellowship to work between 1925 and 1926 in Scandinavia, first in Lund and then Copenhagen. This visit was not as fruitful as it should have been because he had the misfortune to contract tuberculosis and had to go to a Swiss clinic to recover. But he was able to spend at least some time in the laboratory of O. Winge, later to become the main pioneer of yeast genetics.

Sterling's postgraduate work at Michigan was on the genus *Oenothera*, and his earlier papers contributed to the understanding of the *Oenothera* system of balanced segmental interchanges and its genetic consequences. This line of

work gave scope for his talent for solving logical puzzles as well as to his skill as a microscopitst. In 1928, the same year he obtained his Ph.D., he was appointed to an assistant professorship in genetics under T. H. Morgan at the California Institute of Technology, where except for two sabbatical years and a secondment, he remained throughout his career.

During his long period at Caltech, Sterling's interests extended into several distinct areas of genetics. He continued work on *Oenothera* until 1941 and, around 1937, started an investigation of the self-incompatibility system of *Oenothera organensis*, a plant that existed in the wild only in a few locations in the Organ Mountains of New Mexico. He worked out the genetic basis of the pollen-style reaction and showed that it conformed to the *Nicotiana* one locus–multiple allele gametophytic system. He developed the method for observing the growth of individual pollen tubes down styles and was thus able to distinguish the 50 percent pollen function characteristic of crosses between plants with one allele in common. By skillful grafting experiments he was able to show that pollen rejection was an autonomous function of the style. The culmination of this work was a population survey that led to a fairly complete description of the number, distribution, and spread of the self-incompatibility alleles within the small population. This was one of the classic analyses of a plant outbreeding system—a system that unhappily now exists only in the archives, since *O. organensis* is probably extinct in its natural habitat.

After G. W. Beadle moved to Caltech from Stanford to take up the chairmanship of the Biology Division, Sterling Emerson joined enthusiastically in the new work on the biochemical genetics of *Neurospora crassa*. He was attracted

by the elegance of the genetic system as well as by the prospect of finding out more about how genes work. In particular, he became fascinated with the complexity of metabolic pathways and the explanation that they gave of how genes could interact. He always loved making elegant diagrams, and the *Cold Spring Harbor Symposium* volume of 1950 contained one of his more ambitious efforts, presenting a synoptic view of competitive reactions and antagonisms in amino acid biosynthesis as revealed by studies of mutants. His own contribution in this area had a characteristically genetical angle. In collaboration with Marko Zalokar, he had discovered a mutant that was not only resistant to sulfanilamide but even required the drug for growth. He found that certain revertants were heterocaryons with a proportion of the nuclei carrying a mutation that blocked the biosynthesis of *p*-aminobenzoic acid. The explanation was that the original mutant required sulfanilamide in order to counteract *p*-aminobenzoate acid, to which it was hypersensitive, and that the new mutation suppressed the phenotype simply by reducing *p*-aminobenzoate to a nontoxic level. This suggested a new and delightfully simple explanation for the classical genetical phenomenon of heterosis, which had hitherto been explained as due to complementary action, either of different genes or of different alleles of the same gene (overdominance). The *Neurospora* example demonstrated the possibility of heterosis resulting from combinations of alleles that were not complementary in action but merely additive, the average of the activities of two different alleles being just what the situation demanded.

Another of Sterling Emerson's interests in *Neurospora* can be seen as an extension of his early interest in cytology. For several years, in collaboration with his wife, Mary, he

experimented with ways of obtaining viable protoplasts from mycelium. Their best success was with a morphological osmotically sensitive mutant (*os*), which, through a process of selective breeding, eventually yielded a stable plasmodial strain called "slime." This strain, totally unrecognizable as the derivative of a filamentous fungus, turned out to carry two other mutations as well as *os*. It has never been easy to recover anew from crosses but it can nevertheless be maintained vegetatively and has been used in a number of laboratories for a variety of experimental purposes. Sterling himself used it to study mitotic nuclear division under the microscope *in vivo*. Meiosis and the immediate postmeiotic mitotic divisions in the *Neurospora ascus* had been described and photographed by Jesse Singleton and Barbara McClintock, but vegetative nuclear division had always been very obscure. The live plasmodium, however, could be prepared for microscopy as a very thin layer and, with the oil immersion lens and phase contrast, nuclei could then be seen dividing with unprecedented clarity. Chromosomes appeared only as dots appearing fleetingly on the spindle, but the behavior of the nucleolus and the nuclear membrane was particularly clear. Sterling took his microscope kit and slime culture to the first Neurospora Information Conference, held in La Jolla in 1958, and demonstrated the system to an admiring audience. Unfortunately, a proper photographic record was difficult to obtain, and no publication ever emerged from this highly original work.

Undoubtedly, Sterling Emerson's most constant scientific interest throughout his career was in genetic recombination. This interest was fostered by his early work on the *Oenothera* balanced translocation system and it took a new turn in 1933–35 with his collaboration with G. W. Beadle (then in his first Caltech phase) on the analysis of cross-

over relationships in *Drosophila* using attached-X chromosomes. Emerson and Beadle were able to show that each cross-over between chromosomes at the first division of meiosis could, with equal likelihood, involve either one of the two chromatids into which each chromosome was divided. The particular advantage of attached-X chromosomes was that they permitted the recovery together of two of the four X chromosomes emerging from a single oocyte meiosis. This half-tetrad analysis, however, was still second-best to whole tetrad analysis, which was achievable in *Neurospora* and other Ascomycete fungi.

Fungal tetrad analysis fascinated Emerson for most of the rest of his life. His contributions in the area were both theoretical and practical. He became the author of a number of definitive reviews of the use of fungi for formal genetics, with special emphasis on the analysis of crossing-over. He was naturally extremely interested in the early reports by C. C. and G. Lindegren on gene conversion in yeast meiotic tetrads, and was initially very skeptical about them. His thorough understanding of the possibilities of aberrant chromosome behavior enabled him to suggest a number of alternative explanations that, in his view, had to be rigorously ruled out before one could admit exceptions to Mendel's First Law. However, as the further evidence accumulated during the 1950s, not only from yeast but from *Neurospora* and other fungi as well, Emerson incorporated gene conversion into his own thinking about recombination mechanisms. Taking up the heteroduplex/mismatch correction model of Robin Holliday, he was the first to attempt an algebraic formulation that would predict the frequencies of different patterns of conversion and crossing-over in terms of heteroduplex formation and correction parameters. He was probably the first to point out

that, on the Holliday model, the correction frequencies on the two participating chromatids need not necessarily be the same, and his analysis of the available data indicated that in general they were not the same. Unfortunately, this left the formula with as many parameters as observable quantities, but it nevertheless served as a useful framework for thinking for a decade or more.

When approaching retirement, Sterling Emerson decided that it was time for him to make his own contribution to the fungal recombination data. He decided on the Ascomycete species *Ascobolus immersus*, which had the great advantage of providing spore color markers that could be scored visually in the meiotic tetrad (actually an octad, with a further mitotic division affording the opportunity of detecting postmeiotic segregation). A French strain of the species had already been extensively investigated in the University of Paris at Orsay, but Sterling isolated his own strain from the environs of Pasadena. The Pasadena strain turned out to have markedly higher conversion frequencies than the French, but with considerable variation in this respect. In collaboration with Clare Yu-Sun and Bernard Lamb (a visitor from England), some of this variation was identified as due to differences in *cis*-acting conversion-promoting sequences, closely linked to the segregating markers. These studies, now carried considerably further by Lamb, are still highly relevant to the whole question of how meiotic recombination is initiated, and foreshadowed current research that has just recently penetrated to the molecular level.

Throughout his research career, Sterling Emerson did what interested him, and his interests were, by modern standards, exceptionally broad. He combined the skills of the analytical geneticist and chromosome cytologist with a

naturalist's knowledge of plants and animals. He acquired an excellent knowledge of biochemistry and, for a time, became quite deeply involved in immunology. His excursion into the latter area resulted in only one publication, and that one fell by the wayside. It is nevertheless worth recalling as an example of his bold thinking. In the early 1940s biochemical genetics was getting under way, and, while there was no clear idea about the nature of the gene or of how it replicated itself, there was speculation about template models for gene replication and expression. Emerson, following an idea of A. H. Sturtevant, thought it possible that a protein might mirror the unique surface shape of the gene that specified it, and hence that an antibody formed against the protein might also interfere with the replication of the gene. Accordingly, he tried out rabbit anti-*Neurospora* antibodies as mutagens on *Neurospora*. Some mutants were indeed recovered, and they seemed to be sufficiently numerous to be significant. Unfortunately, the evidence never got any stronger. Had nature been ordered differently, that work might have won a Nobel Prize.

Emerson spent only two extended periods away from Caltech after his appointment in 1928. In 1951-52 he spent most of the academic year in Cambridge, England, where he took over the supervision of the graduate student of his friend (a colleague on *Oenothera* expeditions) David Catcheside, who was himself on sabbatical. He is still remembered by those students for his sympathetic help and friendship. He moved in summer 1952 to the Pasteur Institute, Paris, where he worked for a few months in the laboratory of Boris Ephrussi. His other absence from Caltech was a more radical break. Between August 1955 and September 1957 he served a geneticist in the biology branch of the Atomic Energy Commission in Washington. In this capacity he spent much

time assessing applications for funding, and he had to exercise judgment over virtually the whole range of the genetics and molecular biology of the day. Few could have been better prepared for the job or more conscientious about mastering the detail involved. I believe that he enjoyed the broad scientific interest of the post—probably more than he did the Washington environment.

Sterling Emerson lived a simple and unpretentious life. His relaxations were often linked to his work, to which he was always devoted. He liked algebraic problems and playing with numbers. He loved making pictures and diagrams. Some of his early representations of hypothetical DNA structures in recombinations conveyed real insights. A striking painting of a canyon in the Organ Mountains, one of the *Oenothera organensis* sites, hung over his fireplace. His artistic urge also found an outlet in making ornaments, some of them marvels of craftsmanship, out of wood obtained from his garden. He was always ready to relax socially, and liked drinking beer; a very extensive and varied collection of beer; cans filled part of his garage. In personality he was dignified, humorous, and considerate. In later years he took great pleasure in his grandchildren. As his son-in-law, I found him an unfailingly helpful and sympathetic friend.

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Charlotte Friend

CHARLOTTE FRIEND

March 11, 1921–January 13, 1987

BY LEILA DIAMOND

In 1956, at a meeting of the American Association for Cancer Research (A.A.C.R.) in Atlantic City, Charlotte Friend reported on the isolation of a virus that produced a fatal leukemia when inoculated into adult mice.[1] This was a time when the concept of viruses causing cancer was still viewed with extreme skepticism and the presentation of such data by an attractive young woman not long out of graduate school was met with disbelief and derision.[2] The audience's arguments against her findings were essentially the same as those Peyton Rous had heard in the early 1900's when he described a chicken tumor that was inducible by a transmissible agent. They argued, on the one hand, that the agent isolated was not a virus because it induced a malignant disease and, on the other, that the disease could not be a malignancy because it was virus-induced. However, the rapid confirmation of Friend's findings by the highly respected pathologist Jacob Furth led to a change in attitudes, and the scientific community soon realized that a virus which rapidly induces a malignant disease in adult mice provides an excellent model in which to study both viral oncology and the pathogenesis of neoplasia. Friend's virus became the primary system for research on viral

leukemogenesis and today it is acknowledged that no one who works on tumor viruses fails to be touched by the contributions of Charlotte Friend.[3]

Charlotte Friend was born in 1921 in New York City on Houston Street in lower Manhattan to parents who had immigrated from Russia as young adults. Her mother had been trained as a pharmacist but gave up any professional ambitions to raise a family. Friend's father, a successful businessman, died when she was three years old and her mother moved the family of four children to the Bronx in order to be near, and have the support of, other relatives. The substantial inheritance left by Friend's father was dissipated in the financial disaster of 1929, and the fact that the family had to accept "home relief" from the city in order to survive had a lasting effect on Friend. She always admired her mother for having been able to keep the family together during this period and for never letting the children doubt that they would complete their education.

While growing up, Friend took advantage of all the opportunities and wonders that New York offered. She became a very knowledgeable and avid devotee of all its cultural activities and successfully competed for admission to Hunter College High School, a part of the city's excellent, tuition-free education system for gifted students. After finishing high school, she attended Hunter College at night while working in a physician's office during the day.

Upon graduating in 1943, Friend enlisted in the United States Navy and was assigned to Midshipmen's School at Smith College from which she graduated as an Ensign in April 1944. She was soon promoted to Lieutenant j.g. and appointed second-in-command of the hematology laboratory at the naval hospital in Shoemaker, California. From early childhood she had thought about becoming a scien

tist, but this was her first real experience working in a laboratory and it convinced her that this was what she wanted to do with her life.

When the war ended, Friend had the financial support of the G.I. Bill of Rights to continue her schooling. She considered attending medical school but chose instead to enroll as a graduate student in the Department of Microbiology at Yale University. She already appreciated the importance of the advice and help of outstanding scientists for her research, and frequently came to New York City on weekends to consult with the eminent immunologists Elvin Kabat and Michael Heidelberger at Columbia. She received a Ph.D. from Yale in 1950 with a thesis on the effects of sodium salicylate (aspirin) on antigen-antibody reactions.

Friend was hired by Cornelius P. Rhoads, the director of what was then the new Sloan-Kettering Institute for Cancer Research, to work in the virus laboratory of Alice E. Moore. Rhoads was a very dynamic and enthusiastic individual who was extremely supportive of the members of his Institute, and he and Friend developed a strong mutual respect and admiration. At Sloan-Kettering, Friend met Cecily Cannan Selby, a recent Ph.D. from the Massachusetts Institute of Technology who was interested in cell structure. This was in the early days of electron microscopy and, when Selby found a microscope in the institute that was not being used, she and Friend decided to examine the fine structure of the cells of the Ehrlich ascites carcinoma, a transplantable tumor of mice that at the time was a commonly used model for cancer research. They unexpectedly observed cytoplasmic "particles of constant diameter in close array" that were similar to those seen in thin-sections of virus-infected cells,[4] and Friend then sought to determine whether these particles were biologically active.

She inoculated cell-free extracts of the ascites cells into newborn mice, following a procedure for transmission of a murine leukemia virus that Ludwik Gross had introduced a few years earlier.[5] The mice remained healthy over a fourteen-month period of observation but, when sacrificed and autopsied, six mice were found to have enlarged livers and spleens. Friend may have been surprised or dismayed to see what looked to be leukemia when she had inoculated an extract from carcinoma cells, but she was smart enough and curious enough to pursue the observation. Because newborn mice were unavailable, she injected cell suspensions from the enlarged spleens into *adult* mice and, within a few months, several had palpable spleens. By the third passage of either cell suspensions or filtrates of cell extracts, a high percentage of mice were developing leukemia with a latent period of only two to three weeks. The disease Friend was seeing was very different from the lymphoma induced by Gross's virus: it was characterized by erythroblastosis and profound anemia; it was transmissible in adult noninbred mice; and the latent period before the first symptoms appeared was very short, the latter fact being powerful evidence that the transmissible agent was directly involved in the induction of the leukemia.

It is interesting to note that the cytoplasmic particles originally seen by Selby and Friend[4] were very different in size and structure from what was eventually proven to be the etiologic agent of Friend leukemia. In very elegant electron microscope studies done with Etienne deHarven, Friend found that her agent was a type-C virus[6] or what later became classified, on the basis of genomic structure, as a retrovirus (reverse transcriptase-containing RNA virus). Friend and deHarven were among the first to describe the life cycle of these doughnut-shaped viruses that "budded," a

term suggested by their technician, from the cell surface of the leukemic cells.

Charlotte Friend never forgot the reception she and her new murine leukemia virus received at the 1956 A.A.C.R. meeting. Those who were present remember the dignity and courage with which she responded to the barrage of questions. She herself described the proceedings beautifully and in detail in her Presidential Address to the same society twenty years later.[2] She said that, despite warnings that serious objections would be raised, "by no stretch of the imagination could the violent storm of controversy that erupted after (her) presentation have been anticipated." She wondered why her friend who chaired the session did not use Rous's plea to "keep open minds" as an opportunity to cool the heated atmosphere and finally bring the session to a close. It is a mark of her character that she did not reveal the identity of that chairman in her Presidential Address and that they always remained the dearest of friends.

She was proud to have "emerge(d) unbowed—if a little bloodied"[2] from that experience and later was able to joke that those who persisted in their heretical beliefs about tumor viruses were being accused of having "either holes in their heads or holes in their filters." However, it may be that because of that rather traumatic experience, she never did develop into a strong, confident speaker. Throughout her career, whenever she had to give a talk, she was always very nervous and on edge in anticipation, and spent a great deal of time and effort writing out exactly what it was she wanted to say.

As co-editor of the *Journal of Experimental Medicine* and a strong supporter, Rous worked with Friend on the writing and editing of the first full-length publication describing the new virus.[7] He made many suggestions regarding docu

mentation, details and presentation, for he believed that she was "in a position to settle all doubts as concerns a virus causing leukemia in mice" if she presented what she had discovered "in a convincing way." The resulting publication provided the information the scientific community needed to accept the virus and to recognize its potential as an ideal model system with which to work.

The neoplastic nature of the disease induced was subsequently confirmed by the demonstration that transplantable solid tumors could be obtained with leukemic tissues from virus-infected mice. The leukemia was originally described as being not clearly granulocytic or monocytic, and it required extensive experimentation by Friend[8] and others to demonstrate that the primary target for malignant transformation was, in fact, an erythroid precursor. Development of the disease is now thought to involve at least two events: an early stimulation of erythropoiesis followed by a clonal event that results in transplantable, immortal erythroleukemia cells.

Following the discovery of the Gross and Friend viruses, a number of other RNA viruses that induced leukemia in mice and other species were isolated. What had originally been disbelief now turned to accolades and Friend began to be honored for her work. In 1962 she received the Alfred P. Sloan Award for Cancer Research and elected to use the money to travel around the world, spending three-month periods in research institutes in France, Israel and Australia working with such scientists as Andre Lwoff, Leo Sachs and Donald Metcalf. She has written that the trip was one of the most important experiences of her life, a major reason being that she fulfilled her long-cherished dream of working at the Pasteur Institute.

Despite all the work that has been done on Friend Leu

kemia Virus (FLV), we still understand very little about the molecular mechanisms by which it replicates and transforms. We do know that these mechanisms are extremely complex, so it is perhaps not surprising that over the years there have been disagreements and controversies regarding various aspects of the virus and the disease induced. The original virus isolate produced a leukemia associated with anemia but with its distribution to other laboratories and passage from host to host, virus strains that produced polycythemia rather than anemia appeared. These strains caused formation of macroscopic foci of primitive erythroid cells on the spleen surface which appeared prior to the hepatosplenomegaly and could be quantitated. These were foci shown to be due to the presence in preparations of polycythemia-inducing strains of a defective spleen focus-forming virus (SFFV) that was competent for cell transformation but not for virus replication. Some investigators reported that only the polycythemic strains of Friend Virus induced leukemia in adult mice and that the anemic strain was effective only in neonates. It was suggested that, contrary to what Friend had originally reported, more than one virus was required for the pathogenesis of the leukemia (see reviews by Friend and Pogo [9] and Ostertag *et al.*[10]).

Friend always resisted that idea. Perhaps the cool reception she and the virus received originally had sensitized her to what she may have considered criticism of that early work and her powers of observation. She maintained that in her hands, even after twenty years of continuous passage, the original anemic strain of FLV (FLV-A, what she referred to as the wild-type or prototype virus), its host range, latent period and age dependence, and the syndrome that that virus induced were no different from what she had first reported. She insisted that FLV-A did *not* con

tain a defective, spleen focus-forming component[11] and that it was different from the virus strains others may have worked with subsequently. Her friend Frank Lilly once "tried to convince her that she should be proud to have discovered not just one but in fact two viruses that were totally unique in the mouse leukemia virus world. But she would have nothing to do with that idea."[12] And, indeed, others have shown that molecularly cloned FLV-A, with no SFFV component, induces an anemic form of an erythroproliferative disease in newborn mice which resembles the early stages of the disease induced by wild-type virus.[13] However, no one has yet explained the mechanism by which the profound anemia induced by such virus in either newborns or adults progresses to leukemia.

Most virologists have taken the position that the Friend Virus is a complex composed of a defective SFFV that depends on replication-competent FLV for its own replication, and that both viruses are required for production of fatal leukemia in adult mice. Friend always acknowledged that during *in vivo* passage, virus variants might have arisen through recombination with cellular elements or endogenous viruses and was not surprised that an agent such as SFFV was found in some virus stocks. However, she wanted to understand what might have happened in other laboratories, to discuss the various possibilities with other investigators, and to analyze the passage histories of the various virus strains. Those such as Arthur Axelrad and Frank Lilly who had the patience for such discussions remained good, lifelong friends. Others who wanted to get on with it and not be overly concerned with what might have happened to the virus years ago lost touch with her and, unfortunately, perhaps lost respect for her and her accomplishments as well.

Rhoads, the director of Sloan-Kettering, had died in 1959 and the subsequent administration was much more structured than his had been. Friend did not have the warm relationship with the new director that she had had with Rhoads and did not think she was getting the recognition she deserved. Thus, she was receptive when approached about joining the faculty of the new medical school being organized at Mt. Sinai Hospital in New York. In 1966 she accepted a position there as professor and director of the Center for Experimental Cell Biology. She requested, and received, an appointment that carried no teaching responsibilities. She wanted to be free to do what she did best and most enjoyed—research. The new laboratory was rather modest in size and amenities, and a somewhat isolated basic science entity. In her new position, Friend was responsible for raising essentially all the money needed for staff, supplies, equipment and support services. She became tightly locked into the federal grant system for the major requirements of the center which she headed, and in her later years, this became a tremendous burden that interfered with her enjoyment of doing research.

It was at Mt. Sinai that Friend made another seminal scientific contribution when she showed that cancer cells can be induced to differentiate by an exogenous agent and, thereby, lose their ability to multiply. She had observed earlier that the cells of the solid tumors produced by transplantation of leukemic tissue from Friend Virus-inoculated mice showed no recognizable erythroid elements, but that the erythroid nature of the cells could be demonstrated under certain conditions. For example, Friend and Cecilia Patuleia were able to establish permanent cell lines in culture from the tumor cells and to show that, even when cloned, these cultures consisted of undifferentiated

cells and a small percentage of cells at various stages of erythroid maturation.[14, 15] Their observation that these malignant cells were, in fact, capable of undergoing maturation was met with disbelief by some colleagues, even though the evidence should have been incontrovertible from their slides and photographs. "How can tumor cells that have been in culture for 6 months give rise to erythroblasts?" they asked. "There must be a contaminant." But again in the face of skepticism, Friend persisted, knowing that her cell system provided a superb "model for the study of leukemia as a disease resulting from a maturation defect."[16] She began to explore the possibility that the differentiation block in the leukemic cells could be removed.

This led her to the discovery that Friend erythroleukemia cells (FELC) in culture could be further stimulated to differentiate along the erythroid pathway by the addition of the solvent dimethyl sulfoxide (DMSO) to the medium.[17] I had been using DMSO as a solvent for hydrophobic compounds in cell cultures. I remember her phoning one day to ask about the concentration to use for an experiment she wanted to try. A few days later she called back, bursting with excitement about her cells being "pinkies, all pink, all pink." Her associate, Bill Scher, also remembers her running up and down the hall holding up the tube with the pellet of pink cells for all to see. She went on to show that, with some highly inducible erythroleukemia cell lines, the percentage of benzidine-positive (hemoglobin-producing) cells could be increased to over 85 percent, from a baseline of 1 percent, after four-five days in medium containing DMSO. Friend had clearly and dramatically demonstrated that expression of the malignant phenotype could be reversed experimentally.

Her observation was quickly reproduced and confirmed

in other laboratories and it soon became apparent that the morphological and biochemical alterations that followed induction of differentiation were similar to those occurring in normal erythropoiesis. Friend cells became a widely used model for studying control of hemoglobin synthesis as well as for analyzing the overall regulation of gene expression in cell proliferation and differentiation.

This new discovery resulted in another exciting period of recognition for Friend. She was elected to the Hunter College Hall of Fame and received the Yale Science and Engineering Association Award. She was honored with the Dameshek Medal, the Prix Griffuel, and the Papanicolaou Award. In 1976 she was accorded the ultimate recognition by her peers, election to the National Academy of Sciences.

In the late 1960s a young Italian pathologist, Giovanni Rossi, spent several years working in Friend's laboratory. They became close scientific colleagues and devoted friends, and in 1977 when she had the opportunity to spend a sabbatical year abroad, she went to Rome where Rossi had settled. She had a wonderful time working at the Italian National Research Council Laboratory where Rita Levi-Montalcini was director. The two women had great respect for each other and when Friend left Rome, Professor Levi-Montalcini gave her an engraving entitled "The Spiral of Archimedes," done by her twin sister, Paola.

Charlotte Friend first learned that she had lymphoma on her sixtieth birthday in 1981. She told very few people and was adamant that others not know. She did not want those who might be reviewing her grants or manuscripts to be influenced one way or the other. Despite undergoing extensive, debilitating therapy, she continued to spend time in the laboratory, to write, to attend meetings and discuss work with other people, to send out manuscripts and grant

proposals and, when necessary, to argue with editors, reviewers and administrators. She did everything she could to keep her laboratory afloat, always with the hope that it would be perpetuated if she were no longer around. However, it had always been important to her that she stay on top of everything going on in her laboratory. She had preferred to do things herself and not to turn projects over to others. And so, she had never built up an active group of young investigators studying problems of interest to her. In the end, there was no one to maintain the center and continue her work.

One of Charlotte Friend's last public appearances was at Brandeis University, where she received an honorary Doctor of Science degree in May 1986. She was very proud to have been selected for this honor and left her hospital bed to make the trip to Waltham, Massachusetts. She participated in the commencement procession in a wheelchair and, despite a broiling sun, stayed for the entire lengthy ceremony. She died eight months later on January 13, 1987.

During the height of her career, Charlotte Friend was perhaps one of the most well-known and well-liked cell biologists and cancer scientists. She was a very warm and social person, albeit somewhat shy. She had a good sense of humor and a rather charming way of interacting with people. She was extremely generous when it came to distributing her virus (FLV) and her cells (FELC) to those who wanted to work with them, and she would give those investigators all the guidance and assistance they needed for their work. Many remember with pleasure visiting her laboratory, going to lunch, and talking about what they were doing or would do with the wonderful tools she had provided. And if they were from out of town, she always made sure they were properly looked after. Her apartment

in the Stuyvesant Town complex on East 14th Street came to be known as "The Friend Hotel," for friends and colleagues from near and far were welcome to stay there when visiting New York—and they frequently did, some for weeks at a time.

Charlotte Friend had a genuine concern for people and took an interest in their personal lives, their families, and their problems. She was always available to listen and frequently spent evenings in the laboratory or at home doing just that. She had a dedicated staff that would have followed her to the ends of the earth. Several, such as the pathologist Jamil Haddad and the technician J. Gilbert Holland, worked with her for over thirty years.

She served as the matriarch and leader of what was a very close-knit family. She was deeply devoted to her mother, who lived with her until her death in 1961, and to her siblings and nieces and nephews. It was she to whom the immediate and extended family turned for advice and help. She particularly enjoyed advising and assisting others with their medical problems and frequently boasted of "practicing medicine without a license," perhaps reflecting regrets about not having gone to medical school.

She was a renaissance woman who loved and knew intimately the theater, dance, music, opera, and literature. No matter how tired she was or how difficult the day had been, she would jump at the chance to see a new show if someone came up with a pair of tickets at the last minute. She enjoyed traveling, seeing new sights, and meeting different people. Wherever she went, there were two things she had to do: buy stamps for her brother Morris who was a collector, and get a memento of the trip for herself, usually a unique piece of jewelry or interesting work of art. But no matter where she had been and how much she had en

joyed the trip, it was "The City" that thrilled her most and to which she returned with joy. She loved the view of the Manhattan skyline from her apartment and could never bring herself to move to a place that might be more convenient or more luxurious.

Charlotte Friend was a woman of strong convictions and a fighter, with no compunctions about defending her ideas and the causes in which she believed. For example, she wrote letters to newspaper editors and spoke up without fear in support of blacklisted academics and dissidents, even during the McCarthy and Nixon eras when doing so could jeopardize one's grants and career. She believed whole-heartedly in the State of Israel and was an outspoken defender of its policies. She was a fervent supporter of the women's movement and frequently, without fanfare, went out of her way to ensure that women were well-represented on symposium programs and advisory and review committees. She served as a role model for many women starting their careers at a time when there were not many such models.

In the 1970s, when the demands on the relatively few senior women scientists were enormous, she worked extremely hard as president of the American Association for Cancer Research, the New York Academy of Sciences, and the Harvey Society, the first woman so honored in the long history of that society. During this same period, she also served as a member of the Advisory Committee for the Virus Cancer Program of the National Institutes of Health and a member of the Board of Scientific Counselors of the Division of Cancer Cause and Prevention of the National Cancer Institute. Over the years, she served on a number of other advisory committees and on the editorial boards of several cancer and hematology journals. She took all

these responsibilities very seriously and was noted for her incisive reviews and for her thoughtful and astute comments in committee meetings.

Charlotte Friend used to say that she started an industry, and it was true. In the two decades following the initial isolation of FLV, perhaps a third of those doing cancer research spent some time working on one or the other of the model systems she had provided. Even today, many aspects of the Friend virus complex (FLV/SFFV) remain unique among tumor viruses so that it continues to be an important, widely utilized model system (reviewed in ref. 10). For example, it acts as an acute transforming virus but does not contain an oncogene. It is immuno-suppressive and, therefore, a model for human immuno-deficiency virus (HIV). It stimulates abnormal erythroid hyperplasia by binding of virus (SFFV) glycoprotein to a growth factor (erythropoietin) receptor, a novel mechanism that may explain how other viruses can interfere with normal growth regulation.

Friend paved the way for a great many other avenues of research. She was the first to show, using her virus, that animals could be immunized with retrovirus preparations and protected against development of the disease.[18] Her experiments indicating that such protection is possible are frequently cited by those now trying to develop a vaccine against HIV. Leukemic cells induced by Friend Virus have been used in the first demonstration that a virus-induced malignancy requires for its expression the alteration or deletion of an "anticancer" or suppressor gene. Friend was one of the first to show that cells maintained in culture can actually undergo the successive steps leading to differentiation to a specific cell type. Her system was the forerunner for the establishment of other cell culture models to study

cytodifferentiation and the development of diverse lineages. Her demonstration of inducible differentiation of leukemic cells by DMSO has served as the inspiration, as well as the prototype, for evaluating the potential therapeutic effects of differentiation-inducing agents in human cancer.

Charlotte Friend was in the tradition of many women scientists who have made contributions to botany, astronomy and microbiology. She, too, was a naturalist, an observer and, in many ways, a loner. She enjoyed the aesthetics of biology, the overview rather than the molecular. She was an inventive, instinctive scientist who had fun doing science. She did not want a large laboratory, only her devoted staff and enough funding to be able "to play," as she called it. She did, however, seek recognition and fame, and this she achieved. Her ideas and discoveries have had, and will continue to have, a major impact on our thinking about the causes, prevention and cure of cancer.

CHARLOTTE FRIEND'S complete bibliography can be found in "Viral Oncogenesis and Cell Differentiation: The Contributions of Charlotte Friend," L. Diamond and S. R. Wolman, editors, *Annals of the New York Academy of Sciences*, vol. 567, pp. 5–13, 1989. This memoir was submitted October 9, 1990.

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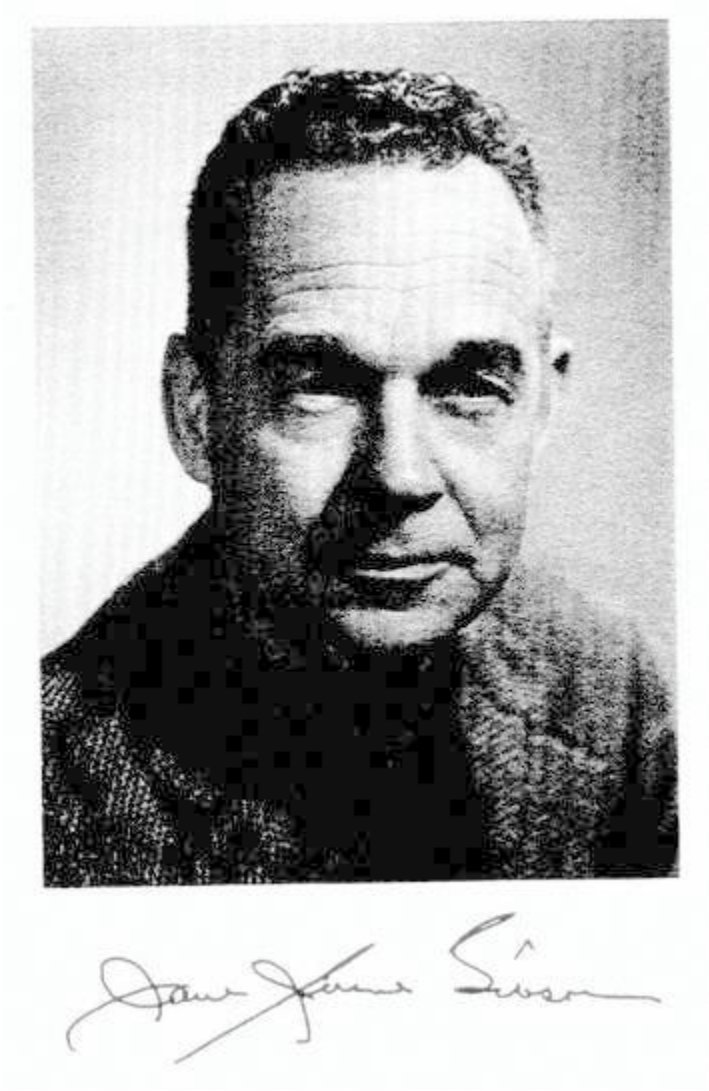

JAMES JEROME GIBSON

January 27, 1904–December 11, 1979

BY JULIAN HOCHBERG

As I WRITE THIS, ten years have passed since James Jerome Gibson died, and his influence on perceptual psychology and related disciplines is as strong or stronger than ever. His analyses and arguments still continue to change the ways in which problems of perception of space and the environment, whether by humans or by computational models, are approached; books continue to be written about him (the latest was by Reed in 1988[1]); and the solutions that he posed to problems he set, some of them in 1950, are still (or only now) being tested experimentally. To the degree that the Gibsonian revolution succeeds, it will replace all previous assumptions about how we must analyze information about the world that is offered to the sensory system by the environment; accordingly, it will replace our assumptions about what, in the course of perceptual development, must be learned and about how it is learned.

James Gibson was a man of great personal charm who was deeply and cheerfully engaged by ideas and who wrote and debated clearly, forcefully, and tirelessly. He was born on January 27, 1904, in McConnelsville, a small town in southeastern Ohio. His father, Thomas Gibson, was a surveyor for the railroads whose job took his family through

the Dakotas and Wisconsin until they settled in Wilmette, a suburb of Chicago. Gibson's mother, Gertrude, taught country school until her marriage to Thomas. James had two younger brothers, Thomas and William; the latter also became an academic, prominent in the field of American literature.

In 1921 Gibson enrolled in Northwestern University, transferring after his freshman year to Princeton. There he majored in philosophy, and, after a course in experimental psychology taken in his senior year with Herbert S. Langfeld, newly come from Harvard, he stayed on as a graduate student in psychology. From Edwin Bissell Holt, who came to Princeton in 1926, Gibson learned an enthusiasm for radical empiricism—the doctrine that the characteristics of our behavior (and indeed of our nervous systems themselves) reflect the ways in which the regularities of the world write upon the blank tablet of the organism that learns to behave appropriately in that world. Holt's was a sophisticated and elegant motor theory of consciousness in which the forms and contents of cognition are themselves aspects of bodily responses to the world.

Undertaken in this context, Gibson's doctoral dissertation, in 1938, refuted a recent thesis by Wulf (1922)[2] reporting that subjects' memories of visual forms changed spontaneously toward simpler and more compactly organized configurations or Gestalten. Wulf was a student with Kurt Koffka, in Berlin, and Wulf's results were important because they seemed to reveal the operation of innate factors in form perception. The changes Gibson found, however, were more attributable to perceptual habit than to the organizational determinants of Gestalt theory, results consistent with Holt's empiricist framework.

This approach, based on a thoroughgoing empiricist behaviorism, was soon subject to a challenge that it did not

in the end survive. Gibson had received his B.S., M.A., and Ph.D. degrees in psychology from Princeton in 1925, 1926, and 1928, respectively, and went to teach psychology at Smith College in 1928, where he found Kurt Koffka, brought there in 1927. Koffka, with Max Wertheimer and Wolfgang Köhler, was one of the three most influential of the Gestalt psychologists. Koffka was then undertaking his general treatise, vigorously and explicitly opposed to the widely accepted theoretical framework epitomized by Helmholtz; to Koffka, the central question was "why do things look as they do?" and the answer lay in the organization imposed by the "field forces" of the central nervous system. Nearby, at Northampton, was another prominent Gestalt psychologist, Fritz Heider, who had introduced the terms *distal* and *proximal stimulation* to refer, respectively, to the physical properties of objects and to those of the stimulus patterns they provide to the sensory organs. To both Gestalt theorists, the organization necessary to provide for object perception could come only from the viewer and from the proximal input. Gibson was exposed to these eloquent anti-empiricist, antipositivist, antibehaviorists from 1928 until 1941, and, although he never accepted Gestalt theory and was eventually to take a position diametrically opposed to Heider's on the source of perceived object properties, his own approach as it evolved over the years was at least as close in several important respects to Koffka's as it was to Holt's.

In 1932 Gibson married Eleanor Jack, who was herself to become a major figure in the psychology of perceptual learning and development, an occasional collaborator, and a constant colleague. They had two children, James Jerome, Jr., in 1940, and Jean, in 1943. Gibson pursued a number of research topics during this period, most notable being

his studies on what has since become known as the "Gibson effect," in which the free inspection of a curved or tilted line results in an adaptation and after effect, so that a subsequently viewed line appears oppositely curved or tilted (1933, 1937, 1–3); the work pitting visual against proprioceptive indications of the gravitational vertical (1938, 2), initiated with O. H. Mower during a semester sabbatical that Gibson spent at Yale in 1936; and an analysis of automobile driving as visually guided behavior (with L. E. Crooks, 1938, 1).

The United States entered World War II in 1941, and in 1942 Gibson entered the Army Air Force. He was stationed briefly in Washington, where a program of psychological research was being organized, then in Fort Worth at the Flying Training Command for one and one-half years, and then at the Santa Anna Army Air Base for another two and one-half years. He went from captain in 1942 to lieutenant colonel in 1946. He was director of the Motion Picture Research Unit in the Aviation Psychology Program, the motion picture unit that was to develop visual aptitude tests for the screening of pilot applicants, and that toward the end of the war was given the immensely important question of how a training film conveys the information that film is best able to present. These matters and research on aircraft identification (done with R. M. Gagne) were published in 1947 and 1948 and were of central importance in the evolution of Gibson's approach.

With the end of the war, the Gibsons returned briefly to Smith College, moving to Cornell University in 1949, to which I came as a fresh Ph.D. the same year. Jimmy and Jackie, as they are known to virtually every psychologist in this country and abroad, remained on the Cornell faculty until their retirements. Jimmy taught there from 1949 un

til 1972; because of the antinepotism rules then in force at Cornell, Jackie did not get a proper appointment until 1966, made possible by Jimmy having then received a National Institute of Mental Health Senior Career Development Award. During a leave from Smith, Gibson had been a research associate at Yale in 1935–36; during his tenure at Cornell, he was visiting professor at Berkeley (1954–55), a senior research scholar at Oxford, on a Fulbright (1955–56), a member at the Institute for Advanced Studies at Princeton in 1958–59, and at the Center for Behavioral Science in Palo Alto in 1964–65.

Gibson was never happier than when immersed in debate about ideas, which he almost always was. We were colleagues at Cornell from 1949 to 1964 and remained friends until 1979; we were engaged in continuous argument until 1964 and more intermittently during subsequent summers. Gibson had several goals, some of them essentially philosophical, and, intensely self-critical, he kept his approach under constant review and revision. Above all and throughout, however, he wanted a scientific discipline that would start to answer, as directly and immediately as possible, the perceptual question of why things look as they do—not simple patches of color in the laboratory, or line figures in demonstrations, but the things and layouts of the world in which we move and act, walk and drive and fly.

In 1950 Gibson published *The Perception of the Visual World*. I believe that book was the most important work on perception since that of Helmholtz's volume three of *Physiological Optics*, approximately a century earlier. It was a comprehensive approach to the perception of surfaces, things, and movement through the environment, primarily the outcome of his observations and thoughts about the visual

task involved in flying and landing aircraft. It had been foreshadowed by two shorter publications in 1947 and 1948, and Gibson's much earlier interest in the perceptual guidance of automobile driving.

The book was clearly intended to initiate a revolutionary movement. I believe that intention has, just as clearly, been successful. Some forty years after its publication, the book is still widely cited and controversial, the direct source of substantial current experimental research, and the starting point for more extreme departures from what had been the established way of thinking about perception. In order to explain Gibson's remarkable contribution, I will have to set his proposal against the background structure of presumptions and goals that were shared by the various disciplines—sensory physiology, psychology, philosophy, art theory, and now artificial intelligence—that are concerned with perception.

Gibson proposed a global psychophysics. Most prior psychophysical research dealt with the effects of local aspects of stimulation: for example, measuring how much two adjacent patches of light, at different wavelengths, must differ in energy if a viewer is to detect their difference, a line of inquiry shaped early by Helmholtz and Maxwell. The major purpose of psychophysical research was to analyze the fundamental human sensory capacities, or sensations, and their corresponding neural bases, such as the three cone types successfully predicted by the Young-Helmholtz theory. The two-dimensional receptor mosaic of cones and rods, and the sensations they provide when stimulated, were long thought to provide the sensory units by which all that we see is first analyzed and the sufficient units from which all visual perception derives.

By themselves such sensory units cannot even remotely

explain how objects and their distal attributes (such as size, shape, and reflectance) and the spatial layouts of the world (surfaces, distances, and movements) are perceived. An object's distance from the eye could not, of course, be conveyed by the light at any local receptor. In a tradition that goes back to fifteenth-century treatises in philosophy and art, perceived distance was therefore explained in terms of characteristic patternings, now called "depth cues," that modulate the light that the tridimensional normal world provides the eye's bidimensional sensory mosaic. Other properties were held to be perceptible only by routes that are even less direct: for example, although retinal image sizes and luminances vary, respectively, with object sizes and reflectances, and the latter two are essentially invariant physical attributes, retinal size also depends on the objects' distances, retinal luminance varies with illumination, and these viewing conditions are highly variable. The seeing conditions must therefore be discounted in some way: perceived size, it seemed clear, must rest on the depth cues as well as on retinal size; perceived reflectance must rest on illumination cues as well as retinal luminance.

In general, it seemed most parsimonious, and closest to what was believed true of neurophysiology when Gibson's first book was being written, that no new prewired nervous structures, beyond the receptor level of rods and cones, were needed to account for these abilities: the depth cues were supposedly learned from experience with the world, through mechanisms of associative learning that provided for learning in general; and object properties, like size, are perceived only after these depth cues are used to interpret the retinal image by means of nonsensory processes, like Helmholtz's still popular speculations about "unconscious inference," that perform what amount to problem-solving

computations to arrive at the objects' properties. Only then are such properties apparent to the viewer.

This simple armature underlay most thinking about man, mind, and behavior through mid-century. It was entertained in one form or another by most psychologists, physiologists, philosophers, political scientists, and theorists about art and meaning, and indeed by most thinkers within the Western tradition.

To Gibson, writing in 1950, sensations were irrelevant, the products of artificial and impoverished laboratory situations; the depth cues were merely artists' tools; and inference was an unnecessary postulate, when discussing normal perception, because the properties of objects and surfaces in the world—their slants, distances along the ground, sizes, etc.—are all perceived directly and are not inferred from the patterned mosaic of sensations through the use of higher mental processes. That is, the effective patterns to which our visual systems respond are themselves higher-order variables of stimulation. They are mathematically definable aspects of the patterning in the light to the eye, extended in space and time, that are in correspondence with those distal physical properties in the environment that are important for us to know. Gibson's book offered plausible candidates for such higher-order variables; for example, the gradient of texture-density along the ground specifies the slant of the surface to the line of sight, it specifies the distance of the object standing on the ground, and it specifies the object's size as well, with no inference needed for any of these—hence, the need for, and possibility of, a global psychophysics of objects and events.

There were, of course, precedents for some aspects of these assertions. There had been several earlier proposals of mechanisms that would provide for direct response to

such distal properties of objects as their reflectance and binocularly registered distance (notably by Ewald Hering and Ernst Mach). Gestalt psychologists had argued compellingly that patterns or configurations much larger than the individual receptor were treated as units by the nervous system. Few psychologists believed that the depth cues were used in processes of conscious and deliberate inference—it should be noted that the information provided by the patterning of stimulation was usually called "cues" in American usage, connoting a rapid and unthinking response, as opposed to "clues," which implies higher mental processes. And numerous but isolated psychophysical studies of object properties, often for the purposes of applied psychology, had been performed. But none of these precedents approached Gibson's bold and consistent programmatic account of visual perception.

Gibson's 1950 book and several papers that he and his colleagues published soon after on the optical information that is potentially available to moving perceivers (optic flow patterns and gradients of motion perspective) are only now receiving experimental vindication (e.g., Warren et al., 1989)[3] but appear in myriad computational models of human and machine perception. The global psychophysics that Gibson then championed is now a firmly established field of inquiry.

Gibson received the Howard Crosby Warren Medal from the Society of Experimental Psychologists in 1952, was elected president of the Eastern Psychological Association in 1959, received the Distinguished Scientific Contribution Award of the American Psychological Association in 1961, and was elected to the National Academy of Sciences in 1967. These honors were given primarily in recognition of the global psychophysics and the revolutionary approach Gibson

initiated in 1950. But Gibson's initiatives did not stop there.

In the traditional view that Gibson had opposed in 1950, depth cues are learned much as words in languages are learned, by association with other patterns of sensation—reaching, touching, etc. For the viewer, patterns of stimulation have been "enriched" through associations accrued in the course of perceptual learning. In 1955 James and Eleanor Gibson argued that, because the information needed to account for perception is already present in the light at the eye, perceptual learning consists not of such associative additions but of a process of differentiation, a sharpening of the aspects of the changing flux of light to which the identification occurs. Psychophysics (including Gibson's global psychophysics of 1950) stayed close to physics not only for its measures of stimulation but also for the response properties it studied. Both a behaviorist background and a concern with practical problems would incline one to turn first, as Gibson did, to the perception of surfaces' distances and orientations. But if perceptual learning is driven by aspects of the world that the organism needs to distinguish, such psychophysics seems arbitrary.

Gibson himself soon left psychophysics behind. From his emphasis on a moving perceiver came *The Senses Considered as Perceptual Systems* (1966). The momentary retinal image, he now argued, is the wrong level of analysis, just as much so as the momentary static patterns of pressures on the fingers are the wrong level of analysis when the fingers explore an object (1962, 2): it is the invariants in the transforming patterns of stimulation of the sensory system that specify the relevant properties of the environment, not the successions of momentary arrays of light or pressure. Our sensory systems have evolved for active retrieval

of information about the environment; they are active systems sensitive to the invariant under transformation, not arrays of passive receptors merely responding to stimulation.

Perceptual information becomes available, therefore, through the interaction of the perceiver and the environment. Gibson's book, *The Ecological Approach to Visual Perception* (1979), suggests some of the information that viewers might obtain from interaction with their normal environments, including places and the paths between them along which movement can occur, sit-on-ableness, etc. Again, this approach was not without precedents: in particular, "cognitive maps" and "plans" are featured by other attempts to frame theories about informed purposive behavior. But Gibson's affordances are not mental structures. They are optical structures of information about the environment, structures that exist objectively but that must be defined in terms of the needs and potential behaviors of the individual animal.

Although Gibson's last books seem very different from the first in their goals and in the kinds of analyses they advocate, a consistent thread unites all three: a vigorous and direct attempt to frame an approach that operates at a level appropriate to the perceptual domain of interest. As to the first book, the virtually unbridgeable conceptual gap between retinal points of classical psychophysics, and the surfaces and distances of the real world, was finessed by the global psychophysics Gibson proposed in 1950. By the time of his second book, in 1966, the hopeless complexity of obtaining a stable world from moving eyes and head was simplified at a stroke, in Gibson's concepts of the optic array, optical proprioception, and sensory systems. The uncharted wilderness faced in getting from either of these

to a system capable of describing and studying how we navigate successfully in a world of objects and vistas was given a taxonomy and the potential for explanatory principles by 1979, as laid out in Gibson's third book. Although it is too soon to assess whether its consequences for research and theory will emerge as a coherent program and how inclusive its influence will be, the last two books have already had a remarkable impact—a society and journal dedicated to the study of event perception; an honorary degree bestowed on Gibson by Uppsala University in 1976; a flood of articles in the name of ecological psychology (and many in opposition as well); and at least four books since 1966 devoted to Gibson's views, not counting a Festschrift (MacLeod and Pick, 1974),[4] Michaels and Carello (1981),[5] Brickhard and Richie (1983),[6] Lombardo (1987),[7] and Reed (1988).[8]

Many of those who have taken up this approach, as well as those who oppose it, are philosophers, but there is also a solid core of experimental psychologists who are committed to it, and interest in the approach has shown no sign of flagging over the decade. James Gibson died on December 11, 1979. There seems to be a good chance that he will have left us with not only one but two successive and successful restructurings of perceptual psychology and its related disciplines.

THE BIOGRAPHICAL FACTS I have used come largely from Gibson's brief autobiography in *A History of Psychology in Autobiography*, vol. 5, eds. E. G. Boring and G. Lindzey (New York: Appleton-Century-Crofts, 1967); from Reed's biography; and from personal recollection.

NOTES

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ALBERT BAIRD HASTINGS

November 20, 1895–September 24, 1987

BY HALVOR N. CHRISTENSEN

A. BAIRD HASTINGS was born in Dayton, Kentucky. When he was six years old, his family moved to Indianapolis, where he lived until he entered college. His father died of tuberculosis while Baird was in his second year of high school. No special interest in science was uncovered in Baird's study at Shortridge High School, where he liked Greek and Latin and aspired to become a classics teacher.

Upon the death of his father, Baird prepared to leave high school to help support his family. The teacher who had profoundly inspired him, Ella Marthens, urged otherwise, however, and she helped to arrange an assistantship in biology for him, given only that he should take a course in zoology. Subsequently, mathematics through solid geometry and physics, but no chemistry, supplemented that obliged biology study. Baird remarked how frequently career success is attributed to the influence of a superior high school teacher rather than to college teachers.

Baird told of a notable evening in his senior year at the home of Marthens and a teaching colleague, attended by Baird's favorite crony and classmate, Alan Boyd, at which a group decision was to be reached about Baird's college attendance. Baird insisted that it be at Michigan, where two cousins, James and Charles Baird, had attended and

had, among other distinctions, played and coached football, respectively. Under the assumption that Baird must quickly learn to make a living to help his family, the group decided that he must register for engineering, specifically chemical engineering, a subject unfamiliar enough to avoid any perceived limitation in Baird's abilities. His first encounter with the required general chemistry did not yet divert him from engineering. Odd jobs of various sorts helped family finances, and the second marriage of his mother made further borrowing unnecessary. But in the summer after his second year, Baird liked very much more the physical chemistry course under Dr. Floyd Bartell that he had included in his program. At the end of this course, Bartell asked Baird if he would like to serve as his assistant in the physical chemistry course. The assistant had to prepare the apparatus and solutions needed and also help with instructing the students in the laboratory. The offer required, however, that Baird become a major in chemistry, a shift only slowly and reluctantly accepted by the engineering school, indeed by default, and, as it happened, with an unjust discount of Baird's prior marks.

Among the provisions of this post was a 20 × 20 foot laboratory belonging to Bartell, which adjoined his own lab. As Baird remarked, "That was in the fall of 1915, and from that moment until 1966, I've had a laboratory of my own. This provision has determined everything I've done since."[1]

DOCTORAL STUDY SUPPORT BY THE PUBLIC HEALTH SERVICE

At the end of 1916, Baird had taken all the courses, undergraduate and graduate, offered in physical chemistry, so Bartell asked him what he would do upon graduation. Baird supposed he would get a job, not difficult

then. Bartell instead urged him to go on with graduate work. Baird expostulated: "You mean work for a Ph.D.? That's ridiculous! You have to be a Van't Hoff to do that." Bartell responded, "I've watched you, Baird, and I find you work hard and are resourceful." In his life story Baird commented that he accepted this evaluation as a watchword. "I tried ever after to be resourceful in the lab." He was able to enter graduate school in January 1917, even though he was not scheduled to receive his baccalaureate degree until June. Since there was no more physical chemistry to take, he elected to begin graduate courses with some advanced quantitative chemistry, minerology, and bacteriology under F. G. Novy.

Because Bartell was interested in membranes and osmosis, Baird proceeded with preliminary research on the permeability of collodian membranes. Thus, membrane studies became the beginning of his lifelong interest in the distribution of solutes in heterogeneous systems. Another event, the appearance of Bayliss's *Principles of General Physiology* , a remarkable book in its first edition, stimulated Baird's interest toward biological subjects, just when his interest had been narrowing to physical chemistry.

But in April 1917 the United States entered World War I, with strong consequences for the direction of Baird's progress. As most of his friends left to go to camp, the underweight Baird began a desperate campaign to enlist. By the fall of 1917, his persistent efforts to be accepted into the military having failed, Baird returned to the University of Michigan. His Ph.D. study in physical chemistry was, however, deferred (permanently, as it happened) because Bartell himself was about to take a commission in the Chemical Warfare Service. Therefore, Baird helped Bartell in his course in the fall of 1917 as an instructor. A

chance encounter with Hector Britton, who held a summer post as a chemist with the Public Health Service working on a multidisciplinary study of fatigue, led Baird to take Britton's place (on being reassured that this was indeed war work) when the latter returned to his Ph.D. study in organic chemistry. Officialdom was tending at this point to conclude that fatigue as encountered in munitions plants was due to acidosis. Baird's experience in setting up and using the Hildebrand bubbling hydrogen electrode persuaded Joseph W. Schereschewsky of the Public Health Service that Baird probably knew as much as anyone about the measurement of the state of neutrality.

Baird liked to say that his whole life story was essentially determined when he accepted the post as sanitary chemist with the Public Health Service on November 1, 1917, to study these matters. "Everything else followed logically," he said. Although he had no study in physiological science up to that point, Baird quickly perceived that physiological neutrality was not a simple subject. His initial assignment was to measure the pH of morning and evening urine of workers engaged in various operations at the Ford Motor Company. By mid-December, even though Kjeldahls and measures of free and conjugated phenols and of three kinds of sulfur had been added, he was ready to write a letter to Frederic S. Lee, head of physiology at Columbia University, who was directly in charge of Baird's activity, to the effect that the program was no way to study fatigue, that it was a waste of federal money and of his time, and that, unless the government was prepared to study fatigue in animals under controlled laboratory conditions, he did not want to proceed. From that letter came orders for him to proceed to the Department of Physiology at Columbia and to carry out research on the chemistry of fatigue. The logical progression continued.

Baird wrote that nobody ever had better tutorial training than he received in that department. Beyond Frederic Lee, he acknowledged how much he came to owe Professors F. H. Pike, Russell Burton-Opitz, and Ernest L. Scott. When the war ended, Lee invited Baird to continue for a Ph.D. degree. Baird pointed out that he had expected to return to Ann Arbor to go on with his studies for a Ph.D. degree in physical chemistry with Bartell. The decisive circumstance was that Baird and Margaret Hastings were married May 31, 1918, and that on May 14, 1919, their son Alan Baird Hastings was born. The ongoing Public Health Service stipend of $2,400 was twice the Michigan stipend. So on the grounds of economic need, Baird decided to become a physiologist. "It had nothing to do with the desire to become a physiologist"—a strange admission in light of his subsequent lifelong affinity for physiology.

Ernest L. Scott became his immediate thesis adviser. With Scott he completed the studies that each of them had separately initiated on sulfur and phenol metabolism. Baird's results were then published in Public Health Service reports as his first papers. In the meantime he continued his study of what would subsequently be called changes in the acid-base balance as the result of exercise. Columbia University was generous in accepting Michigan's credits for Baird's interrupted courses. To earn the needed initial credits in physiology, Baird assisted in teaching the laboratory course. For biochemistry, since not much time could be spared from his remunerated research, he attended a course that met all day Saturday in the second semester for medical students who had failed their course the preceding semester. As Baird noted, "And that is all the formal biochemistry I ever had." Can the sort of biochemistry he missed up to 1921 help us appraise his total influence on this emerging science?

Baird's thesis research also included a part on changes in the fragility of red blood cells upon exercise, a quickly successful problem suggested by Scott. They found that after a prolonged period without exercise the blood of a dog accumulates a lot of old red blood cells, about to be broken up. Strong exercise broke up these doomed blood cells faster than the spleen could remove them, leading to the pink plasma of a hemoglobinemia. The project also involved observing changes in red blood cell fragility arising from blood oxygenation and reduction and from CO_2 addition and extraction. This work brought Baird's interest into the osmotic consequences of changes in the distribution of chloride and bicarbonate, an interest greatly extended later at the hospital of the Rockefeller Institute.

In his concurrent attempts to study the alkali reserve of blood plasma in exercise and fatigue, Baird adapted a hydrogen electrode, one previously described by J. B. McClendon, for titrating the plasma to measure the alkali reserve. He wrote up this procedure and the particular electrode adaptation with the idea that it might be published. He brought it along to consult with his friend, Dr. Glenn E. Cullen, who was then Van Slyke's first assistant at the hospital of the Rockefeller Institute. Cullen was pleased with it and at once took it into Van Slyke's office. Cullen soon came out and said, "Dr. Van Slyke wants to see you." Van Slyke, then editor of the *Journal of Biological Chemistry*, accepted the paper for publication then and there, on March 9, 1921.

ROCKEFELLER INSTITUTE PERIOD

Van Slyke then asked Baird what he planned to do upon completion of his Ph.D. Van Slyke approved his intent to proceed to Washington, D.C., to develop the Public Health Service program in physiology for which Schereschewsky

had arranged his training. Van Slyke also emphasized the accompanying possibility of an association there with the newly appointed William Mansfield Clark. But then Van Slyke added, "There might be another possibility—don't do anything until you hear from me."

Baird waited from March until June for Van Slyke to feel free to propose that Baird become his first assistant—"probably the best job in the country in 1921 for a fresh Ph.D." It placed Baird in charge of Van Slyke's research labs. The experiments were planned together, but the organization and execution were in Baird's hands. Ever afterward, however, Baird had a guilty feeling that he had let down Schereschewsky, who had left him at Columbia to finish his Ph.D. so that Baird could start the Department of Physiology at the National Hygienics Laboratory. "My guilt accounted for my willingness from that moment to do anything that the Public Health Service asked me to do," Baird said. In Van Slyke's lab, Baird's associates began at once to call him a biochemist, a name he did not deny, even though "I knew in my heart I wasn't one." Clearly, Baird then followed Van Slyke's prior example upon his earlier arrival at the institute with arduous study to deserve this name.

Baird joined with Van Slyke, John Plazin, Michael Heidelberger, James M. Neill, and occasional visitors in the so far unsuccessful attempts to clearly delineate differences in the CO_2 absorption curves of oxygenated and reduced blood. One day the frustrating technical difficulty brought Baird and Neill out into Central Park for relief. In the ensuing conversation, it was obviously Baird who proposed the subsequently familiar two-compartment system for equilibrating blood and a desired gas phase, to allow separation of these phases for analysis without dis

turbing the equilibrium. This simple but resourceful device greatly accelerated progress in the lively program that ensued. Baird would stay overnight in the hospital, sleeping in an in-a-door bed so that he could start the experiments at 7 a.m. and have samples ready for analysis in an hour and a half when the rest of the team arrived. By 10 or 11 the same evening, the data would have been calculated and plotting begun. Now the plots became remarkably consistent, and subsequent productivity became equally remarkable.

So the laboratory study of the acid-base balance of blood entered a rich phase on its way to becoming an ultimate classic as described in 1932, in *Quantitative Clinical Chemistry* by Peters and Van Slyke. "Van Slyke always said that this was the happiest and most productive time of his life, and it certainly was for me," Baird said. He further regarded the next five years he spent in Van Slyke's laboratory as the most important experience he ever had. The quality of that experience stands clear in his National Academy of Sciences' memoir for Van Slyke in 1976, although Baird's five years of participation are scarcely mentioned.

In describing this rich experience, Baird also emphasized the significance of his placement, along with that of Van Slyke, the only two biochemists among a half dozen clinicians engaged in important clinical research. Thus, early in his career he learned not only to respect but also to be sympathetic toward clinical investigators and their clinical problems. "This, perhaps more than what I learned in biochemistry, determined my future," Baird said. He also noted the importance of the output from the Hospital of the Institute of numerous people who became leading professors of medicine—for example, Walter W. Palmer, Oswald H. Robertson, Franklin McLean, and C. Phillip Miller, Jr.

Baird held that "the quantitative study of disease was born to a considerable degree at the Rockefeller Institute." Tosteson quotes Baird as saying much later, "Whatever biochemistry is today—it owes as much to clinical medicine for its high place among the biological sciences—as medicine owes to it."

During these five years, Baird also initiated his studies of the physiochemical basis for bone deposition, in particular by a pioneering application of the DeBye-Huckel theory to the stepwise dissociation of carbonic and phosphoric acids. In the spring of 1925, Flexner asked Baird, now an associate, to supervise a two-week visit by Otto Warburg. Baird was commissioned, upon learning to use the Warburg apparatus for measuring tissue respiration, to teach its use in the Cancer Research Laboratory of the Institute. Baird told the story of how it became obvious to him that Warburg had heretofore in his work not measured the pH but calculated the hydrogen ion concentrations, all the while assuming exactly concurrent rather than successive dissociation of the two hydrogen ions of carbonic acid. On Warburg's return to Germany he published a brief correction with thanks to Hastings. Furthermore, he invited Hastings to Berlin-Dahlem, and, during the following summer stay by the young Hastings family, Baird learned to his pleasure the use of the gold-leaf electroscope, actually for measuring the coefficient of solubility of radon in yeast cells and red blood cells.

Baird always gave his wife, Margaret Johnson Hastings, much credit for inspiring him with her high academic standards and with helping him make career decisions throughout their lives together. Margaret proposed the Sunday teas at which the Hastings later entertained first-year Harvard medical students. Members of Baird's department also were ben

eficiaries of her gracious hospitality. As Buchanan remarks in his preface to *Crossing Boundaries*, the Hastings lived courtly and elegant lives. They maintained close associations with numerous relatives and friends, as their musical and artistic son, also named Baird, recounted.

UNIVERSITY OF CHICAGO PERIOD

In 1926, Baird took wing by accepting a professorship in the Department of Physiological Chemistry at the University of Chicago. A year and a half later his professorship was transferred to the Department of Medicine with the creation of the first of the two successive Lasker foundations. "I had a staff of three and $50,000 of hard money to spend," namely on the study of degenerative disease, Baird said. After an earlier excursion with Harold B. Van Dyke to compare the blood distribution of bromide as a function of pH with that of the previously studied chloride ion, Hastings undertook the major problem of describing the movement of water and ions between the extra-and intracellular phases of muscle and other tissues. The first problem was to figure out how to determine what fraction of a piece of tissue is extracellular and what portion is intracellular, and even whether the extracellular fluid portion could be considered an ultrafiltrate of the blood plasma.

First, Baird had to escape from the prejudice that the Donnan equilibrium would sufficiently account for the distribution of ions. Only when he and Lillian Eichelberger showed that muscle cells are not freely permeable to ions, and contained little or no chloride ion, had they struck a productive track. Wallace Fenn, J. P. Peters, and Daniel Darrow were then approaching the same conclusion about muscle. The same approach proved applicable to liver and heart, although the inhomogeneity of kidney and brain

complicated the assignment of the cellular and extracellular compartments for them.

With Henry Harkens as a doctoral student, the correction of experimentally perturbed acid-base balance as measured in the blood was defined as following at least as closely the line describing constant CO_2 tension as the line representing the constancy of pH. The latter course is often still taught, even though Baird redemonstrated the other relation later in his life. With Nathan Shock, a micro acid-base pipette was designed that permitted the pH, CO_2, and hematocrit to be determined simultaneously on the same 0.1 milliliter of blood. Successive measurement on fingertip blood samples readily confirmed the same pathway for correction of the perturbed neutrality. A triaxial plot then logically put the three parameters—the CO_2, the bicarbonate, and the pH—in equivalent geometric relations.

At the University of Chicago, Baird, with Compere, demonstrated that plasma potassium rapidly doubles and then continues to rise to lethal levels in adrenalectomized dogs. The concurrent fall in plasma sodium later came to be regarded as even more characteristic of adrenal insufficiency. Study of the oxidation reduction potentials of reactions involving flavin analogs of riboflavin was initiated with Barron and continued after 1935 with Klemperer at Harvard. The effect of pH changes indicated a transition from a two-electron step to two one-electron steps, subsequently seen as important because it pointed to free-radical participation.

Also at the University of Chicago, the equilibrium determining the deposition and dissolution of bone salt was clarified by x-ray demonstration that the latter is a carbonate-apatite rather than a form of a simple calcium carbonate or calcium phosphate. With Franklin McLean, Baird

initiated work that ultimately showed that the isolated beating frog heart can really serve as a calcium-ion electrode. With it the binding of calcium ion to serum proteins was shown to represent an equilibrium relation, which could be described by the subsequently widely used McLean-Hastings nomogram. These two findings, measurement of the calcium-ion concentration and physicochemical identification on the solid phase of bone, made it possible to perceive that our plasma and interstitial fluids are normally supersaturated with respect to the two principal ions entering into the formation of bone. Subsequent handling of the problems of bone formation and maintenance in the face of parathyroid and other influences flowed from these important studies. McLean and Hastings also showed with James Davis that thyroxin very gradually lowers the oxygen consumption of the surviving frog heart.

During an interval in 1930 as a visiting professor at the Peking Union Medical College, Baird worked with Hsien Wu of Folin-Wu fame and with Francis Dieuaide and gained experience in studying the acid-base balance in edema.

THE HARVARD PERIOD

Following the death of Otto Folin, Hastings was asked in 1935 by Harvard President James B. Conant to assume the Hamilton Kuhn professorship as head of the Department of Biological Chemistry at Harvard Medical School. Baird recalled that in questioning his own readiness for the post, he commented to Conant that in 1935 "biochemistry has become largely a special subject of organic chemistry," a view, he remarked, that had not applied ten years before and no longer applied three decades later. Conant minimized the long-range importance of Baird's deficiency in biochemistry. After Baird's interesting but discouraging

study of the state of the department, he somehow came to see the challenge of the Harvard headship as attractive.

On assuming the post, Baird retained the members of the department, adding only Friedrich Klemperer from the University of Chicago. The latter set up and directed Baird's laboratory. Elmer Stotz, a doctoral student who had received no thesis assignment in three years, completed that requirement under Baird's direction in one year, performing an enzymologic oxidation-reduction study. New doctoral students and postdoctoral guests followed, the latter especially from abroad, rapidly increasing research activity in areas sparked or led by Baird's interests. A lively and unified department resulted, one in which I as a newcomer could not readily distinguish new from ongoing members. As economic times gradually improved in the late thirties, and the merits of the various members were made more apparent by Baird's leadership, the members went forth almost in a wave into academic chairs and other important positions. Baird's deep concern for the careers of others continued throughout his life.

Baird, in his feeling of inexperience, began teaching the medical class with considerable temerity. In leading the course he developed a personal program on body fluids and solid compartments and on their neutrality. He also added a distinguished and personalized laboratory experience in that area, carried out in successive exemplary collaborations with the Department of Physiology. The department's attention to the medical course in its semester became virtually total, despite the overall research momentum.

With Jeanne F. Manery, Baird reported the distribution of inorganic ions in various tissues and showed that the sodium and chloride in soft tissues, except the red blood

cells, cartilage, and gastric mucosa, were largely extracellular. Studies with Oliver H. Lowry on electrolyte distribution showed important changes associated with aging.

Because of the subsequent changes in biochemistry, we readily forget the fantastic quality and scope of its physicochemical period, as discussed in Baird's 1940 Harvey Lecture. Baird joined in the changes in direction.

Lowry's finding of an especially rapid exchange of hepatic potassium for sodium led Baird in subsequent work to prefer a potassium-enriched Ringer solution for studying glycogen formation by liver slices, although calcium and sodium ions were ultimately also shown to be needed for optimal glycogen formation in work with Buchanan. The latter work initiated the tracer studies of glycogen synthesis with the short-lived C-11 isotope, first in pyruvate. This study required rapid laboratory synthesis of the labeled pyruvate upon removal of the freshly formed isotope from the cyclotron. The biological experiment in the rat and the isolation and radioactive analysis of the hepatic glycogen then had to follow promptly as a team effort because decay halved the radioactive emission rate every twenty minutes. The group found that lactate labeled at carbons two and three led to about twice the labeling of glycogen seen from carboxyl-labeled pyruvate, a result implying that the carboxyl group of pyruvate is lost in part during its transit of the reactions producing glycogen.

It was Bergit Vennesland who suggested, on the basis of new findings of Harland Wood and Chester Workman for microorganisms, that bicarbonate be tested as a precursor of hepatic glycogen. To general surprise, certainly that of Hastings, the $^{11}CO_2$ served to form glycogen in about the amount expected if it had replaced the lost carboxyl group of lactate. This was pioneering proof that CO_2 is fixed

metabolically in mammalian organisms, although Earle Evans and Louis Slotin had already reported that pigeon liver homogenates catalyse the incorporation of CO_2 into 2-ketoglutarate formed from pyruvate.

The Singer-Hastings nomogram was devised in the mid-forties to clarify how acid-base balance data should be interpreted clinically. With a succession of colleagues, Baird undertook, particularly after the war, the study that can be described as "factors affecting choices among alternate pathways of metabolism." Using ^{14}C-labeling, Baird and his colleagues determined the rate at which glucose is phosphorylated to glucose-6-phosphate; how much of that product is metabolized to pyruvate by the Embden-Meyerhoff pathway; how much is further metabolized via the citric acid pathway to carbon dioxide and water, and how much is diverted through the pentose phosphate pathway; how much is converted to glycogen via the uridine phosphate-glucose pathway; and how much is simply hydrolyzed to glucose by the hepatic enzyme glucose-6-phosphatase. Once these rates were known for normal rats, they studied the pathways taken quantitatively instead in diabetic animals and how these choices were altered by insulin or steroid administration or by adrenalectomy, for example. The results answered an old question by showing that both underutilization and overproduction of glucose contribute to diabetes. Other prior goals were pursued in an extended series of collaborative studies, often with postdoctoral students of medicine. This remarkable group of persons became professors of clinical medicine in an unusual number of cases.

In 1940 the scope of the department's doctoral and postdoctoral program was further broadened by the appointment of Eric G. Ball, who ultimately joined with Baird in running the department while Baird's time came to be

divided between his academic program and his service in Washington as a member of the wartime Committee on Medical Research (CMR) from 1941 to 1946.

The ten-odd members of the CMR, led by A. N. Richards, worked most conscientiously to get the greatest public value out of the virtually blank check provided to it. Baird continued his teaching at Harvard on a half-time basis. Of the 594 research contracts funded by the CMR on a wide range of problems, those on antimalarials, blood and blood substitutes, and penicillin became the best known. The history of the penicillin project presents a dramatic example in the nationwide coordination secured and is a monument to the CMR and many of the nation's able scientists. Of the $24 million dispersed in the five years from 1941 to 1946, only half a million was spent on the research and development of penicillin and three times as much for its testing and clinical evaluation. Baird's remarkable mission to Moscow introduced a variation in this period of his national service. He spent four weeks there in early 1944 in exchanges of information and samples (e.g., penicillin).

President Truman spoke for the nation in his quoted remarks on dismissal of the CMR: "I don't know how to thank you on behalf of the government, and I don't know what we are going to do to enlist men like you to serve in the future." This appreciation, clearly felt widely and by Truman's successor, greatly affected the subsequent peacetime support of research. The CMR was demobilized at meetings in January 1946 by a series of votes as to where each still-active research contract should be assigned. As a result, almost all of them were made the responsibility of the National Institutes of Health (NIH). A very simple enabling act of Parran and Dyer had been approved by Congress in 1945, wherein the word "cancer" in the Can

cer Act of the mid-thirties was simply changed to "medical." "On the strength of that change the NIH has been entitled to do everything they have done since." The better projects already under way were supported by funds transferred to NIH from the OSRD as the latter passed out of existence.

Appropriate administrative machinery was set up. To the pre-existing National Cancer Council, on which Baird had been serving, was added the National Health Advisory Council, of which Baird became a member. Subsequently, he served on the National Arthritis and Metabolic Disease Council and the Heart Council, four councils in all. C. J. Van Slyke had played a large part in suggesting the study section and review procedure. Parran, Dyer, and Van Slyke put into operation their conviction that "The Public Health Service should be the only agency whereby the scientists of this country were able to fund the work that they, the scientists, felt worth doing." In his following two decades, Baird served on a long list of such federal and foundation assignments, in which he vigorously defended this understanding of the restricted governmental role in determining what research should be supported. For example, in the largely disregarded Long report in 1955, Baird joined in defending the administrative as well as advisory roles of the councils and the process of peer review. He said, "Medicine has been very different because of the postwar extramural program of the NIH," and Baird was one of those whose persistent influence contributed greatly to that change.

Throughout his career, Baird showed a strong motivation to serve his institutional context in ways that strengthened it, and his counsel was sought again and again on broad institutional questions. One such question arose as to how Harvard should effect its scheduled disposition of a

unique program known as the Department of Physical Chemistry. The life of this organization, anomalous for a medical school, had long been fixed as associated with the professional lifetime of its director, Professor Edwin G. Cohn, from whose abilities and interests its special form had grown. Accordingly, in Baird's historical account, the department disappeared with Cohn's death in 1953. Its escalating and important wartime responsibilities had, however, in the meantime made it a formidable structure that exerted temporary control over widely dispersed national and industrial research activities. It exerted a supervision of standards that for peacetime was surely more appropriate to the U.S. Public Health Service or other governmental agencies than to a private university. Nevertheless, the large federal funds that flowed to this organization must surely have generated temptations for Harvard to retain as much as possible of this resource, perhaps setting aside questions of the ultimate consequences to the various related academic programs of the university.

One wonders how many universities would have shown the courage to unload so large an enterprise as Harvard did. Furthermore, how often would one so closely involved in the question be entrusted to head a committee to recommend a list of decisions? Hastings had contributed heavily in his services on the CMR, however, to the concentration of power represented by this "department" and therefore presumably bore some responsibility for the possible consequences of the mode of its dissolution.

Harvard President Pusey appointed Baird to head an advisory committee with a multi-institutional membership. Its recommendations, reached after long deliberation, were accepted to pass one particular activity to the Public Health Service, another activity back to industry, to make certain

dispositions of the various labs, and to keep the Protein Foundation administratively separate from Harvard. What was left was amalgamated with the Department of Biological Chemistry, thereby adding Oncley, Surgenor, and Hunter to that department. These adjustments occurred with a minimum of unnecessary public attention.

EARLY HARVARD RETIREMENT

The handling of the laboratory experiments on the acid-base balance in an integrated fashion between the departments of biological chemistry and physiology through Baird's years at Harvard should surely be part of any history of interdisciplinary integration in medical education. A concept of a sweeping rather than a selective and topical integration prominently entered the scene after World War II, often selecting an anatomical basis for that integration. At points this drive could almost be called antidisciplinary when it became part of a "managerial revolution" in which the traditional function of department heads was sharply diminished. A mobilization of the worthy creative teaching urges of younger faculty members was also involved. This revolution was new enough so that Baird could not have foreseen its full implications for him. As he bent with the ambitious program for comprehensive teaching integration at Harvard, he became troubled with losses of his personal teaching responsibilities along lines about which he felt particularly conscientious.

At the same time, his full satisfaction in research was one that had always required more personal participation than he found he could now maintain, and not merely the administrative oversight that protected the research privileges of his collaborators, even if flavored by the courtesy of his receiving an occasional invited assignment in a cur

rent experiment. Problems also had to be met in maintaining the strength of biochemistry as an academic department in competition with the understandable ambitions of associated hospitals to build centers of biochemical strength, and those challenges were met.

In his life story Baird tells of the satisfaction he gained during his career in helping colleagues who had reached a point where a career change was needed, by assisting them in identifying a successful pathway to a change. Franklin McLean had reached what he regarded as a predictable end to his deanship at Chicago and needed to be reminded that he could indeed continue as the excellent researcher he was. Shields Warren apparently needed persuasion to see that he was ideally qualified for the directorship of the Division of Biology and Medicine of the Atomic Energy Commission. Frances Dieuaide needed guidance to the medical directorship of the Life Insurance Medical Fund. Upon Donald Van Slyke's retirement as a member of the Rockefeller Institute, Baird achieved what he felt was a rescue when he virtually insisted that Van Slyke become associate director for biology and medicine at the Brookhaven National Laboratory. Now that Baird needed a career change himself to correspond to his personal requirement for significant lifelong activity, he found the courage to veer strongly to a new course that he ever after regarded as fortunate.

The factors considered above led Baird to broach to Harvard a desire to withdraw from the position of head, in order to return to the laboratory at Harvard to try to again enjoy personal experimental work. Unfortunately, concerns about the university's freedom to appoint a successor to the headship precluded that accommodation, one that appears nowadays to be made more freely. Hence, the appeal of a call to the Scripps Clinic and Research Foundation, which Baird

had already felt, led him at age sixty-three to ask for early retirement from the headship at Harvard. This request was granted reluctantly, allowing Baird to establish a research laboratory at Scripps at the beginning of 1959. This event led to Eric Ball's service as interim chairman at Harvard, until a successor to Baird was identified in Eugene Kennedy.

LA JOLLA PHASES

Baird began research by himself at the Scripps Clinic and Research Foundation in La Jolla. He did bring along temporarily a skilled former assistant in Frances B. Nesbitt to teach him hepatic glycogen analysis, for which he had become embarrassed to depend on others. A resident former technician, Mrs. Jane Bein, was then added. These two together first confirmed the effect of pH increases in stimulating glucose synthesis in liver slices, provided that the buffer used was bicarbonate-carbonic acid and not the artificial "Tris," nor orthophosphate at unphysiological concentrations. When the bicarbonate and carbonic acid concentrations were kept at a fixed ratio by varying the two together, it became clear that at constant pH the effect of changing the aggregate CO_2 concentration on glycogen synthesis from glucose was a large one, just as large as the effect of raising the pH at constant HCO_3 or at constant pCO_2. The effect of CO_2 concentration was not seen with pyruvate as the glycogen precursor, so it had no connection with the carboxylation of pyruvate.

Eugene Dowdle had, in the meantime, been added as a postdoctoral associate. In 1960 Baird was awarded an NIH research grant, his first ever, to his astonishment for seven years rather than the cautious three years he had requested. This support extended then through his seventieth birthday. He also obtained his license for the use of radioactive

isotopes. He now added Ted Mahowald, replacing Dowdle, and Darrel Fanestil, who later became a distinguished professor of nephrology at the University of California at San Diego. The subsequent recruitment of William J. Longmore allowed extension of the work to include lipids.

The stimulating effect of CO_2 was found to apply also to the conversion of fructose and glycerol to glycogen, results pointing to the phosphorylation step as possibly the sensitive one. By ingenious summation of the glucose phosphorylated twice or several times, via a dephosphorylation by glucose-6-phosphatase followed by rephosphorylation, the effect of CO_2 was indeed found to fall on the phosphorylation step. No specific enzyme was firmly identified as the one influenced by CO_2, although Fanestil showed that the hepatic mitochondrial ATPase activity was strongly increased with elevation of CO_2 at constant pH. Longmore and Baird confirmed this effect and extended it to renal mitochondria. Baird, with Betty Baker, showed that it also applied to brain ATPase activity. Baird asked retrospectively, "Could we have been at fault to look for effects of CO_2 only on enzymes that operate in a single phase, rather than across a membrane?" In this light, ATPase operation in a heterogeneous system became a plausible point for the CO_2 sensitivity to apply.

With Longmore, strong stimulatory effects of CO_2 concentration were also shown on the synthesis from labeled acetate of long-chained fatty acids, whether these entered triglycerides or phospholipids. In contrast, no effect was seen on cholesterol synthesis from acetate. This contrast corresponded to a plausibly direct consequence of the precursorship of CO_2 to malonyl CoA in fatty acid biosynthesis.

Biomedical investigators have sometimes become content to identify a metabolite as simply a modulator of an

enzymatic process, without a chemical explanation of that action. Baird was, however, dissatisfied to be unable by tests, for example, for carbamate formation, to identify the effect of CO_2 with a specific structure on a catalytic protein molecule, somewhat as illustrated by hemoglobin. He also liked to picture, in the evidence obtained for regulatory effects of CO_2, a possible explanation for the special protection the constancy of the pCO_2 receives in the correction of the organismal neutrality, as he had shown repeatedly through the years: "This in a sense is my legacy to physiology. . . . It wasn't until the 1960s that there was a rational biochemical explanation for the apparent concern of the body about its CO_2 tension as well as about its pH," Baird said.

During the time that Baird's lab at Scripps was in operation, at least ten guest investigators carried out research with him. He also supervised the doctoral thesis research of Michael Pilson in marine biology at the Scripps Institute of Oceanography on the electrolyte composition of the body fluids of the abalone.

At this point the best development of the Scripps Research Foundation and its increasing space called for the appointment of a senior biochemist who would be happy to generate and lead a biochemical department. Baird had, however, no interest personally in again developing a big department of biochemistry. "I might better have stayed at Harvard," he said. So he participated in the recruitment that brought to Scripps Frank Huennekens, who developed a strong department of biochemistry.

Baird's autobiography makes clear the excitement and pleasure he derived from the almost two decades he spent next in contributing to and observing the development of another new department, namely, neurosciences, and of a

new medical school at UCSD. The comparisons he made with earlier institutions and their development enriched for him this "second La Jolla phase" of his career. This and his other continuing professional activities may more reasonably be perused in his autobiography than detailed here.

Baird Hastings was a person beyond category. One does not do justice to him by appraising him solely as a leader in any one discipline. He was a man for all seasons. Rather, one needs to consider his contributions to biomedical science as a whole, to medical education, to scientific exposition and editing, to communication between the clinical and basic sciences, also between disciplines and persons, and to helping others with career problems at all stages—the list goes on.

NOTE

1. The several brief quotations in this memoir are taken from Hasting's life story, *Crossing Boundaries*, and can generally be located with its index.

HONORS AND DISTINCTIONS

MEMBERSHIPS

American Academy of Arts and Sciences, 1936; American Philosophical Society, 1941; National Academy of Sciences, 1937; National Research Council, 1937; Royal Danish Academy of Sciences and Letters, 1951

PROFESSIONAL SOCIETIES

American Association for the Advancement of Science, 1965 (Vice President, 1965; Chairman, Medical Science Section, 1965); American Association for Cancer Research, 1946–58; American Association of Clinical Chemists, 1965; American Chemical Society, 1917–; American Institute of Nutrition, 1940–; American Physiological Society, 1927–; American Society of Biological Chemists, 1921 (Treasurer, 1936–40; Vice President, 1943–44; President, 1945–47); Association of American Physicians, 1936–; Association of Harvard Chemists, 1962; Biological and Medical Sciences Research Club of San Diego, 1963–68 (President, 1963–64); The Biochemical Society, 1949–73; Central Society for Clinical Research, 1928; The Endocrine Society, 1955; The Gerontological Society; The Harvey Society, 1921; Radiation Research Society, 1958; San Diego Zoological Society, 1963; Society of Chemistry of Peru, 1957; Society of Columbia Chemists, 1961; Society for Experimental Biology and Medicine, 1920– (Vice President, 1943–45; President, 1945–47); Society for the Study of Development and Growth, 1948–; Tapei International Medical Society, 1962–; Western Association of Physicians, 1960–; The Yu Wang Fu Association, 1931; Los Angeles Academy of Medicine, 1965

HONORARY DEGREES (SC.D.)

University of Michigan, 1941; Harvard University, 1945; Oxford University, 1952; Boston University, 1956; St. Louis University, 1965; Columbia University, 1967; Indiana University, 1972

AWARDS

The President's Medal for Merit, Committee for Medical Research, 1948; Honorary Professorship, University of San Marcos, Peru, 1957; Distinguished Service Award, Medical Alumni Association, Univer

sity of Chicago, 1961; The Banting Medal of the American Diabetes Association, 1962; American College of Physicians, 1964 Award; U.S. Public Health Service citation for service, consultation, and advice, 1917–64, 1965; Modern Medicine Distinguished Achievement Award, 1965; A. Baird Hastings Symposium, University of Michigan, October 23–24, 1965; Massachusetts Institute of Technology, silver plaque citation, 1965; Brookhaven National Laboratory, citation for service, 1965; Sesquicentennial Award, University of Michigan, 1967; Citation, Department of Physiology, Columbia University, 1967; Distinguished Achievement Service Medallion, San Diego Heart Association, 1972

VISITING POSTS AND LECTURESHIPS

Lecturer, University of Southern California, summer 1924; Visiting Scientist, Kaiser Wilhelm Institute for Biology, 1925; Visiting Professor of Biochemistry, Peiping Union Medical College, 1930–31; Benjamin Knox Rachford Lectureship, University of Cincinnati, 1937; Harvey Lecture, 1940; Visiting Scientist, Carlsberg Laboratory, Copenhagen, 1950; Fulbright Lecturer, Oxford University, 1952; Member, U.S. Delegation to the International Conference on Peaceful Uses of Atomic Energy, Geneva, 1954; Visiting Professor, John Curtin School for Medical Research, Australian National University, Canberra, 1957; Banting Memorial Lecture, American Diabetes Association, 1962; Lecture for American College of Physicians Award, 1964; Black Memorial Lecture, Los Angeles Academy of Medicine, 1965; Guest Investigator, U.S. Naval Medical Research Unit No. 2, Tapei, Taiwan, 1966; Visiting Professor, School of Medicine, Pahlavi University, Shiraz, Iran; Visiting Professor, Department of Pharmacology, Washington University School of Medicine, 1969

EDITORSHIPS AND ADVISORY BOARD SERVICE TO PUBLICATIONS

American Journal of Physiology, 1956–63; Endocrinology, 1953–67; Handbook of Physiology, 1959–66; Journal of Applied Physiology, 1956–87; Journal of Biological Chemistry, 1941–54, 1955–59; Physiological Reviews, 1932–35; Proceedings of the Society for Experimental Biology and Medicine, 1935–87. Advisory boards: The Handbook of Biological Data, 1949–53; Biochemical Preparations, 1945–68; Comprehensive Biochemistry, 1957; Methods of Biochemical Analysis, 1953–60

ADVISORY AND CONSULTATIVE SERVICE TO GOVERNMENTAL AGENCIES

Associated Universities, Inc., Brookhaven National Laboratory: Trustee, 1948–51; Visiting Committee to the Medical Department, 1956–64; Chairman, 1962–64; Consultant, 1959–64; Research Collaborator, 1964

Atomic Energy Commission; Member, Board of Review, 1947; Member, Committee on Biology and Medicine, 1947–50; Consultant, Director, Division of Biology and Medicine, 1950–63; Member, Oak Ridge National Laboratory Advisory Committee for Biology, 1955–57

Member, Committee on Medical Research as presidential appointee, 1941–47

National Academy of Sciences–National Research Council, 1937–87; Member, Division of Medical Sciences, 1937–87; Member–at Large, 1964–87; Executive Committee, 1964–66; Fellowships Board, 1937–54; Chairman, 1951–54; Member, Division of Biology and Agriculture, 1944–59; Member, Board on Food and Nutrition, 1944; Committee on Growth, 1945–46; Advisory Committee on Atomic Bomb Casualties, 1951–59; Advisory Committee to Evaluate the N.I.H. General Research Support Program

U.S. Army Quartermaster Research and Development Command: Member, Advisory Board, 1955–58; U.S. Army, Walter Reed Institute of Research, Member, Scientific Advisory Board, 1956–1962

U.S. Public Health Service, National Institutes of Health: Member, National Advisory Cancer Council, 1943–46; Member, National Advisory Health Council, 1947–48; Member, National Advisory Arthritis and Metabolic Disease Council, 1956–60

Member, National Advisory Heart Council, 1960–64; National Heart Council Israel Research Survey

Consultant, National Heart Institute, 1964–67

Program Consultant, National Institute of Child Health and Human Development, 1964–65

Training Review Committee for Aging, National Institute of Child Health and Human Development, 1965–69

ADDITIONAL ADVISORY ACTIVITIES

Advisory Council, Life Insurance Medical Research Fund, 1946–50; Associate, John Winthrop House, 1947–59

Board of Directors, American Bureau for Medical Aid to China, 1962–68; Director Emeritus, 1968–

Board of Scientific Advisors, Merck Institute for Therapeutic Research, 1957–62

Board of Syndics, Harvard University Press, 1936–46; 1947–51; 1953–55; 1956–58

Consultant, The Regents of The University of California, Laboratory for Nuclear Medicine and Radiation Biology, 1959–

Consultant in Chemistry, Peter Bent Brigham Hospital, 1935–59

Faculty Advisory Committee, Nieman Fellow, 1949–59

Member, Advisory Council, Children's Hospital Research Foundation, 1949–59

Member, Executive Committee of the Growth Society, 1945–46

National Advisory Board, Physiological Research Laboratory, Scripps Institute of Oceanography, 1963–65; Chairman, 1963–65

National Scientific Advisory Committee, Oklahoma Medical Research Foundation and Institute, 1963–; Chairman, 1964

Overseer's Committee to Visit the Harvard University Press, 1950–65

Research Council, San Diego Zoological Society, 1964–70; Scientific Advisory Board, Cancer Research Institute, New England Deaconess Hospital, 1949–70

Scientific Advisory Board, Massachusetts General Hospital, 1959–64; Scientific Advisory Board, McLean Hospital, 1945–59

Scientific Advisory Committee, The Nutrition Foundation, 1947–61

Trustee, Protein Foundation, 1959–70

Trustee, Worcester Foundation for Experimental Biology, 1950–54

Member, National Advisory Board, Scripps Clinic and Research Foundation, 1965–77

Member, Visiting Committee for the Medical School of the University of Oklahoma, 1969–70

Member, Research Committee, San Diego County Heart Association, 1966–; Chairman, 1969; Member, Task Force, 1972

Member, National Advisory Committee, 1971; Advisory Confer

ence on Aging, 1970; Member, post–Conference Board, 1972

Member, National Advisory Committee, Marine Biomedical Institute, University of Texas Medical Branch, Galveston, 1971–77

Member, American Academy of Arts and Sciences Committee on the History of Biochemistry and Molecular Biology, 1968–87

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1919 Effect of fatigue on bicarbonate content of plasma. *Am. J. Physiol.* 49:134–35.

An investigation of changes in the blood and urine resulting from fatigue. Public Health Reprint 546.

1920 With E. L. Scott. Some phases of protein catabolism and fatigue. Public Health Reprint 617.

1921 The lactic acid in the blood of dogs in exercise. *Proc. Soc. Exp. Biol. Med.* 18:306–7.

With C. D. Murray and H. D. Murray, Jr. Certain chemical changes in the blood after pyloric obstruction in dogs. *J. Biol. Chem.* 46:223–32.

With H. A. Murray, Jr. Observations on parathyroidectomized dogs. *J. Biol. Chem.* 46:233–56.

A hydrogen electrode vessel adapted for titrations. *J. Biol. Chem.* 46:463–66.

With H. C. Coombs and F. H. Pike. The changes in the concentration of carbon dioxide resulting from changes in the volume of blood flowing through the medulla oblongata. *Am. J. Physiol.* 57:104–9.

1922 With G. E. Cullen. A comparison of colorimetric and electrometric determinations of hydrogen ion concentrations in solutions containing carbon dioxide. *J. Biol Chem.* 52:517–20.

With D. D. Van Slyke. The determination of the three dissociation constants of citric acid. *J. Biol. Chem.* 53:269–76.

With J. H. Austin, G. E. Cullen, F. C. McLean, J. P. Peters, and D. D. Van Slyke. Studies of gas and electrolyte equilibria in the blood. I. Techniques for collection and analysis of blood, and for its saturation with gas mixtures of known composition. *J. Biol. Chem.* 54:121–47.

With D. D. Van Slyke, M. Heidelberger, and J. M. Neill. Studies of

gas and electrolyte equilibria in the blood. III. The alkali binding and buffer values of oxyhemoglobin and reduced hemoglobin. *J. Biol. Chem.* 54:481–506.

With D. D. Van Slyke, and J. M. Neill. Studies of gas and equilibria in the blood. IV. The effect of oxygenation and reduction on the bicarbonate content and buffer value of blood. *J. Biol. Chem.* 54:507–26.

With C. A. L. Binger, and J. M. Neill. Edema associated with moderate bicarbonate administration during convalescence in pneumonia. *Arch. Int. Med.* 31:145–50.

1924 With D. D. Van Slyke, J. M. Neill, M. Heidelberger, and C. R. Harington. Studies on gas and electrolyte equilibria in the blood. VI. The acid properties of reduced and oxygenated hemoglobin. *J. Biol. Chem.* 60:89–153.

With H. A. Salvesen and J. F. McIntosh. Blood changes and clinical symptoms following clinical and following oral administration of phosphates. *J. Biol. Chem.* 60:311–26.

With H. A. Salvesen and J. F. McIntosh. The effect of the administration of calcium salts on the inorganic composition of the blood. *J. Biol. Chem.* 60:327–39.

With J. Sendroy, C. D. Murray, and M. Heidelberger. Studies of gas and electrolyte equilibria in the blood. VII. The effect of carbon monoxide on the acidity of hemoglobin. *J. Biol. Chem.* 61:317–35.

With J. M. Neill, H. J. Morgan, and C. A. L. Binger. Blood reaction and blood gasses in pneumonia. *Clin. Invest.* 1:25–45.

With J. Sendroy, Jr. Studies of acidosis. XX. The colorimetric determination of blood pH at body temperatures without buffer standards. *J. Biol. Chem.* 61:695–710.

1925 With J. M. Neill. The influence of the tension of molecular upon certain oxidations of hemoglobin. *J. Biol. Chem.* 63:479–92.

With C. D. Murray. The maintenance of carbonic acid equilibrium in the body with special reference to the influence of respiration and kidney function on CO_2, HCO_3, and CO_3 concentrations in plasma. *J. Biol. Chem.* 65:265–78.

With J. Sendroy, Jr. and W. Robson. Studies of acidosis. XXI. The

colorimetric determination of the pH of urine. *J. Biol. Chem.* 65:381–92.

With J. Sendroy, Jr. The effect of variation in ionic strength on the apparent first and second dissociation constants of carbonic acid. *J. Biol. Chem.* 65:445–55.

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1926 With H. J. Stewart and J. H. Crawford. The effect of tachycardia on the blood flow in dogs. I. The effect of rapid irregular rhythms as seen in auricular fibrillation. *J. Clin. Invest.* 3:435–47.

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With J. Sendroy, Jr. Studies of the solubility of calcium salts. II. The solubility of tertiary calcium phosphate in salt solutions and biological fluids. *J. Biol. Chem.* 71:783–96.

With J. Sendroy, Jr. Studies of the solubility of calcium salts. III. The solubility of calcium carbonate and tertiary calcium phosphate under various conditions. *J. Biol. Chem.* 71:797–846.

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1928 With H. B. Van Dyke. The response of smooth muscle in different ionic environments . *Am. J. Physiol.* 83:563–77.

With D. D. Van Slyke, J. Sendroy, Jr., and J. M. Neill. Studies of gas and electrolyte equilibria in the blood. X. The solubility of carbon dioxide at 38° in water, salt solutions, serum, and blood cells. *J. Biol. Chem.* 78:765–99.

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With D. D. Van Slyke, A. Hiller, and J. Sendroy, Jr. Studies of gas and electrolyte equilibria in the blood. XIV. The amounts of alkali bound by serum albumin and globulin. *J. Biol. Chem.* 79:769–88.

With J. Sendroy, Jr. The activity coefficients of certain acid-base indicators. *J. Biol. Chem.* 82:197–246.

1931 With E. L. Compere. Effects of bilateral suprarenalectomy on certain constituents of the blood of dogs. *Proc. Soc. Exp. Biol. Med.* 28:376–78.

With H. N. Harkins. A study of electrolyte equilibrium in the blood in experimental acidosis. *J. Biol. Chem.* 90:565–95.

With H. H. Roseberry and J. K. Morse. X-ray analysis of bones and teeth. *J. Biol. Chem.* 90:395–407.

With H. B. Van Dyke. Studies of bromide and chloride distribution in the blood. I. In vitro experiments on bromide and chloride distribution. *J. Biol. Chem.* 92:13–25.

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With B. F. Avery. A gasometric method for the determination of lactic acids in the blood. *J. Biol. Chem.* 94:275–80.

With L. J. Bogert. The calcium salts of bone. *J. Biol. Chem.* 94:473–81.

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(Twenty-five further bibliographic items appeared by 1989, not, however, in the category of laboratory research.)

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Einar Hille

EINAR HILLE

June 28, 1894–February 12, 1980

BY RALPH PHILLIPS

EINAR HILLE'S many achievements as a mathematician and a teacher made him a major force in the American mathematical community during most of his lifetime. He was at heart a classical analyst, yet his principal work was the creation and development of the abstract theory of semi-groups of operators, which culminated in his definitive book on *Functional Analysis and Semi-Groups* (1948, 2). In all, Hille authored or coauthored 175 mathematical papers and twelve books. During the twenty-five years of his tenure at Yale (1938–62), he was the director of graduate studies and as such played an important role in making the Yale Mathematics Department one of the best in the country. He was president of the American Mathematical Society (1947–48), and a member of the National Academy of Sciences, the Royal Academy of Sciences of Stockholm, and the American Academy of Arts and Sciences.

Hille was born in New York City under somewhat unfortunate circumstances in that his parents had separated before his birth and his mother was left with the task of raising him alone. Two years later they moved to Stockholm and remained there for twenty-four years, all that time within a few blocks of a parish church where an uncle of Hille's

was then the rector. He wrote of those years: "I was an only child and naturally was spoiled in many ways. That the result did not become completely unfit for human company was largely due to my mother's strong criticism. Nothing was good enough for me, but only my best was good enough for her and as often as not that did not satisfy."

About his early talent, Hille wrote: "My interest in mathematics came fairly late. I recall having had trouble with the seven table in the third grade and that I badly flunked a test on decimal fractions in the sixth grade. But from the ninth grade on mathematics was one of my best subjects and I did outside reading in this subject regularly from the tenth grade on."

Hille entered the University of Stockholm in the fall of 1911 with the aim of becoming a secondary school teacher. For this it was necessary to get a master's degree, and this involved taking three main subjects, at least two of which formed a "teachable" combination. He picked chemistry, mathematics, and physics. Hille started with chemistry but by the end of two years realized that he had little talent in this field. From the beginning, however, to relieve the tedium of the laboratory, Hille started to visit mathematics lectures and thus began his real introduction into the subject under the guidance of Professors I. Bendixson, I. Fredholm, H. von Koch, and docent M. Riesz. Hille received his master's degree in May 1914.

By this time Hille had decided to go for a Ph.D. in mathematics. Riesz suggested the topic of Hille's first mathematical paper, which had to do with properties:

$$L(r) = r\int_0^{2\pi} \left| f'(re^{i\theta}) \right| d\theta,$$

where $f(z)$ is holomorphic and $f'(z) \neq 0$ in the disk (:z: <

R). Hille got the licentiate of philosophy degree in 1916 on the basis of this research.

Hille served in the Swedish Army during 1916–17, where he managed to find time to start three investigations, one of which became the basis for his Ph.D. dissertation (1918). This had to do with an integral identity (a form of Green's identity) that he used to obtain information on the distribution of zeros in the complex plane of certain second-order ordinary differential equations. Hille was awarded the Mittag-Leffler Prize for this work. He spent 1919 –20 doing office work in the Swedish Civil Service and teaching on the side at the University of Stockholm.

His big break came in 1920 when a fellowship from the Swedish-American Foundation enabled him to spend the year at Harvard University; this was followed by a second year as a Benjamin Pierce Instructor. Encouraged by G. D. Birkhoff, Hille continued to work on the problems engendered in his dissertation (1921, 1; 1922, 1-3; 1923; 1924, 2-6; 1925). Of his later papers, four (1927, 1; 1933, 5; 1943, 1; 1948, 1, in part) are also concerned with the same general set of ideas.

In 1922 Hille moved on to Princeton with the rank of instructor; after his first year he was promoted to assistant professor. To begin with his research continued along the same lines as before; however, he did finish two papers (1924, 1; 1926, 1) at this time on the Dirichlet series, which he had already started in Sweden. Then in 1925 he began working on expansions in terms of Laguerre (1926, 3) and Hermite (1926, 4) polynomials. The latter paper contained results on the Abel summability of such series as well as a study of the Gauss-Weierstrass transform.

With Veblen's help, Hille got a National Research Council fellowship for the year 1926–27 during which he di

vided his time between Stockholm, Copenhagen, and Göttingen. Three publications grew out of this period (1927, 1, 2; 1928, 1), but they were really incidental to the beginning of a close and fruitful collaboration with J. D. Tamarkin that started around this time and continued up to Tamarkin's untimely death in 1945. A touching account of this collaboration can be found in Hille's "In Retrospect."[1, 2]

Hille and Tamarkin started with the problem of the frequency of the characteristic values of linear integral equations (1928, 3; 1931, 1) and continued on to study other phases of integral equations (1930, 2; 1934, 4). This was followed by papers on the Fourier series (1928, 4; 1929, 1; 1930, 3; 1931, 4; 1932, 1; 1933, 1, 2; 1934, 5), Fourier transforms (1933, 3, 6; 1934, 2; 1935, 1, 2) and Hausdorff means (1933, 4, 7, 8; 1934, 3). In all they wrote twenty-six joint papers during the period 1927–37.

Also while at Princeton, Hille became interested in an old problem concerning the width of the strip of uniform nonabsolute convergence of an ordinary Dirichlet series. In 1913 Bohr had shown that this width could be at most one-half and when the summation extends only over the primes that the width is zero. Using a result of Littlewood, Hille was able to prove that, if the summation extends only over those integers that are the product of n primes, the width of the strip is at most $(n–1)/2n$. Finally, F. Bohnenblust, who was Hille's assistant at the time, was able to construct examples for which these upper limits were attained. Two papers (1931, 2, 3; 1932, 3), written jointly with Bohnenblust, contained these results.

In 1933 Hille went to Yale, where he stayed until he reached the mandatory retirement age of sixty-eight in 1962. During all this time his primary responsibility as both teacher and administrator was with the graduate studies. He was

director of graduate studies from 1938 to 1962 and as such had a very close relationship with the students. His lectures were always very polished; in fact, he usually wrote them out in longhand in his notebook the night before. In all he had twenty-four Ph.D. students while at Yale. They were Eugene Northrup, 1934; Augustus H. Fox, 1935; William B. Cater, 1939; Irving E. Segal, 1940; Mary K. Peabody, 1944; Joseph S. Leech, 1947; Robert A. Rosenbaum, 1948; Walter J. Klimczak, 1948; Evelyn Boyd (Collins), 1949; Arthur S. Day, 1949; Joseph R. Lee, 1950; John F. L. Peck, 1950; Hai-Tsin Hsu, 1950; Arthur R. Brown, 1952; Thomas L. Saaty, 1952; James L. Howell, 1954; Stephen E. Puckette, 1957; Roger H. Geeslin, 1958; Cassius Ionescu-Tulcea, 1958; Charles A. McCarthy, 1959; Norman S. Rosenfeld, 1959; Saturnino L. Salas, 1959; Thaddeus B. Curtz, 1960; and Sister Mary Zachary Brunell, 1964.

Up to this point in this chronicle my main source has been Hille's own account of his early years published in the essay, "In Retrospect"[3] and preprints entitled "Home, Schools, Avocations" and "Accomplishments." Material for the previous paragraph was taken from Jacobson's article entitled "Einar Hille, His Yale Years, A Personal Recollection."[4] In what follows I have relied on my forward to Hille's selected papers[5] and Yosida's article, "Some Aspects of E. Hille's Contribution to Semi-Group Theory."[6]

In 1936 Hille met Kirsti Ore, the sister of the Yale mathematician Oystein Ore. Einar and Kirsti were married the following year. Kirsti was a devoted wife, and they had two sons, Harald, born in 1939, and Bertil, born in 1940.

Hille's most important research was on the theory of semi-groups of operators, which he developed almost single-handedly over a twelve-year period beginning in 1936. It all started with an investigation on the Gauss-Weierstrass

and the Poisson transforms, both of which happened to satisfy the semi-group property: $T(t + s) = T(t)\,T(s)$. Hille was interested in the degree of approximation to the identity of $T(t)$ for small t, and he found that he could obtain the desired results using only the semi-group property without invoking the explicit form of the transformations (1936, 1).

Hille's next effort in this direction was somewhat tentative. Starting with a semi-group of positive self-adjoint contractions acting on a Hilbert space, he was able to derive a representation theorem and from this prove the analyticity in the semi-group parameter in the right half-plane (1938, 3). At this point he realized the true potential of the theory and he extended the previous results to general holomorphic semi-groups of operators on a Banach space (1938, 4; 1939, 1; 1942, 4). These three papers are the basis for the most beautiful chaper in Hille's book on semi-groups of operators. This chapter contains a basic generation theorem, giving necessary and sufficient conditions for an operator to generate a semi-group holomorphic in a sector, as well as a characterization of the convex hull of the spectrum of the infinitesimal generator in terms of the exponential growth of the semi-group of operators along the various rays in the sector of definition.

Hille spent 1941–42 on sabbatical at Stanford, where he became involved with G. Polya, A. C. Schaeffer, and G. Szego in the extension of certain oscillation theorems of Polya and Wiener on Fourier series to classical orthogonal polynomials (1942, 1, 2; 1943, 1). In the spring of 1942 he joined forces with Max Zorn, and together they wrote a paper on additive semi-groups of complex numbers (1943, 2).

In 1942 (starting with the paper [1942, 3]), Hille began

an attack on the larger class of semi-groups of operators that are merely strongly continuous. In this paper he discovered the representation of the resolvent of the generator in terms of the Laplace transform of the semi-group. It should be noted that Hille was mainly motivated in this by the theory of analytic functions of exponential type as developed by Polya and not, as one might expect, by the standard Laplace transform approach to the initial value problem in partial differential equations. In fact, it was not until 1949, with the research of Yosida[7] on the diffusion equation, that this most important application of the theory of semi-groups of operators was considered.

In August of 1944 Hille delivered the colloquium lectures at the American Mathematical Society meeting and immediately thereafter he started in earnest writing his book,[8] *Functional Analysis and Semi-Groups*, which was finally published in 1948. It was both a textbook on functional analysis and a monograph on the theory of semi-groups of operators. As far as I know, this was the first time that functional analysis was presented as a tool for classical analysis. In addition to the usual theory of Banach spaces and linear transformations, Hille was able to organize into a unified whole the calculus of vector-valued functions, function theory for vector-valued functions, and the operational calculus. It should be noted that this book was for many years one of the principal texts on functional analysis.

The basic result, giving necessary and sufficient conditions for a closed linear operator A with dense domain to be the infinitesimal generator of a strongly continuous semi-group of contraction operators, appeared in print for the first time simultaneously in Hille's book and in a paper by Yosida.[9] This result is now referred to as the Hille-Yosida generation theorem. The logarithm of the norm of a semi-

group of operators is a real-valued subadditive function on the half-line. With this in mind, Hille extended the earlier theory on subadditive functions on the positive integers to measurable subadditive functions on the half-line.

Hille's chapter on ergodic theory is based on an earlier paper (1945, 1) and deals with the Abel limit:

$$(A) - \lim_{\lambda \to 0,\infty} T(t) = \lim_{\lambda \to \infty,0} \lambda R(\lambda),$$

where $R(\lambda)$ is the Laplace transform

$$R(\lambda) = \int_0^\infty e^{-\lambda t} T(t)\, dt.$$

By means of Tauberian theorems, Hille was able to show that under certain auxiliary conditions Abel summability implies the stronger Cesaro summability. He also proved that the Abel limits at both 0 and ∞ were projection operators related to the semi-group.

The spectral theory chapter is outstanding. It is based on an operational calculus explicitly constructed for the generators of semi-groups of operators. The basic relation between the function $f(\lambda)$ and the corresponding operator $f(A)$ is given by

$$f(\lambda) = \int_0^\infty e^{\lambda t}\, d\beta$$

and

$$f(A) = \int_0^\infty T(t)\, d\beta,$$

A being the infinitesimal generator of $T(t)$; thus, both $f(\lambda)$ and $f(A)$ are Laplace-Stieltjes transforms. In earlier versions of the operational calculus, $f(\lambda)$ was always taken to be holomorphic on the spectrum of A. However, Hille treated functions $f(\lambda)$, which are holomorphic in the interior of the spectrum of A but may be merely continuous on those points of the spectrum that lie on the abscissa of

convergence for the Laplace-Stieltjes transform of β. A spectral mapping theorem relates the fine structure of the spectrum of A to that of $T(t)$ by means of an ingenious argument (1942, 4). It should be remarked that Hille made no use of the theory of Banach algebras in this discussion even though his book contains an appendix on Banach algebras.

Part three of Hille's book deals with a wide variety of examples of semi-groups taken from classical analysis. The chapters on trigonometric semi-groups and translation semi-groups are related to factor sequences for Fourier series and factor functions for L_p spaces, which Hille dealt with in earlier papers ([1924, 1; 1926, 4; 1933, 1, 5]). The chapter on partial differential equations is somewhat disappointing in that it did not anticipate the most successful approach to the subject via the Hille-Yosida theorem. The concluding chapter contains a rich variety of examples taken from summability theory, Markoff chains, stochastic processes, and fractional integration. In each of these examples Hille threw new light on the subject with his semi-group theory.

In 1948 Hille gave his retiring presidential address on the theory of Lie semi-groups of operators (1950, 1) at the annual meeting of the American Mathematical Society. This work contains both a study of the underlying parameter group π and an investigation of its representation ($T(p)$; $p \in \pi$) as bounded linear operators on a Banach space. Hille showed that corresponding to every canonical sub-semi-group there is an infinitesimal generator, that these generators form a positive cone, and that they satisfy the analogs of the three fundamental theorems of Lie.

In 1952 Hille asked me to collaborate with him on the second edition of his book.[8] I was occupied with this task

during much of the 1952–53 academic year and all of 1953–54, which I spent at Yale. I found Hille to be a generous colleague, extremely patient, and perhaps a little too permissive for the good of the book. Although the new edition (1957, 2) is one-and-a-half times the size of the original, it is largely in fact and entirely in spirit very much like the original edition.

The 1957 edition consists of a thorough reworking of the first edition plus several new results necessary to bring it up to date. The theory of commutative Banach algebras is introduced early in the book and plays a major role in the chapters on spectral theory and holomorphic semi-groups. The influence of Yosida and, to some extent, Feller is quite evident; and of course I took advantage of my being coauthor by including my own results on extended classes of semi-groups (distinguished by their behavior at the origin) and their generating theorems, perturbation theory, the adjoint semi-group, the operational calculus, and spectral theory. There is also a new chapter on Hille's theory of Lie semi-groups of operators and an expanded section on the integration of the Kolmogoroff differential equations based mainly on two of Hille's papers (1954, 5, 6). The chapter on partial differential equations was omitted because by that time it required a book of its own. However, we did include a discussion of the abstract Cauchy problem that had been initiated by Hille and on which we had both worked.

Yosida's 1949 paper[10] on the diffusion equation showed that semi-group theory was an ideal tool for studying the initial value problems in mathematical physics. It was typical of Hille that he launched into an attack on this problem on two different levels: the abstract and the concrete. On the abstract level he formulated what he called the abstract Cauchy problem (ACP): for a given Banach space

X and y_o in X and linear operator U with domain $D(U)$, find a solution to the problem $y'(t) = U[y(t)]$, $t > 0$ such that $\lim_{t \to o} y(t) = y_o$ and $y(t)$ is absolutely continuous and $y'(t)$ exists and belongs to $D(U)$ for all $t > 0$. A solution is said to be of normal type if as $t \to \infty \limsup t^{-1} \log 1y(t)1 < \infty$.

Hille investigated the ACP in a series of papers (1951, 2; 1953, 3; 1954, 1, 4; 1957, 1). He showed that the ACP has at most one solution of normal type if U is a closed operator whose point spectrum is not dense in the right half-plane. On the other hand, if the spectrum of U covers the entire plane and X is an L-space, the ACP may have explosive solutions (1950, 3; 1954, 1). It is obvious that if U generates a semi-group of operators, then the ACP is solvable for every y_o in $D(U)$, and the solutions will be of uniform normal type for all y_o of norm ≤ 1. Hille was able to prove the converse assertion (1954, 1); after reading his manuscript, I managed to prove a stronger form of the converse theorem, and this is what appears in our book.

On the concrete level, Hille began working on the forward diffusion equation:

$$\frac{\partial f}{\partial t} = Lf \equiv \frac{\partial}{\partial x}\left\{\frac{\partial}{\partial x}(b(x)f) - a(x)f\right\} \quad \alpha < x < \beta,$$

acting on $L_1(\alpha, \beta)$. He was able to obtain new proofs (1949, 1) of Yosida's results under less restrictive conditions. These results were communicated to Feller, who suggested to Hille that he attack the backward diffusion equation.

$$\frac{\partial g}{\partial t} = Cg \equiv b(x)\frac{\partial^2}{\partial x^2}g + a(x)g \quad \alpha < x < \beta,$$

acting on $C[\alpha, \beta]$, by the same methods. This suggestion proved very fruitful. Another effect of this interchange of ideas was to get Feller interested in the problem, and with the aid of Hille's preliminary results, Feller[11] was able to

find a fairly complete solution for both the forward and the backward equations.

Hille's investigation proceeded more slowly, and it was not until 1954 that he published a comprehensive account (1954, 1); see also (1956, 2). He had given himself the problem of finding necessary and sufficient conditions on the coefficients a and b that the maximally defined operators L and C (i.e., with no boundary conditions) generate semi-groups of positive contraction operators. Although superseded in many ways by Feller, Hille's paper contains a wealth of additional information about L and C.

In 1953 Hille began working on the Kolmogoroff differential equations:

$$Y'(t) = AY(t) \quad \text{and} \quad Z'(t) = Z(t)A,$$

where the matrix $A = (a_{1j})$ is a Kolmogoroff matrix:

$$a_{ii} \leq 0,\ a_{ij} \geq 0 \ \text{ for } i \neq j$$

and

$$\Sigma_i\, a_{ij} = 0 \ \text{ for all } i,$$

and both Y and Z belong to the Markoff algebra M of matrices $U = (u_{ij})$, $u_{ij} \in C$, such that

$$|U| = \sup_i \Sigma_j\, 1u_{ij}1 < \infty.$$

The domain of A is defined as $D(A) = (U \in M; AU \in \mathrm{M})$, and the subspace M_A is the closure of $D(A)$.

One of Hille's main results (1953, 5; 1954, 3) is the following: Suppose A is triangular, that is, $a_{ij} = 0$ for $j > i$, and define the restriction A_o of A with domain

$$D(A_o) = (U \in D(A);\ AU \in M_A).$$

Then A_o generates a strongly continuous semi-group of

transition operators satisfying both Kolmogoroff differential equations. Another result (1954, 6) has to do with null solutions: suppose that $Z(t)$, satisfying the second Kolmogoroff differential equation, is differentiable in the norm topology for $t > 0$, that $\lim_{t \to 0} 1Z(t)1 = 0$ and that $Z(t)$ is of normal type. Then for A triangular and arbitrary B in M, the equation $Q`(t) = Q(t)\ (A + B)$ has a solution with the same properties.

Hille followed this up with a series of papers (1961, 2; 1968, 2; 1966, 2) on differential equations in a Banach algebra of the form

$$w'(z) = f(z)\ w(z).$$

Here z is a complex variable while $f(z)$ and $w(z)$ belong to a complex noncommutative Banach algebra B with unit $f(z)$ being analytic in z. He studied the solutions of this equation in a simply connected domain of holomorphism of $f(z)$, in a neighborhood of a simple pole of $f(z)$, and in a partial neighborhood of a multiple pole.

Hille also became interested in transfinite diameters at about the same time, that is, 1961, and pursued this off and on for another five years. To understand the problem, we go back to Kolmogoroff's abstract definition of an averaging process A:

(i) A assigns to any finite set of positive numbers $(x_1, \ldots, x_m)$ positive average $A(x_1, \ldots, x_m)$;

(ii) $A(x_1, \ldots, x_m)$ is continuous, symmetric, and strictly increasing in each argument;

(iii) $A(x, \ldots, x) = x$;

(iv) If $A(x_1, \ldots, x_k) = y$, then

$$A(x_1,\ldots x_k,x_{k+1},\ldots,x_m) = A(y,\ldots,y,x_{k+1},\ldots,x_m).$$

Given a compact metric space E, consider sets of n points,

and for each set define the x_i's to be the $m = n(n-1)/2$ distances between them. Then, the $A(x_1, \ldots, x_m)$ are bounded as a function of these sets with a maximum value $\delta_n(E)$. It can be shown that $\delta_{n+1}(E) \leq \delta_n(E)$. The transfinite diameter is defined as

$$\delta_0(E) = \lim_{m\to\infty} \delta_m(E).$$

In 1923 Fekete proved that for a compact set E in the plane the transfinite diameter was equal to the Chebyshev constant $\chi(E)$. It is possible to extend the notion of the Chebyshev constant to compact sets E in a metric space. Hille proved (1962, 1) that in this generality $\chi(E) \geq \delta_0(E)$. In two further papers on this subject (1965, 1; 1966, 1), he calculated the transfinite diameters of the unit spheres of some complex Banach spaces.

After retiring from Yale in 1962, Hille stayed in New Haven for two more years and then started on a nomadic existence that took him from one visiting teaching post to another for the next eight years before ending up at the University of California at San Diego. In between he worked at the University of California at Irvine, the University of Oregon in Eugene, and the University of New Mexico in Albuquerque.

During all this time he continued to be very active mathematically. Starting in 1959, he produced nine textbooks and, in addition, investigated the Thomas-Fermi equation (1969, 2; 1970, 1), Emden's equation (1970 (2), 1972 (5,6)), and the Briot-Bouquet equations (1978, 1–4).

The last time I saw Einar was at the Laguna Beach Conference in his honor (January 8–9, 1980). At the time he was terminally ill, but he somehow managed to take leave of the hospital and attend the conference under Kirsti's gentle care. It was typical of Hille that even in his weakened condition he was able to deliver an interesting lecture—his last.

The effort that Hille put into mathematics, in all its aspects, was awesome. I suspect that deep in his subconscious was always the quote from Kipling that he inserted as the frontispiece to the first edition of *Functional Analysis and Semi-Groups*:

> "And each man hears as the twilight nears,
> to the beat of his dying heart,
> The devil drum on the darkened pane:
> "You did it, but was it Art?"

There is no doubt in my mind but that Hille carried the right to be satisfied on this score.

NOTES

1. Einar Hille, *Classical Analysis and Functional Analysis, Selected Papers*.

2. Einar Hille, *Functional Analysis and Semi-Groups, Am. Math Soc. Colloq. Publ.*, XXXI (1948), xii + 528.

3. Hille, *Classical Analysis and Functional Analysis, Selected Papers*.

4. N. Jacobson, *Einar Hille, His Yale Years, A Personal Recollection: Integral Equations and Operator Theory*, Vol. 4 (1981):307–10.

5. Hille, *Classical Analysis and Functional Analysis, Selected Papers*.

6. K. Yosida, "Some Aspects of E. Hille's Contribution to Semi-Group Theory," *Integral Equations and Operator Theory*, 4(1981):311–29.

7. Yosida, op. cit., pp. 311–29.

8. E. Hille and R. S. Phillips, "Functional Analysis and Semi-Groups," *Am. Math Soc. Colloq. Publ.*, xxx1 (1957; revised ed. 1964), xii + 808.

9. Yosida, op. cit., pp. 311–29.

10. E. Hille, "Jacob Tamarkin—His Life and Work," *Bulletin of the American Mathematical Society*, 53(1947):440–57.

11. Yosida, op. cit., pp. 331–29.

12. W. Feller, "The Parabolic Differential Equations and the Associated Semi-Groups of Transformations," *Annals of Mathematics*, (1952):468–519.

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NATHAN ORAM KAPLAN

June 25, 1917–April 15, 1986

BY W. D. MCELROY

NATHAN ORAM KAPLAN was born in New York City on June 25, 1917. When he was two years old his family moved to Los Angeles where, after attending primary and secondary schools, he entered UCLA to major in chemistry. After graduating from UCLA he went to Berkeley for graduate studies. Until this time, Nate's main interests were in baseball and track. He ran the quarter mile and was a member of the track team at UCLA. However, he was also interested in the history of science writing, for which he received an award from the city of Los Angeles.

At Berkeley, Nate's latent talents in research were uncovered and he virtually exploded into recognition. Working in Professor David M. Greenberg's laboratory, he used radioactive phosphate, produced by Martin D. Kamen (a lifetime friend and colleague) with the cyclotron at the Radiation Laboratory, to study phosphate metabolism in rat liver. As he developed experience with radioactive phosphate, he established a collaboration with M. Doudoroff and W. Z. Hassid, two young bacteriologists who were studying phosphate-dependent sucrose degradation by an enzyme from *Pseudomonas sacchraphila*. With Nate's help, they established that the enzyme transferred the glucosyl moiety

of sucrose to radioactive phosphate. Since this was the first demonstration of a sugar transfer reaction, Doudoroff and Hassid were recipients of the Sugar Research Award, the monetary part of which they shared with Nate.

World War II interrupted Nate's research career in biochemistry. From 1942 until 1945 he worked as a research chemist on the Manhattan Project. In 1945, when Nate attended an American Chemical Society meeting in New York, one of his relatives arranged a blind date for him and the couple met on the steps of the 42nd Street library. This was the first meeting of Nate and Goldie. Soon afterward Nate joined Fritz Lipmann's laboratory at the Massachusetts General Hospital. Every other weekend Nate would travel from Boston to New York to see Goldie and over the Thanksgiving weekend of 1947, Goldie agreed to marry him. This worried Lipmann, who thought that Goldie might be a "wild New Yorker."

Nate's research career flourished under the influence of Lipmann. During his time at Mass General he isolated coenzyme A, was instrumental in determining its structure, and helped establish the universality of coenzyme A in "two-carbon" metabolism. For this and earlier work that led to the discovery of coenzyme A, Lipmann shared the Nobel Prize in Physiology and Medicine in 1953. For his contributions to the work on coenzyme A, Nate shared the Nutrition Award in 1948 and received the Eli Lily Award in Biochemistry in 1953.

Nate left Lipmann's laboratory in 1950 to become assistant professor of biochemistry at the University of Illinois Medical School in Chicago, primarily because Sidney Colowick, who had just left the Cori laboratory at Washington University in St. Louis, was there. Problems developed for Colowick and Kaplan at Illinois and they were both hired

(by W. D. McElroy) as assistant professors at the McCollum-Pratt Institute of the Department of Biology of Johns Hopkins University. At Hopkins, Nate and Sidney developed a successful and productive collaboration studying the chemistry of the pyridine nucleotide coenzymes and the enzymes that are involved with them. This collaboration led to the founding in 1955 of the classic series, Colowick and Kaplan's *Methods in Enzymology*, which now has more than 140 volumes with more in press.

In 1957 Nate left Johns Hopkins University to become founding chairman of the Graduate Department of Biochemistry at Brandeis University. To establish the new department he, in association with Martin Kamen who joined him at Brandeis, hired about a dozen carefully selected young assistant professors and brought them to a campus where very little space was available for them for at least a year. Under these conditions and with Nate as catalyst, an uncommon camaraderie developed between faculty, postdoctoral fellows, graduate students, and staff that led to scientific productivity of such caliber that his fledgling department gained international recognition in a very short time. By recognition for his department, Nate Kaplan played a major role in establishing Brandeis, which had only been founded in 1948, as a major, research oriented university in the sciences in the 1960s. His research at Brandeis was primarily concerned with the structure-function relationships of dehydrogenases, which led him into the areas of enzyme evolution and isoenzymes. He was one of the first to recognize the potential of using isoenzymes analysis in clinical diagnosis and for this reason developed methods for detecting lactate dehydrogenase isoenzymes in human serum.

In 1968, pulled by the urgings of Martin Kamen who

had already come to USD, and pushed by circumstances of campus politics at Brandeis, Nate joined the Chemistry Department. His appointment and laboratories were in the School of Medicine. He was drawn to the medical school environment by his earlier association with Fritz Lipmann at Massachusetts General Hospital and his collaboration with Abraham Goldin of the National Institutes of Health in cancer chemotherapy, which dated back to his years at Johns Hopkins in the 1950s. In the 1970s, he and Gordon Sato established a successful colony of athymic mice. The mice were used to examine anti-cancer agents making this facility an important component of the UCSD Cancer Center. Nate's laboratory also made important contributions in more traditional areas of biochemical research at UCSD. Using NMR, his students and postdoctoral fellows established the conformations of the pyridine nucleotide coenzymes and other nucleotides in aqueous solution. Other important contributions were on the development of matrices for affinity chromatography of enzymes, immobilization of enzymes, and immobilization of ligands for membrane receptors.

What transcends his scientific accomplishments was the warm and inspiring influence that Nate Kaplan had on those who worked with him. Young investigators from the world over were drawn to his laboratory, where they were accommodated with excellent research problems, excellent facilities, and the qualities of the man himself. These qualities were a combination of warmth, understanding, keen insight, and a contagious enthusiasm for biochemistry which permeated all of his professional activities. Throughout the years from 1945 on, Goldie was supportive, not only as a loving wife, but also as a companion who accompanied Nate to meetings the world over. She proofread and gave

finishing touches to the numerous manuscripts that crossed his desk. Nate shared with Goldie the many problems of a varied career and she responded with good advice for calm and reason in seasons of turbulence. Nate's interests in biochemistry were very broad and included biochemical anthropology, the topic of a popular course that he taught. In the late 1960s and 1970s, partly out of his enthusiasm to learn more about particular aspects of biochemical anthropology, many of his family vacation journeys with Goldie and their son Jerrie ended up in remote places where he could observe, firsthand, social practices that had evolved in response to biochemical defects in the food supply or in the human population itself.

During his career, Nate Kaplan had enormous impact on the field of biochemistry and profound influence on his many associates in this country and abroad. He is deeply missed.

Martin Kamen has written a brief account of Nate's stay at Berkeley. "At the Radiation Laboratory, led by the charismatic Ernest Laurence, the Cyclotron was pouring out an unprecedented flood of radioactive isotopes for use in biological research. Some of his prospective customers were concentrated in the western end of the campus—the Life Sciences Building. Among them were soil scientists (H. A. Barker and W. Z. Hassid), bacteriologists (notably M. Doudoroff), and other groups in biochemistry (under the aegis of David Greenberg) and physiology (led by I. Chaikoff)." This was where Martin first met Nate. In the meantime, Nate had moved from the Chemistry Department to Biochemistry, where he was working with Greenberg on phosphorous metabolism for his Ph.D. dissertation. Here he met Doudoroff, Hassid, and Barker. Barker has recalled these events. "Doudoroff had been studying the utiliza

tion of various sugars by *Pseudomonas sacchraphila* so called because it oxidizes sucrose much more rapidly than the constituent monosaccharides, glucose and fructose. Suspensions of dried cells of the organism were found to decompose sucrose more rapidly in the presence than in the absence of inorganic phosphate." Doudoroff, Kaplan, and Hassid worked together to demonstrate that glucose-1-phosphate and fructose were the products of sucrose breakdown. These results were published in 1943 in the *Journal of Biological Chemistry;* the article was Nate's first scientific publication.

After Nate received his Ph.D., he went to work with Fritz Lipmann at the Massachusetts General Hospital. Mary Ellen Jones has recounted these events. "At the time Lipmann's laboratory was small, only three people, Lipmann, Kaplan and a technician/secretary, L. Constance Tuttle. Lipmann had recently shown that the acetylation of sulfanilamide by pigeon liver extracts required a heat-stable factor which was autolyzed when the extract stood for several hours at room temperature. Kaplan began to purify the factor, now known as coenzyme A, using the restoration of enzyme activity to aged extracts as a measure of the amount of cofactor present." Nate, working with G. David Novelli and Beverly Guirard, soon found that the cofactor contained pantothenic acid, and later Shuster and Kaplan found that a phosphate group was attached to the 3¢-hydroxyl of the ribose ring of adenylic acid. In the meantime Kaplan and Lipmann found that most of the pantothenate in tissues was present in coenzyme A. The time Nate spent with Lipmann was a great learning experience and influenced Nate's outlook on scientific research for the rest of his life.

Nate Kaplan and I had been friends and colleagues since 1950. The nature of our meeting was very unusual. In

1947, Mr. John Lee Pratt had donated a sum of money to start a center for the study of trace metals in biological systems at the Johns Hopkins University. I was an assistant professor in biology at the time, but for some reason, Dr. E. V. McCollum convinced President I. Bowman that I should be given the charge to describe what this new center should do scientifically. At the time very little dynamic biochemistry was being taught, either in the graduate or medical schools in the United States. In other words, there was a large gap between European–English biochemistry and that of the United States. Only in 1941 when Lipmann and Kalckar published their famous reviews was ATP introduced widely in the U.S. biochemical literature. Phosphorus was a macronutrient! I was convinced that a new approach looking at the dynamic functions of metals in enzyme systems was the way to go, so I wrote up a four-or five-page outline of the program and gave it to Dr. McCollum. Six outstanding nutritional scientists from England, Australia, New Zealand, and the United States, and two enzymologists were invited to Hopkins to discuss this proposal. Interestingly enough, they agreed with the plan and, subsequently, I was asked to propose names for the directorship. I submitted the names of a number of outstanding enzymologists, including Dr. Sidney Colowick. Unfortunately, most were not interested in the function of trace elements in enzyme function and metabolic processes in general and, unfortunately, right after the war there were not many enzymologists looking for jobs, so we had no takers. After a year things appeared to be desperate, and Dr. McCollum, without consulting me, convinced President Bowman that I should be named director of the center, which we subsequently named the McCollum–Pratt Institute. Within a few weeks after I assumed the directorship, I had a call

from Dr. Stanley Carson at the Oak Ridge National Laboratories indicating that Dr. Colowick might be available. I immediately called Sid and made him an offer. The next day he returned my call and said he was interested if he could bring a young associate named N. O. Kaplan. I invited both of them to visit Hopkins, and they arrived within two days. That was the first time I met Nate Kaplan. Within two weeks I had all the paperwork finished and approved by the Academic Senate, the dean, and the president. To this day it is the fastest appointment that I have ever made, and they readily accepted. It is interesting that there are no letters on file concerning the qualifications of Nate, only a phone call from Fritz Lipmann and Mike Doudoroff. What a wonderful way to make an appointment; they were two of the best I ever made.

The original members of the McCollum–Pratt, in addition to myself, were Kaplan, Colowick, the late Alvin Nason, Henry Little, and Robert Ballentine. We were housed in a greenhouse on the Homewood campus. There were two large laboratories on the first floor. Nate and Sid shared one, and the other three shared the second. My labs were in the Biology Department about two minutes from the greenhouse. It was not the best of arrangements as we know them today, but it turned out to be a very scientifically productive environment. Housed in the basement was Dr. Elmer V. McCollum, who had just retired as chairman of the Department of Biochemistry in the School of Hygiene at Johns Hopkins. He and Nate became very close friends. With Nate's interest in history, he spent hours in the basement learning all he could about the history of nutrition and biochemistry from Dr. McCollum. It is interesting that the year that Warburg discovered the requirement of Mg^{2+} for the triose phosphate dehydrogenase was

the same year that McCollum demonstrated it as an essential micronutrient in animals. In this environment, Nate was "all ears," and it had a great influence on his teaching of biochemistry in later years.

I never asked Nate or Sid to be concerned with trace metal biochemistry, but I was reasonably sure how it would work out, because when bright people work side by side, things happen. The plan was to bring young postdoctoral students from laboratories where nutritional trace element work was being performed. Dr. Alvin Nason and I agreed to work with them on enzymological problems. At the time, I had a number of nitrate mutants in *Neurospora* that could reduce nitrate to nitrite, but the latter would not be further metabolized. There were reasons to suspect that molybdenum might be involved in the nitrate reductase reaction, so we invited Dr. D. J. D. Nicholas from Long Ashton, England, to join us in this research; he was an expert on removing trace metals from proteins and growth medium. After about six months, we had drawn a blank. Then one day, while talking with Nate, he suggested trying FAD instead of FMN as an electron donor. Fortunately, Nate had some FAD in the deep freeze, and the first time we tried it, we found that TPNH (NADPH) would reduce the nitrate to nitrite. This, of course, led to the eventual discovery that reduced FAD was the immediate electron donor for the reduction of molybdenum and subsequently the reduction of nitrate. So Nate was into trace metal metabolism! Demonstrating that the proximity of two types of investigators often leads to an exchange of ideas, techniques, and materials that is of great mutual benefit.

This was one of Nate's great assets. He was willing to help anyone in need—graduate students, postdocs, faculty and visiting scientists, and an undergraduate looking for a

problem. It is interesting that Dr. David Greenberg recalls that when Nate worked with him on war research Nate "had no interest in mineral metabolism. He used ^{32}P to study various aspects of carbohydrate metabolism."

Molybedenum was not the only trace element problem that Nate worked on. At the time, Al Nason was working on tryptophan metabolism in the zinc-deferent *Neurospora*. Without going into detail, this led to the discovery of an interesting and potent DPNase, which increased dramatically in zinc-deficient mycelia. It turned out to be very stable and easy to purify, in contrast to the mammalalian DPNases.

Following the discovery of *Neurospora* DPNase, Nate and Sid continued their work together on various aspects of this and other enzymes concerned with DPN, particularly the exchange reactions involving ADP ribosyl enzyme and various nicotinamide derivatives. The best known of these was the acetylpyridine analog, which was very active as a coenzyme in many dehydrogenases. The ratio of the activity with DPN and the acetylpyridine analog was a very sensitive measure of the differences of various dehydrogenases in different species and in different organs. I believe this work was the basis for Nate becoming interested in evolution. He studied the isozymes of various dehydrogenases and noted their changes during development. Probably his best-known work in the area was concerned with the M and H isozymes of lactic dehydrogenase, this latter work leading to his interest in cancer metabolism. It was from this interesting work that Nate really became a biologist. Working on lactic dehydrogenases from various crabs, he found that the horseshoe crab (*Limmulus*) did not fit the general properties of other crabs. Fortunately his asso

ciate, Margaret Ciotti, pointed out that *Limmulus* belonged to the spider group.

When Nate moved to Brandeis, he was very excited by the challenges of setting up a new department. He once wrote, "Johns Hopkins had been very good to me in allowing me to develop my potential." As W. P. Jencks recalls, "In 1957 Nate O. Kaplan and Martin Kamen founded the Graduate Department of Biochemistry at Brandeis. Louis Rosenstiel, who had been the head of the Schenley Corporation for many years, was interested at this time in supporting a research institute dedicated to research on a form of cancer. President Sachar, the founder of Brandeis, explained to him that the best way to learn about cancer was to study the broader problem, in particular to do basic research. It quickly became clear that the best way to do basic research was in an institute of biochemists, and the best institute of biochemists could be established in a small, new university. Such a group would function best with graduate students. Thus, it was inevitable that the Graduate Department of Biochemistry should be established. Mr. Rosenstiel was one of the most perspicacious donors anywhere, a rare individual who preferred to "buy brains, not bricks." He gave $1,000,000 to start the department and supplemented this later with additional support to the department and university. Kaplan and Kamen were able to turn this investment into a 2,300 percent profit from various sources, to provide a strong base of support for the department.

At that time, Brandeis University was less than ten years old. The administration was housed entirely in a small white house, the library was in the former stable of the Middlesex Veterinary School and the whole School of Science was in one large glass box, the Kalman Building. The

entire Biochemistry Department moved into two teaching laboratories in this building and started to do research. Nate and Martin immediately brought in a flock of productive graduate students, postdoctorals and physicians from all over the world to work with the younger as well as the older members of the department. These members consisted at this point of Mary Ellen Jones, Lawrence Levine, Larry Grossman, Morris Soodak, and William Jencks. In addition to the founders, Gordon Sato, Helen Van Vunakis, Thomas Hollocher, John Lowenstein, Robert Abeles, Gerry Fasman, Robert Schlief, Al Redfield, and a number of others joined the department later.

After a year and a half, the department moved into its own Friedland Building, where it rattled around actively, expecting to have space for its activities into perpetuity. But in a few years Friedland was full and bulging with activity. This happened in spite of the decision of the department to remain small and maintain the communication, collaboration, and cohesion that had contributed so much to its success. So the Kosow–Wolfson–Rosensweig building was built, with the expectation that it should provide enough space forever. But it also filled rapidly and some members of the department were housed later in the Rosenstiel Basic Medical Sciences Research Center building. Louis Rosenstiel had given another large gift to the university to establish this center, which contains faculty members from several of the science departments at Brandeis in addition to biochemistry.

Initially the department made idealistic plans for idealistic students who would know how to plan and build their careers in science. Basic research was encouraged in all ways and directions. Nate brought with him the laboratory rotation program from McCollum–Pratt and all first-year

students spent six-week rotations carrying out six different research projects in six different laboratories during their first year. Several courses were offered, but there were few requirements and examinations. It took several years for the inherent weaknesses of human beings to reveal themselves; then some examinations and requirements were reluctantly established. Still, the tradition of research-oriented department has been maintained successfully to the present.

In accomplishing all of this Nate Kaplan played a major role in establishing Brandeis as a high-level research-oriented university in the sciences. By action and example, he contributed in a major way to the buildup of the science faculty and facilities for all disciplines, so that the university is now recognized as one of the few leading universities that is both highly successful but small enough so that communication is easy and the bureaucracy is (relatively) small.

Nate's ability to lead, plan, negotiate, and raise money from many willing and generous sources made of all this possible. Most departmental business was conducted in the hall. It is hard to resist change or start theoretical-political arguments while standing in a hall, so that this worked very well. He demonstrated an uncanny ability to go in the right direction and to find out how to get there. Numerous crises arose as new research programs grew in a new university, but he found ways to deal with these successfully and build up an infrastructure that made productive research and teaching possible.

How did Nate make all this work so well? It would be hard to predict that it would. It rested on his ability to sense what needed to be done and how to do it, without ever seeming to plan or calculate. He built the support of

the entire department and in turn demonstrated unwavering support and loyalty to his students, postdoctorals, and faculty.

All of this time he somehow also led a large and diverse research group that studied the biochemistry of DPN (not NAD) and many other subjects. This included highly productive students at all levels, from high school to professors of medicine. The many scientific contributions of this group are well known and are too extensive to review here.

When he went to the University of California at San Diego (really La Jolla), he left a successful department that had passed through its adolescence and was able to continue successfully on its own. However, no one has ever replaced the leadership and support that he provided so well.

Morris Friedkin and William Allison recall Nate's return to the West Coast. "After having developed a world class Department of Biochemistry at Brandeis, Nate was drawn back to the West Coast, to the University of California, where he had begun his career. It wasn't easy to leave Brandeis where, together with Martin Kamen, he had been instrumental in helping a young school get its feet on the ground. In leaving Brandeis he would be giving up the day-by-day personal interactions of a small institution for the milieu of a large university."

In the mid-1960s, Nate vacillated between going to the San Francisco Medical Center or to La Jolla where a new campus and medical school were being developed. In 1968, he opted to join Martin Kamen in the Department of Chemistry at UCSD, where an innovative relationship between the basic departments of chemistry and biology and the medical school was envisaged. At UCSD, there would be no Department of Biochemistry. Colleagues with the same

scientific interest would be scattered through many buildings.

It wasn't surprising that when Nate wrestled with the complexities of the academic structure of UCSD, nostalgia of the good old days at Brandeis would well up. This explained Nate's great joy when he returned to Brandeis in 1982 to receive an honorary degree. At UCSD, Nate continued his studies on various lactate dehydrogenases. He sought for greater insight into the structure and properties of the pyridine nucleotides (Nate was never comfortable calling DPN by its newfangled name: NAD). With students and colleagues he utilized NMR with great ingenuity. These are but a few examples of the many directions Nate's fertile and lively imagination carried him.

Nate was attracted to a medical school environment because of his interest in chemotherapy dating back to the 1950s. Because of his findings with nicotinamide derivatives, he thought an analogue of NAD might interfere with the cellular metabolism of cancer cells. Although such compounds were found that were effective against experimental mouse tumors, they proved to be too toxic. However, Nate's objective to develop practical chemotherapeutic agents did not wane. Together with Gordon Sato, Nate established a very successful athymic mouse colony. A small building was designed not only to house the athymic mouse colony, but also to provide facilities for tissue culture work with many human cancer cell lines.

Nate departed from the basic arena of enzyme mechanisms to enter a new field in which a variety of techniques associated with the disciplines of immunology, virology, electron microscopy, and cellular biology were utilized. Nevertheless, he had an abiding love for biochemistry, believing strongly that biochemistry had become the language of bi

ology. He wrote, "students should not lose sight of the eloquence of the experiments of Warburg because it is the same eloquence which is inherent in the isolation, characterization, and manipulation of genes."

Nate's broad experience was appreciated worldwide. Because of his unusual acumen and intuition, his advice was sought after by scientists at universities and industries worldwide.

Even when he knew his days were numbered, he threw himself into long-term projects. To the very last, he was fascinated with the dynamics of change, be it an enzymatic event, an evolutionary process, or the migration of people.

Nate had an enduring interest in the history of science, in biochemical anthropology, and in the communication of ideas. He has left a heritage of scholarship and of research into the chemical nature of life documented in hundreds of articles.

Upon reading Nate's contributions to science and reflecting on his outlook of those factors that influence the training and development of any scientist, it is apparent that he had high praise for the research teachers responsible for his education. In the early years, it was Fritz Lipmann who had a major impact on Nate's scientific perception. Nate learned how to keep an eye out for the unexpected and not hesitate to change the goals of a research problem to accommodate a new situation. In this way, Nate always has a number of incomplete problems which he gave to postdoctoral or graduate students. It was natural for him to do this—a main reason he was so well liked by students at all levels.

As a graduate student at Berkeley, Nate had the opportunity to learn about radioactive phosphate from Professor D. M. Greenberg. He studied the turnover of ATP and the influence of insulin and other factors on the acid soluble

phosphate in liver. He submitted these results for his Ph.D. dissertation in 1943.

Nate also had the fortunate opportunity to attend a microbial metabolism course given by H. A. Barker. From Nate's description, it must have been very much like Van Niel's course offered at the Hopkins Marine Station. While enrolled in this course, Lipmann's article on phosphate bond energy appeared in Volume 1 of *Advances in Enzymology* (1941). This article, along with Barker's course, had a tremendous influence on Nate and is probably the reason he decided to continue his career in biochemistry. He gave credit to Barker for getting him into Lipmann's laboratory after the war. While at Berkeley, Nate also became friends with W. Z. Hassid, Sam Ruben, Martin Kamen, and Michael Doudoroff. It was these interactions that led Nate to work on sucrose metabolism in *Pseudomonas sacchraphila*.

When Nate was associated with the Manhattan Project, he was sent to Detroit for several months to carry out a special assignment. He met Dr. Maurice Franks, who was an instructor in medicine at Wayne State Medical School. Dr. Franks was an internist with a special interest in diabetes, and he and Nate induced diabetes in rats by the use of alloxan. They were able to show that the diabetic state that developed was accompanied by a marked drop of ATP in the liver and an increase in inorganic phosphate. It was striking that a very large amount of phosphate was excreted. This suggested that it might be worthwhile to investigate phosphate levels in diabetic coma. Fortunately, Dr. Franks had access to human patients through the clinic at the emergency room in Detroit City Hospital. They learned that severely comatose patients exhibited a lower serum inorganic phosphate that coincided with an increase in urinary phosphate. They administered large doses of inor

ganic phosphate to these patients and, in the presence of insulin, the phosphate levels approached normal and excretion decreased. They concluded that inorganic phosphate was helpful in the treatment of coma. Phosphate treatment has since proven to be of some value in comatose patients.

Nate left Dr. Lipmann's laboratory to join the Department of Biochemistry at the University of Illinois Medical School in Chicago, where he became a colleague and very close friend of Sydney Colowick. His stay at Illinois was a brief one and not very productive. Both he and Sid left Illinois to come to the McCollum–Pratt Institute at Johns Hopkins University. Nate started a project at Hopkins involving the study of the mechanism of Coenzyme A action in pyruvate oxidation. There was conclusive evidence from work in Lipmann's laboratory that CoA was involved in the oxidation of keto acids, not only in microorganisms, but also in plant and animal tissues. During the course of these studies, Nate used cyanide to inhibit respiration. An excess of NAD was added in order to measure the reducing equivalents generated from pyruvate dehydrogenases under these conditions.

During the initial experiments, Nate observed NADH could be formed when pyruvate was oxidized but the same results were obtained when the enzyme preparation was omitted. In collaboration with Sydney Colowick it was determined that cyanide was adding to NAD to yield an adduct which has UV adsorption in the same region as NADH. They characterized the NAD cyanide compound and found it to be a good method for measuring oxidized pyridine nucleotides. NADP also could be determined by the cyanide reaction. They later learned from the literature that Meyerhoff and his associates had also observed such a reaction.

The cyanide adduct was a good qualitative measurement of the quaternary pyridine ring. They used this method for determining the oxidized forms of the coenzyme in extracts of various organisms and tissues. During this time, Alan Nason was working on zinc deficient *Neurospora* . The deficient *Neurospora* showed very little glycolytic activity, and alcohol dehydrogenase was not present in the cells. Reduction of NAD could not be demonstrated even upon addition of known dehydrogenases to the extracts. Discussing the problem with Nason, Nate believed there was a possibility that NAD may be hydrolized and was unavailable for reactions in the deficient *Neurospora*. They used the cyanide method to measure NAD levels in the zinc-deficient *Neurospora* and found the amount was negligible when compared to controls. Adding exogenous NAD, they observed a rapid destruction of the coenzyme. They continued their work and detected an enzyme which could split NAD at the nicotinamide ribosidic linkage. Nate and Sid called it NAD adenase. This enzyme was later named NAD glycohydrolase. The enzyme was a very potent one and present in relatively large amounts in zinc-deficient *Neurospora*. The coincidence of Nason being present in the institute and working on deficient organisms, particularly of zinc, was an important beginning in Nate's lifetime interest in the pyridine nucleotides.

During these studies it was observed that NAD hydrolysis by the enzyme was not complete as measured by the cyanide reaction; however, when assayed enzymatically using alcohol dehydrogenase all the reactive coenzyme was destroyed. This indicated a possibility that a molecule was present in the preparations that had the nicotinamide ribose linkage but was not subject to attack by NADase. Large amounts of NAD were hydrolyzed with the *Neurospora* NADase

until all the biological activity had disappeared. They attempted the isolation and the purification of the compound, which was resistant to the action of the NADase but still maintained a reaction with cyanide. They were successful in isolating a compound that proved to be the alpha isomer of NAD. This material exhibited very low or no activity with most dehydrogenases. It was noted that most commercial preparations of NAD, at that time, contained approximately 15 percent of alpha NAD. They were also able to cleave NADP and obtain pure adenosinediphosphate ribose using the *Neurospora* NADase. When Nate and Sid studied NADase isolated from mammalian sources they found some extremely interesting differences. The animal enzyme was inhibited by nicotinamides whereas the *Neurospora* enzyme was quite insensitive to the free vitamin. Later Leonard Zatman observed that radioactive nicotinamide could be incorporated into NAD and demonstrated that an exchange reaction was occurring. This led Nate and Sid to study other pyridine compounds and conclude that many similar pyridines could undergo exchange reactions to form new derivatives of NAD. One of the more interesting reactions was the exchange of the isonicotinic acid hydrazide to form an isonicotinic acid hydrazide analog. Using the exchange reaction, Nate was able to prepare the acetyl pyridine derivative of NAD, which turned out to be extremely important as it was the compound used later by Nate to compare the biochemistry of various dehydrogenases. The reduced form of the acetyl pyridine NAD had an absorption maximum at 375 nm as compared to 340 nm for NADH. Thus, they could independently study various dehydrogenases. This, of course, eventually led to the important research on isozymes.

It was during this same time period that Nate and Sid

decided to begin studies on oxidative phosphorylations in the microbe *Pseudomonas aeruginosa*, a well-known bacteria with a very high oxidative capacity. Kornberg had previously shown that extracts of these organisms contained an NADP-isocitric dehydrogenase as well as a second dehydrogenase that used NAD as the electron acceptor. Sid and Nate made the interesting discovery that a transfer of hydrogen from the NADPH to NAD was occurring when both pyridine nucleotides were present in the reaction mixture. It was this discovery that led to many efforts to characterize the transhydrogenase that was obviously present in the system. They were able to demonstrate that this was a direct hydride transfer. Here again the various analogs of NAD were used extensively, particularly the thionicotinamide analog. This compound had an absorption maximum around 400 nm, was actually quite yellowish, and could be observed without the spectrophotometer. The work on NAD and NADP and the analogs, which they were able to make by the exchange reaction, formed the basis for an intense collaboration between Nate and Colowick concerning the function of these coenzymes in various dehydrogenases.

When Nate moved to Brandeis he began extensive work on isozymes. He was able to show that the heart and muscle lactate dehydrogenase of a given species were quite different using NAD analogs. Nate found that the heart enzyme of one species was much more closely related to the heart enzyme of another species as compared to the muscle enzyme of the same species. This led, in collaboration with a number of workers, to the study of changes in lactate dehydrogenase during development in chickens. He began to investigate the type of LDH that occurred in the embryonic chick breast muscles and was surprised to find that the enzyme isolated from muscle was actually the heart

type LDH, as determined by immunological methods. He observed that during development the genes for the M types were being expressed at an increased rate and it became the principal LDH type at the time of hatching. Immediately after hatching, there was a great increase in the LDH, so that the breast muscle of the chicken is largely M4 enzyme with traces of H4 present. In contrast, the embryonic chick heart contained pure H4 enzyme. A connection was made to an observation that Markert had reported with regard to the fact that LDH was actually a tetramer. Their results supported the view that there were five forms of LDH consisting of the two parent types, occurring as H4 and M4, with three intermediate hybrid types, which migrated predictably in between H and M forms on polyacrylamide gels.

At this time, a young postdoc by the name of Alan Wilson joined Nate's laboratory. He was interested in molecular evolution and saw the potential of studying the LDH system. From these studies many interesting taxonomic and enzymatic relationships were observed. For example, the flatfish, halibut, flounder, and sole have only the anaerobic type of LDH (M4) in their tissues as adults. Since they bury themselves in the sand and live in an anaerobic environment, one can see why the M enzymer is present in the heart of these fish. When the flatfish larvae hatch they are free-living forms. They have one eye on each side, but at the time when one of the eyes move from one side to the other there is also a change in the lactic acid dehydrogenase. The young fish have the H type present in heart and other tissues and at the time of the eye movement there is a change to the M form. When Nate and Alan examined a number of invertebrates, they found that the arthropods, particularly the lobsters and crabs, had a very unusual LDH.

The rate of enzymatic lactate oxidatin with NAD was very slow, but this group of arthropods had high activity with the acetal pyridine analog of NAD. It was at this same time that studies on the LDH's in horseshoe crab (*Limmulus*) were started. They thought this organism was a crab and, upon examination, found to their dismay that this LDH reacted very well with the natural coenzyme in contrast to other crabs. Margaret Ciotti was working with him and had some knowledge of elementary zoology. She indicated to Nate that *Limmulus* was not a crab but belonged to the spider family. An examination of spiders, scorpions, and tarantulas revealed that all had enzymes similar to horseshoe crab. It soon became apparent to Nate that the horseshoe crab was related to the spider species and not to the lobster-crab group. It was very surprising to Nate that he would be able to classify an organism using enzymological techniques which agreed with the taxonomic classification. Another interesting aspect of this work was that the *Limmulus* enzyme would not work with pure L-lactate. The enzyme was actually isolated and purified using a DL mixture to assay the activity. It was found that pure L-lactate was not a good substrate but that D-lactate was very effective. It turned out that the LDH for *Limmulus* was D-LDH. This was surprising, because almost all animal LDH's are of the L-configuration and are tetrameric.

An interesting sidelight to these studies occurred when they were working with LDH's from haddock and cod. Nate received a telephone call from the Bureau of Fisheries in Boston inquiring if they could distinguish between haddock and cod using their techniques. There was a suspicion that the filets being sold in the market were not haddock but mostly cod. Since haddock sold at four times the cost of cod, the Bureau of Fisheries was pressured to find

out what was going on. As it turned out, when the two biochemists investigated the frozen filets, most of them contained almost exclusively cod muscle LDH. This led the Food and Drug Administration to obtain an injunction and confiscate all the frozen filets. Today all the filets of haddock are tested for the presence of cod. It is interesting that these observations were put into the *Congressional Record* as an indication and illustration of how molecular biology could be of value to the average consumer.

Following these extensive studies on lactic dehydrogenase, Nate turned his attention to many other enzymes including creatinekinase, malate dehydrogenase, transaminases, and glyceryl phosphate dehydrogenase. He continually looked for enzymatic problems that would help in understanding the molecular evolution of isozymes. These problems necessitated new techniques in protein structure, and many physical approaches were explored such as fluorescence, circular dichroism, and nuclear magnetic resonance.

At UCSD Nate's interest continued on the characterization of various enzymes and was particularly concerned with their evolution. Exposure to Professor Ephraim Katzin at the Weizman Institute in Israel and Dr. Klaus Mosbach stimulated great interest in immobilized enzymes, particularly how these could be used to study the action of chemotherapeutic agents.

In studying the function of immobilized hormones and chemotherapeutic agents, they turned their attention to the use of tissue cultures. Nate renewed his collaboration with Dr. Gordon Sato, who had just moved to La Jolla from Brandeis. Sato had obtained several athymic mice and was planning studies on these animals. Since these mice lacked a thymus, human tumors were not rejected and tumor xenografts could be grown in the animals. This impressed Nate as a potential for studying chemotherapy in animals

as well as investigating the metabolism of the human tumor. These experiments led to some interesting results but not much of any practical interest. He soon came to the conclusion that although the athymic mouse colony was important in a number of studies, they didn't seem to lend themselves to the treatment of human cancer.

Nate was still working in the broad area of immobilized enzymes, athymic mice, and chemotherapeutic agents at the time of his death.

THE QUOTATIONS BY William Allison, Morris Friedkin, Martin Kamen, H. A. Barker, David Greenberg, Mary Ellen Jones, and W. P. Jencks were taken from a memorial publication dedicated to Nate, and appeared in *Analytical Biochemistry* 161:229–44, 1987.

HONORS AND DISTINCTIONS

PROFESSIONAL (ACADEMIC) POSITIONS

1940–42
Assistant Biochemist, University of California, Berkeley
1942–45
Research Chemist, Manhattan Project
1945–50
Associate Research Biochemist, Massachusetts General Hospital, Harvard Medical School
1950–52
Assistant Professor of Biology, McCollum–Pratt Institute, The Johns Hopkins University
1952–56
Associate Professor, The Johns Hopkins University
1956–57
Professor, The Johns Hopkins University
1957–68
Professor of Biochemistry and Chair, Department of Biochemistry, Brandeis University, Waltham, Massachusetts
1968–86
Professor of Chemistry, University of California, San Diego

HONORS AND AWARDS

1946
Sugar Research Award
1948
Nutrition Research Award
1952
National Science Foundation Travel Fellowship
1953
Eli Lilly Award in Biochemistry

1960
Commonwealth Travel Fellow
1964–65
John Simon Guggenheim Fellowship
1970
National Academy of Science
1971
Honorary Fellow Harvey Society
1971
American Academy of Arts and Sciences
1975
John Simon Guggenheim Fellowship
1976
American Association for Clinical Chemistry Award
1982
D.Sc (Hon.), Brandeis University
1983
Fogarty Scholar 1984 in Residence

SOCIETIES

American Association of University Professors
American Chemical Society
American Society of Biological Chemists
American Society of Cell Biology
American Society of Microbiology
American Society for Cancer Research
American Cancer Society
American Institute of Nutrition
Biophysical Society
Biochemical Society
Sigma Xi

EDITORIAL ACTIVITIES

Editor in Chief, *Methods in Enzymology*, 132 volumes
Editorial Advisory Board:

Molecular Pharmacology
Biochemical Genetics
Biochemical Medicine
Chemico–Biol Interactions
Bio–Organic Chemistry
Journal of Insoluble Matrices
Journal of Solid–Phase Biochemistry
Analytical Biochemistry
Journal of Applied Biochemistry

OTHER PROFESSIONAL ACTIVITIES

Member, National Academy of Science Committee for the Overview of the National Institutes of Health

Chairman, the University of Chicago Biomedical Sciences Advisory Committee

Special Senior Consultant to the National Cancer Institute

Member, the American Cancer Society Council Executive Committee

Member, the Oak Ridge National Laboratory Advisory Committee

Member, the Advisory Committee of the Rockefeller Foundation

Member, Review Committee, University of California, Berkeley

Member, Review Committee, Wichita State University

Chairman, National Research Council Advisory Committee to American Biochemical Journals

Member, United Nations Energy Council

Scientific Advisory Committee on Biochemistry and Chemical Carcinogenesis

Member, Publications Committee, American Society of Biological Chemists

Honorary Member, Consejo Superior de Investigaciones Cientificas (Spain)

Member, Scientific Affairs Committee, W. Alton Jones Cell Science Center

Member, Advisory Committee, Rockefeller Foundation

Member, Advisory Committee, Massachusetts Institute of Technology

Member, Advisory Committee, University of Pennsylvania

Member of Council, U.S. National Committee for the International Union of Biochemistry

Honorary Editor, *Journal of Applied Biochemistry*

Honorary Editor, *Bioorganic Chemistry*

Co–Chairman, Editorial Committee, *Analytical Biochemistry*

Member, Investigational Review Committee of Scripps Memorial Hospital

Adjunct Professor and Consultant to Mt. Sinai School of Medicine

Member, Advisory Committee, the Massachusetts General Hospital

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1944 With David M. Greenberg. Studies with radioactive phosphorus of the changes in the acid-soluble phosphates of liver. *J. Biol. Chem.* 156:511–24.

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WILTON MARION KROGMAN

June 28, 1903–November 4, 1987

BY WILLIAM A. HAVILAND

IN THE DEVELOPMENT of physical anthropology in North America, few have been as influential as Wilton Marion Krogman. Until 1980, virtually all professionals in this field with degrees from institutions in the United States traced their academic lineage either from Ernest Hooton at Harvard or to Krogman, first at the University of Chicago and later at the University of Pennsylvania.

His initial professional publication, which appeared in 1927, was the first comprehensive review of research on primate dentition and is regarded as a cornerstone in the subfield of dental anthropology, in which Krogman was active throughout his long career. In subsequent papers he contributed as well to osteology, racial studies, genetics, medical anthropology, paleoanthropology, constitutional anthropology, and human engineering. His major interests and most important contributions were, however, in the areas of child growth and development and forensic anthropology. The latter specialty was practically invented by Krogman, and his book *The Human Skeleton in Forensic Medicine* (1962) remains a definitive source for medical and police professionals alike. Similarly, the standards developed in Krogman's growth studies are used by health

professionals throughout North America to evaluate the growth of children.

PERSONAL HISTORY AND EDUCATION

Born to Lydia Magdalena Wriedt and Wilhelm Claus Krogman in Oak Park, Illinois, Wilton (or Bill as he was commonly called) was one of four children, one of whom was a fraternal twin. Having emigrated from Germany, his parents were attracted first to Forest Park by the presence there of so many other German immigrants. With his brothers, Bill's father was a carpenter and builder, and in Oak Park they built the first house designed by Frank Lloyd Wright. He developed a reputation for perfection in his work and insisted in personally choosing each piece of lumber that he used. As he himself later realized, Bill was deeply affected by his father's rigorous standards of workmanship and the integrity that went into his work.

Although Wilhelm had only a grade school education, he absorbed the German cultural and national emphasis upon education, both formal (schooling) and informal (reading, going to public lectures, and so on). Whenever he went to downtown Chicago, as he frequently did to buy hardware and other materials, he almost always stopped by second-hand book counters. Thus, Bill grew up in a house surrounded by old books and journals, and remembered poring over books on Asia, Africa, and Europe at an early age, so that, as he put it:

> The peoples of the world passed before my eyes. I do not think it an overstatement to say that these formative years at home were important influences in my later interest in ethnology, archaeology and cultural anthropology.[1]

One event from Bill's early childhood that made a lasting impression upon him occurred when he was eight or

nine years old. As he described it, he and his twin brother Wes often pretended to dig for pirate treasure:

> One day, in a prairie area not too far from home . . . , we were about 3 feet deep when the spade struck a resistant object. We began to paw the dirt away with our hands or a piece of wood that was handy. The object was bone! A man? —"dead men tell no tales" we had learned—no, it was an animal skull, and that animal proved to be a horse. Horses were far more numerous in 1911–12 than they are today, so we had a good idea of the bony parts of such an animal: behind the head is a neck, then comes a "shoulder" and two front legs, then a long backbone, then a "hip" and two end legs, then a tail. With this framework in mind we slowly removed the dirt from the entire skeleton of a horse, lying on its side. We did not do a job which would win the approval of a modern archaeologist, but we did do a digging-out that attracted all the children in the neighborhood, as well as a few adults. . . . Here, I venture to say, was an early foray into future Comparative Anatomy, and even Physical Anthropology.[2]

Another important experience occurred when Bill went on to high school, something Wilhelm encouraged his twin boys to do even though he himself and his two older children had not done so. The need to earn money for books and other school expenses prevented young Bill from becoming involved in most extracurricular activities, although he did participate in the debating club, something that taught him to "think on his feet." At first, he was an A student, but then as a sophomore he began to lose ground. He himself described what happened next:

> My desk-room teacher, Miss Wilson, called me in one day, after school, and said, "Wilton, what is happening? You are not doing as well as you should!" I replied, "Oh, Miss Wilson, I work after school, I deliver papers in the morning, I work Saturdays. . . . I'm so tired after supper, I just fall into bed. . . . I'm sorry." She then said, with what I now realize was wonderful foresight, "Wilton, you are growing so fast (I grew 8" in 1917–18) that you are putting all of your energy in your body. Try your best to keep pace—even though slower—with your classmates." By the end of my Sophomore and the beginning of my Junior year I was Honor Roll once more. That wonderful, understanding, advice "carried" me along![3]

From the time he was a first grader, Bill was always at least half a head taller than his agemates, which often led to his being singled out to open or close windows, clean off chalk boards, or anything else where large size was an asset. Surely, both the trials and satisfactions associated with exceptional growth had something to do with Bill's later professional dedication to the study of child growth and development!

In September of 1921 Bill took the Competitive Scholarship Entrance Examination of the University of Chicago, placing first among 490 contestants. Having received a very religious upbringing in a German Baptist home, it was Bill's intention to study for the ministry. But in the course of his studies he was so deeply impressed with the presence of so many common elements in the world's religions that he decided to take a course in "Primitive Religion" in the anthropology department.

> It was thus that in my Sophomore year, in 1922, I first entered the field of anthropology. I never left it. I became convinced that Man was a part of an age-old evolutionary process. This meant that I could not, and did not, accept the concept of Man as an object of special creation by God. In 1922 to be an "evolutionist" was serious in the eyes of many religious peoples and groups. I asked to be released from my pre-divinity status. I told my Pastor and my Board of Deacons that I could not be a hypocrite: believe one thing, preach another. They understood. I told them, which I then believed and which I have always tried to practice, that I might live a ministry by deed and by precept, as I worked with young college people. My faith in God as the Creator of all life has never wavered.[4]

So it was that Bill became an anthropology major with minors in biology and geology-paleontology. Then in his senior year an event occurred that set him on his life career.

> In a course which was a praktikum in physical anthropology, Dr. Fay-Cooper Cole assigned me as a term paper the general subject of the anthropol

> ogy of the teeth. I began to study; my first studies were on the CopeOsborn theory of the evolution of the mammalian molar. Then I focused on the dentition of the Primates, including Man. As I read several names became passwords to me: William King Gregory, paleontologist; Milo Hellman, orthodontist, dental morphologist; T. Wingate Todd, anatomist and physical anthropologist. As I studied I moved on to jaws, to facial structure, to craniofacial complex, and—most important of all—the dynamics of growth and development, and of progressive changes in and through time.
>
> In the Summer of 1925 the Krogman's (mother, father, daughter, twin sons) took an auto trip from Chicago to New York City. The day after we arrived the others went sight-seeing, and I went to 57 W. 57th St. to see Dr. Hellman. With the brashness of youth I literally descended upon him! With me was my term paper, "Anthropological Aspects of the Human Teeth and Dentition." I gave it to Milo's Receptionist and she took it into his operatory. In about five minutes he came out and said, "Cancel the rest of my appointments for the afternoon [it was then about two-o'clock]. I want to talk with this young man." The upshot was that he told me to tidy up a bit here, a bit there, and submit it for the annual Morris L. Chaim Prize of the First District Dental Society of New York City for a contribution to dentistry, either in the area of basic science or clinical service. I recast the paper as Dr. Hellman suggested and submitted it to the Chaim Prize Committee. I won First Prize of $250.00, and the paper appeared in its entirety in Vol. 7, No. 7, of the *Journal of Dental Research* for 1927.[5]

One of the judges of Bill's paper was none other than Todd, who was impressed enough to stop by Chicago to meet him. As Bill told it:

> A few weeks later I received a letter from Todd which began, "The time for commendation has passed. Now . . . " and he then took the paper literally apart! Achilles-like I sulked in my room for three days before common sense took over. I realized that he had done the finest service a senior may render a junior: vigorous, objective and constructive criticism. I recast the paper.[6]

As a graduate student at Chicago, at the same time that he pursued his interests in physical anthropology, Bill gained archeological experience as he was placed in charge of the summer "digs" of the Archaeological Survey of Illinois. Then

in 1928–29, Todd arranged a fellowship for Bill at Western Reserve University, where he wrote his dissertation. In 1929 he received his Ph.D. from the University of Chicago.

PROFESSIONAL DEVELOPMENT AND CONTRIBUTIONS

Bill's first job was as lecturer at Chicago, filling in for Fay-Cooper Cole in introductory anthropology. The experience was a sobering one, as the following typical Krogman anecdote reveals:

> As a brand-new Ph.D. I felt impelled—as I'm sure many other beginning teachers felt—to pour all the vials of knowledge into one teaching quarter's bottle. For my lecture on kinship and marriage I chose the eight-class marriage system of the Warramunga, a tribe of Australian Aborigines. I began, "If A marries B, the children go to C, but if A marries D they go to B. . . . " and so on, with an increasing complexity that taxed my memory and just "lost" my captive audience. Finally, a young man in a carrying stage whisper said, "When does A go to P?" The spell was broken, the snarl reduced to absurdity, and I dropped the ill-chosen illustration. That lesson stayed with me, for I never again sacrificed clarity to unimportant obfuscation.[7]

In 1930–31, Krogman was a National Research Council fellow with Sir Arthur Keith at the Royal College of Surgeons in London. The purpose of this fellowship was to develop a man and a viewpoint, rather than to produce a specific piece of work. Besides having many a fine discussion with Sir Arthur, Bill studied biostatistics with Karl Pearson's son, shared a lab with Louis Leakey, and got to meet with most of the prominent English anatomists and physical anthropologists of the time. From all this came a deep appreciation of the kind of cooperative research in both multi-and interdisciplinary approaches that Bill was to put into practice himself later on.

In 1931 Bill Krogman became Todd's colleague at Western Reserve, as associate professor of anatomy and physical

anthropology. At this time, Todd's department was a kind of mecca for physical anthropologists, providing the opportunity to meet and interact with most of the current leaders in the field, including Ales Hrdlicka and Franz Boas, both of whom Bill greatly admired. While with Todd, three main avenues of teaching and research opened up for him. The first was longitudinal observation and analysis of the biobehavioral growth and maturation of Cleveland children. In Todd's laboratory there were two endowed research programs: the Brush Foundation (with Todd as director), which focused on the overall physical and psychological development of the child, and the Bolton Fund (directed by B. Holly Broadbent, Sr., D.D.S.), which focused on the faciodental growth of the child. Krogman was part of the team that helped perfect the Broadbent-Bolton roentgenographic cephalometer, the principle of which is now in worldwide use for serial growth studies and clinical evaluation by orthodontists.

It was also in Todd's department that Bill began craniological studies that extended into the 1940s. During these two decades he studied and reported on over 65 percent of all the skulls excavated in the Near and Middle East by the Oriental Institute of the University of Chicago and the University Museum of the University of Pennsylvania. These were from sites in Anatolia and Iran, covering a span of c. 4000 B.C. to 500 A.D. From these sites came crania in sufficient numbers to provide accurate determination of "racial" types in a time sequence.

Again with Todd, Krogman began to develop his interest in what later became known as forensic anthropology. Together, the two men pioneered the development of this anthropological specialty. Central to Krogman's advancement was access to two world-famous skeletal collections by

Todd: one of humans and the other of primates. There were 3,300 human skeletons (2,000 white, 1,300 black, both male and female) all carefully documented by age, sex, race, medical history, and so on. In the 1930s nearly 50 percent of the known gorilla, chimpanzee, orang, and gibbon skulls and skeletons were housed in Todd's laboratory. These were the basic materials that aided Krogman in learning cranial and skeletal variabilities with reference to age, sex, race, age changes in later life, and so forth. In 1939 he wrote the official F.B.I. "A Guide to the Identification of Human Skeletal Material" (widely considered to mark the beginning of forensic anthropology in the United States) and in 1962 the definitive volume, *The Human Skeleton in Forensic Medicine* (updated and revised in 1986).

In 1938 Krogman returned to Chicago with a dual appointment as associate professor of both anatomy and physical anthropology. This marked the beginning of his career teaching graduate students (a list of whom would read almost like a "Who's Who" of physical anthropologists). Needless to say, with a full load of teaching and lab work in both departments, Krogman's own research was slowed. Still, he did secure data on the somatometry and maturation of children at the university elementary school. Although the series was too small for definitive results, the effort did serve, in hindsight, as a kind of "dress rehearsal" for his later work at the University of Pennsylvania. Another accomplishment of his Chicago years was publication, in 1941, of *The Growth of Man*, a work of which he was particularly proud.

A year after his return to Chicago, Krogman was afflicted by failing vision in his right eye, along with an anesthetic cornea. Clinical tests and x-rays revealed an endocranial neoplasm, for which surgery was indicated. All this hap

pened at the opening of the fall quarter, with two anthropology courses to teach. Typical of the man, Krogman suggested finishing each course before his scheduled surgery. The students rose to the occasion, meeting evenings and weekends, so that exams and papers were completed and graded by mid-November when the surgery took place. Another setback occurred in 1941, when vision in his left eye weakened. Exploratory surgery revealed adhesions on the left optic nerve, which were removed. However, Krogman was left blind in his right eye and had no feeling or chewing muscles on that side of his face. Because of his partial blindness, colleagues and friends learned not to get too close on that side, lest a vigorous gesture on Bill's part might unthinkingly land a blow on them.

In 1947 Krogman was called to the University of Pennsylvania as professor of physical anthropology in both the Graduate School of Medicine and the School of Dental Medicine. Along with these went a position on the staff of the Children's Hospital of Philadelphia, an ex officio appointment in the university's Department of Anthropology and a curatorship in the university museum. In such a multifaceted position, Krogman was able to realize his research goals to a degree hitherto impossible. With the cooperation of the medical and dental schools along with Children's Hospital, he founded the Philadelphia Center for Research in Child Growth (later renamed, in his honor, the W. M. Krogman Center for Research in Child Growth and Development), for the purpose of developing standards of growth for normal healthy children of elementary and high school age, boys and girls, whites and blacks.

In 1948 Krogman began the longitudinal research required to develop such standards. With the cooperation of the Philadelphia Board of Education and the Archdiocese

of Philadelphia, the initial "normal" sample of 600 white boys and girls, all medically and dentally healthy and representing an ethnic cross section of the city's population, was enrolled. Thereafter, they were seen annually, and a series of black children were added some ten years later. This research was supported almost continuously until Krogman's retirement in 1971 by the National Institutes of Health and involved the participation of literally hundreds of graduate students in anthropology, dentistry, and medicine.

Although basically a research facility, the center served immediate practical purposes as well. All children receiving orthodontic care at the dental school were also enrolled at the growth center, and their growth data became part of their treatment plan. The center's data were also applied in cases of endocrine disorders, pediatric "growth failures," orthopedic problems, the faciodental development of children with cleft lip and/or palate, mandibular resections in oral surgery, and facial growth related to tooth development and eruption in pedodontics.

Krogman published the Philadelphia standards for the physical growth of male and female, white and black, children of elementary and high school age in 1970 as a monograph of the Society for Research in Child Development. The data are used by medical groups across the nation to diagnose and treat growth problems in children. Two years later he published one of his most widely known books, *Child Growth* .

"Retirement" is not the proper word to describe Bill's activities upon becoming professor emeritus at the University of Pennsylvania in 1971. He then moved to Lancaster, Pennsylvania, to become director of research at the H. K. Cooper (cleft palate) Clinic. Here, he continued research

ing and publishing on oral and facial development and growth. Finally, failing health forced him to retire from active service at the clinic in 1983. But even then he did not "quit"—in collaboration with M. Yasar Iscan, he revised his classic, *The Human Skeleton in Forensic Medicine*.

POSITIONS, SERVICES, AND HONORS

Bill Krogman admired Ales Hrdlicka, the "father" of American physical anthropology, for the unselfish way in which he worked for his discipline, and so Krogman also gave unstintingly of himself. From 1933 to 1945 he served as secretary of Section H (anthropology) of the American Association for the Advancement of Science, becoming chair of that section in 1948–49. In 1937–39 he served as president of the Central Section of the American Anthropological Association. Two years after Hrdlicka stepped down in 1942 as president of the American Association of Physical Anthropologists (a position he had held since its founding), Krogman assumed the post, which he held until 1949. From 1947 to 1951 he chaired the Committee on Research in Physical Anthropology of the National Research Council, and from 1955 until 1971 he was chair of the Department of Physical Anthropology in the Graduate School of Medicine at the University of Pennsylvania. From 1959 until 1961 he was president of the Society for Research in Child Development, having served on its Board of Governors in 1949–50 and again during 1957–59. Finally, in 1962–63, he served as president of the International Society of Cranio-Facial Biology.

Krogman's list of richly deserved honors includes Phi Beta Kappa, Sigma Xi, Omicron Upsilon (honorary dental society), and Alpha Kappa Delta (honorary sociology society). He was also an honorary member of numerous other

societies: American Association of Orthodontists, American College of Dentists (fellow), American Society of Dentistry of Children, Canadian Dental Society, New York Academy of Dentistry (fellow), Pennsylvania Dental Association, and the University of Illinois Orthodontic Alumni Association. In 1950 he was awarded the Viking Fund Medal in Physical Anthropology for outstanding contributions to the field. In 1958 he received the Drexel Institute Award for contributions to child growth and development. Election to the National Academy of Sciences came in 1966. A year later the Ohio State Dental Association bestowed on him its Callahan Award and Medal, and in 1969 he received the Ketcham Award from the American Association of Orthodontists. In 1971 Krogman's portrait was commissioned by the University of Pennsylvania to be hung in the School of Medicine. In 1973 he became honorary senior president of the Third International Orthodontic Congress in London. The American Association of Orthodontists conferred its annual award on him in 1982, and the American Cleft Palate Association followed with its honors award a year later. Honorary degrees were awarded by Baylor University (LL.D. 1955), the University of Michigan (D.Sc. 1969), and the University of Pennsylvania (D.Sc. 1979).

PERSONAL STYLE

When Bill Krogman described Todd as "one of the most inspirational men I ever knew . . . a human dynamo . . . sturdily built, literally exuding vitality . . . vigorous in action and speech" with "a strong will, but tempered . . . with an innate kindness and consideration and a ready wit,"[8] he might just as well have been describing himself. He was a big man physically, with a big voice and a "big heart." Students remember him as a superb teacher, whose lectures

were models of clarity, significance, and dramatic presentation. That they were liberally spiced with anecdotes and reminiscences served to make the material in them all the more memorable. Bill's teaching, however, was not restricted to the classroom. He was a readily accessible man, always willing to share his thoughts and offer advice. One learned from just being around him. I never knew a more supportive teacher myself, not just in terms of encouraging the research interests of students and providing jobs for them at the growth center, but in providing jobs for spouses as well, and helping students find jobs after completion of their degree work. He truly cared about his students.

The kind of feelings the man engendered in students and coworkers alike is captured well in this piece by the social worker of the Lancaster Cleft Palate Clinic:

> I was fortunate to be one of the many who benefitted from working with Bill and I stress the word *with*. Although he was my supervisor, he always treated me as a colleague. He was intellectually stimulating, encouraging his staff to aim high and supportive if they didn't reach their goal. He was totally selfless in that he always placed the goals of patients, clinic and the profession ahead of his self interest. During a time when professional selfishness and unethical behavior [are] too common, Bill Krogman displayed the highest standards of professional ethics and generosity. He was quick to share praise and honors with his supervisees [sic].[9]

To many outside his profession, Bill was widely known as "The Bone Detective." He was often consulted by the police and F.B.I. when bones were found in unexpected places, and he frequently spoke about his more interesting cases to interviewers from the popular media or to lay audiences. Few who heard him speak about the "Princes in the Tower" (based on the bones of two young boys discovered in an out-of-the-way part of the Tower of London, which he was called in to examine) or the "Improbable Case of the Cinder Woman" (based on the pseudohypothesis that the body

contains so much entropy that it can suddenly burst into flames) soon forgot the experience. In line with his "bone detection," Bill was also an avid Sherlock Holmes fan. A member of the Sons of the Copper Beeches, the Philadelphia branch of the Baker Street Irregulars, he wrote several articles on the stories of Conan Doyle (including "Sherlock Holmes as Anthropologist"). He also loved to "ham it up," appearing with deerstalker hat, curved-stem pipe, and magnifying glass.

As the latter indicates, Bill had the same kind of playful streak that has been noted in many another people of brilliance (the physicist Richard Feynman, for example, immediately springs to mind). He played as hard as he worked, and some of my fondest memories are of him chortling with glee as his son Mark and I prepared to fire an old Civil War salute cannon or as he ate raw mussels pulled up while fishing, drinking beer, smoking cigars, and telling stories (of which he had an endless store) on my boat off the coast of Maine. For twenty-seven years, he spent the summers with his second family (wife Mary Helen Winkley and sons John W. and Mark A; his first family consisted of Virginia Madge Lane, daughter Marian K.—now Baur—and son William L.) in Sargentville, Maine, where his chief delights were fishing, swimming, beach walking (with some sort of walking stick, he always looked like the archetypal beach comber) and the daily trek to the post office. Having been brought up in a close family himself, it is not surprising that Bill was devoted to his own family. Just how much his family meant to him is revealed, I think, by an experience I had just before I went into the field in 1959. I was talking to him in his office when, instead of talking about future career concerns, as one might expect with a graduate student finishing his course work, out of the blue

he said, "Well, you've now reached the point where you will want to think about starting up a family soon." I've never forgotten that.

IN ADDITION TO THE sources already cited, this memoir owes much to obituaries by Francis E. Johnston (*American Journal of Physical Anthropology* 80:127–28) and M. Yasar Iscan (*Journal of Forensic Sciences* 33:1473–76). Above all, I am indebted to Mary Krogman for supplying various newspaper clippings and other information, as well as to her and Mark for allowing me to share in their reminiscences about "The Old Professor." I value their continuing friendship highly and hope that this memoir will serve Bill Krogman's memory well.

NOTES

1. W. M. Krogman, Autobiographical Statement, National Academy of Sciences, Washington D.C., 1966, pp. 2–3.

2. Ibid, p. 3.

3. Ibid, p. 5.

4. Ibid, p. 8.

5. Ibid, pp. 9–10.

6. Ibid, p. 10.

7. Ibid, pp. 11–12.

8. W. M. Krogman, "Fifty Years of Physical Anthropology: The Men, the Material, the Concepts, The Methods," *Annual Review of Anthropology*, 5(1976):2.

9. Phil Starr, Letter to the Editor, *Lancaster New Era*, November 10, 1987.

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PHILIP LEVINE

August 10, 1900–October 18, 1987

BY ELOISE R. GIBLETT

PHILIP LEVINE'S life spanned a remarkable period of discovery and early development of blood group genetics and immunology that began with Karl Landsteiner's detection of the ABO blood group system in 1901 and ended during the 1980s with the retirement or death of nearly all of its major contributors. Long before the biochemical basis for inheritance was known, these pioneers made farreaching deductions from simple serological observations, confirming in human subjects the basic laws of inheritance and such phenomena as gene mutation, linkage, balanced polymorphism, and population differentiation. Similarly, although immunogenetics was in its infancy, they advanced many immunological principles and discovered the basis for certain diseases—notably hemolytic disease of the newborn. It was this discovery for which Philip Levine will best be remembered.

The sixth of seven children, Levine was born in Kletsk, Russia, in the summer of 1900; his family came to the United States in 1908. Many years later Levine said he still had vivid memories of the antisemitism to which his people were subjected. One has only to read the descriptions by other Jewish immigrants of life in Russia at the turn of the

century to understand why so many of them took refuge in this and other countries.

Levine's family settled in Brooklyn, where Philip was enrolled in the public schools. During his childhood he developed scarlet fever and subsequently nephritis, which required him to take long periods of bedrest and quiet. He described himself then as a loner, spending much of his time reading books on a wide variety of subjects. He also received rudimentary piano instruction from a sister and developed a great love of classical music, piecing together melodies on the piano. In addition, he began a lifelong interest in mathematics as a hobby, being especially fascinated by magic squares, the Fibonacci series of numbers, and similar phenomena. Although he had few athletic inclinations, Levine had a passion for baseball and could name long lists of players, their teams, and claims to fame. Not long before his death, Levine was taken to a baseball game, and his enthusiasm for the sport was still very evident.

Levine graduated from Brooklyn Boys High School in 1916 and received a B.S. degree from City College of New York in 1919, after a four-month enlistment in the Army that ended with the armistice of World War I. He then entered Cornell University Medical College. He had his initial experience with blood groups during his senior year, when he found that his red blood cells (subsequently typed as A_2) were hemolyzed by the serum of a type O fellow student. This observation suggested the possible danger of "universal donor" blood and formed the basis for his first scientific report, published in 1923.

During his third year in medical school Levine received a three-year New York state scholarship that enabled him, after graduation in 1923, to pay for postgraduate allergy

work under the directorship of A. F. Coca, a pioneer in that field and a founder of the *Journal of Immunology*. Levine's work with Coca was largely concerned with the newly discovered Prausnitz-Kustner reaction as observed in patients with hypersensitivity states. As a result of their work, Levine received his M.A. degree in 1925.

In the meantime, Karl Landsteiner had come to the United States (1922) at the invitation of Simon Flexner and set up a laboratory at the Rockefeller Institute. Levine was hired there in 1925 in response to Landsteiner's search for a young physician who could perform venipunctures and help in serological studies. Levine subsequently credited Landsteiner with influencing his work habits through strict adherence to scientific principles and to concise and logical thinking. All essential experiments were repeated, and nothing was left to chance. Exposed to these high standards over a seven-year period, Levine adopted them as his own. Marjory Stroup, an associate of Levine from the 1950s to the 1980s, remembers him as a tireless worker who was always in the laboratory before his colleagues and never left before they did except when he was going to the opera. She frequently served as a sounding board for his papers, which he slowly wrote and rewrote until they expressed his thoughts precisely.

Landsteiner performed his early experiments on human blood in 1901, testing for agglutination of red blood cells from healthy human subjects by the serum of other healthy subjects. In this way he detected the A, B, and O phenotypes. In 1907 pretransfusion ABO typing was introduced by Reuben Ottenberg and subsequently was adopted as standard practice by all transfusionists.

Landsteiner was not particularly interested in the clinical problems of transfusion and did not resume any fur

ther studies on the antigens of red cells until coming to the Rockefeller Institute. Levine's earliest collaborative papers from Landsteiner's laboratory were concerned with the finding of A and B on human spermatozoa as well as the behavior of "naturally occurring" cold agglutinins in human serum.

In 1927 Landsteiner and Levine described some results of injecting the red cells of humans and other primates into rabbits and absorbing the resultant antisera with selected red cells. This kind of experiment led to the discovery of the M, N, and P antigens, representing what were subsequently to be known as the MNSs and P human blood group genetic systems. They also noted the occurrence of M in chimpanzees but not in gibbons, the stronger reactions of anti-P with the red cells of black people, and the presence of "naturally occurring" anti-P in some rabbit and horse sera.

Between 1928 and 1932, they expanded their work on the inheritance and racial distribution of these red cell antigens. Reviewing this work in 1960, Levine wrote, "In considering the heredity of M and N as a genetic system, we excluded independent genes and close linkage; we also considered the existence of more than two alleles interacting with or modifying the effects of factors determining hitherto unknown agglutinable structures." In the early 1930s, these conclusions were highly sophisticated from a genetic point of view and were probably influenced by the work of Thomas Hunt Morgan and his colleagues, who were then studying the localization of genes on the chromosomes of *Drosophila*.

By 1929 Landsteiner and Levine were able to distinguish seventy-two human red cell phenotypes on the basis of their serological reactions with anti-A, -A_1, -B, -M, -N, -P, and a

seventh antibody subsequently identified as anti-Le^a by Arthur Mourant. Stimulated by this early work, many other serologists throughout the world took up the search for human red cell antigenic determinants. Between 1929 and 1975 (the date of the last edition of Race and Sanger's *Blood Groups in Man*), nearly 200 additional inherited serologically detected epitopes had been reported on human red cells. The significance of these genetic markers and their association with human disease were subsequently demonstrated by many investigators, notably including Levine.

As an adjunct to their studies on heteroagglutinins, Landsteiner and Levine hoped to obtain some clues on evolution by injecting human serum into chimpanzees and rabbits. Using the rather crude technique of liquid-phase immunoprecipitation, they detected precipitins in one of three injected chimpanzees, but none in rabbits similarly treated. However, in light of our present knowledge, it is almost certain that the rabbits actually did form antibodies against many human serum proteins, but their detection awaited more sensitive methods. Thus, in later years Robin Coombs and his colleagues introduced the antiglobulin test (long named after Coombs). This test relies on the production of antihuman immunoglobulin in rabbits injected with human serum. The rabbit serum is then used for detecting the coating of human red cells by "incomplete" antibodies difficult to detect by other methods.

In 1932 Levine left the Rockefeller Institute, making a gentleman's agreement with Landsteiner to discontinue working with blood groups. This was not an easy decision for Levine because of his deep commitment to the subject. Nevertheless, after accepting a position on the medical faculty at the University of Wisconsin, he turned his attention to bacteriophage, showing that phage specificity of the Sal

monella species paralleled their antibody specificity. This work was made possible by his observation that phage specificity could be neutralized by soluble extracts of bacteria containing the specific antigens. He also did some typing of blood obtained from the Blackfoot and Blood Indian tribes. More importantly, he successfully sponsored a Wisconsin law granting courts the authority to order blood testing in cases of disputed paternity.

In 1935 Levine was hired as a bacteriologist and serologist at Beth Israel Hospital in Newark, New Jersey. His major focus was now on detecting and determining the specificity of red cell alloantibodies formed in patients who had received blood transfusions. He also became a consultant to the Blood Betterment Association of New York City. Over several years he published a number of papers on serological methods and made useful observations on the selection of compatible blood donors. However, his most important contribution concerned the consequences of red cell alloimmunization, in particular hemolytic disease of the newborn, then known as erythroblastosis fetalis.

In 1937 Dr. Rufus Stetson sent Levine a blood specimen from a female patient who had hemorrhaged after her second pregnancy terminated with a macerated stillborn infant and then suffered a severe reaction when given 500 milliliters of her husband's ABO-compatible blood. When the patient's pretransfusion serum was tested against her husband's red cells by a more sensitive technique, agglutination was observed. Her serum also agglutinated the red cells of most other donors tested, but she was successfully transfused with blood from six serologically compatible donors.

A month later Levine also detected the agglutinin and confirmed that it reacted with the red cells of 80 percent of random group O donors. He also observed that the

patient's antibody was active at 37°C, and thus differed from naturally occurring cold agglutinins. Its specificity was noted to be different from M, N, and P.

Two months later the agglutinin was still present, but it was much weaker. After a year it was no longer demonstrable. Such a sequence of agglutinin appearance and disappearance had been noted before in patients who had transfusion reactions. It was subsequently shown to be due to the change of the specific immunoglobulins from IgM to IgG, the latter "incomplete" antibodies being detectable only with the use of specialized techniques developed later, such as the antiglobulin test.

In their paper (1939, 3) describing the case of the female patient, Levine and Stetson proposed that the mother's antibody was stimulated during pregnancy and the "immunizing property in the blood and/or tissues of the fetus must have been inherited from the father." The possibility that the infant's intrauterine death was also a consequence of red cell destruction by the maternal antibody was not spelled out in this report, but it must have occurred to Levine at the time, particularly since the possibility of maternal alloimmunization had been previously suggested as the cause of other stillbirths. The 1939 paper also described failure of efforts to raise heteroimmune antibodies of similar specificity by injecting human red cells into rabbits. However, in 1940 Landsteiner and Alexander Wiener described the appearance of a heteroagglutinin in the serum of rabbits injected with the red cells of rhesus monkeys. This antibody, called anti-Rh, reacted with the red cells of about 85 percent of human subjects. Wiener and his former student Peters showed that antibodies with the same apparent (anti-Rh) specificity could be demonstrated in the serum of some human subjects who had had hemolytic

transfusion reactions. When Levine and Wiener compared the reactions of the rabbit heteroagglutinin with those of the serum of the female patient and the sera of other mothers whose infants had hemolytic disease, all were found to be identical.

These findings permitted Levine to declare anti-Rh to be the major cause of hemolytic disease of the newborn, in the setting of an Rh-negative mother with an Rh-positive father. Many years later (1961, 1967), Levine and his colleagues showed that there actually is a difference in the specificity of the antibodies raised by injection of rhesus monkey cells into rabbits versus those stimulated in Rh-negative human subjects by transfusion or pregnancy. They proposed the name LW (Landsteiner-Wiener) for the heteroagglutinins, retaining the name Rh for the human alloimmune antibodies. Although of interest from a serological point of view, this finding does not in any way detract from the importance of Levine's original observations on the Rh blood group system and the pathogenesis of hemolytic disease of the newborn (HDN).

Some hints of the complexity of antigens in the human Rh blood group system were noted early by several serologists, especially in England. In 1941 Levine used absorption tests to show that while most cases of HDN were due to immunization to the Rh antigen later called D, many sera also contained an antibody to an antigen later called C, which was shown to be inherited along with D and therefore part of the Rh system. A third antibody, subsequently called anti-G, appeared to have cross-reactivity with both C and D. Furthermore, the existence of still another antigen, called c (because of its antithetical reactions to C) was detected by antibodies found in the serum of immunized Rh-positive subjects. Eventually, two other major antigens

within the Rh system, called E and e, were described. Thus, Sir Ronald Fisher, the English geneticist working with Robert R. Race, proposed the existence of three closely linked genes, each carrying one of six different specificities: D or d (although no antibody defining an antigen antithetical to D has ever been described), C or c, and E or e. He suggested that the chromosome carrying the Rh locus (subsequently found on the long arm of chromosome one) consisted of a complex of three linked genes assembled in eight different ways (in order of frequency): CDe, cde, cDE, cDe, cdE, Cde, CDE, and CdE. All people inheriting a D-containing gene triad (conferring the D antigen specificity to red cells) were considered to be Rh-positive, thus making up about 85 percent of most caucasian populations.

Levine, who in 1944 had established the diagnostic laboratories of the Ortho Research Foundation in Raritan, New Jersey, studied many human serum specimens containing antibodies with these Rh specificities. He adopted the Fisher-Race genetic theory and supported their work wholeheartedly. However, Wiener was unalterably opposed to the linked-gene theory, proposing instead a series of Rh alleles, each conferring two or more Rh specificities. As a consequence, two systems of Rh nomenclature existed, bringing considerable confusion to those attempting to understand Rh inheritance and alloimmunization.

It is remarkable that a controversy of such acrimony arose at a time when the biochemical nature of all genes was completely unknown and scientists had to rely entirely on red cell agglutination reactions (some of them weak and equivocal) to deduce the inheritance of antigenic determinants. Studies on the molecular biology of red cell antigens have lagged far behind those on the HLA histocom

patibility antigens of white cells. However, within the past few years, immunochemical analyses of human red cell membranes have demonstrated at least three, and possibly more, peptides bearing separate Rh specificities. Thus, the likelihood that Rh, like HLA specificity, is dependent on tandem structural genes at a complex locus, is now near certainty.

A large part of Levine's work at the Ortho Foundation was concerned with further studies on Rh and identification of human red cell antigens belonging to other blood group systems such as k (Kell system) and s (MNSs system). He and his colleagues also made important discoveries related to the P blood group system. In 1951 they described anti-Tj ^{a}, found in the serum of a woman who had had many spontaneous abortions. It caused marked hemolysis of the red cells of all subjects tested except those of the patient's extremely rare phenotype called p, in which the red cells were not agglutinated by antibodies reacting with the very common P antigen. In 1963, Levine showed anti-P to be the usual specificity of the Donath-Landsteiner cold-warm hemolysin in paroxysmal cold hemoglobinuria (PCH). Subsequent studies by Donald Marcus and his colleagues showed the biochemical genetics of the so-called P system (including Tj^{a}) to be very complex and outside the scope of this memorial to Levine. However, it is a tribute to the tenacity and persistent curiosity of Levine that in his late seventies he revived an interest in the P system. Noting the presence of P-like epitopes in the extracts of certain malignant tumors, he suggested that anti-P might be used to treat patients with such tumors. He was at that time a visiting investigator at the Sloan Kettering Memorial Institute for Cancer Research in New York City.

In 1943 Levine made the important observation that ABO

incompatibility between an Rh-positive father and an Rh-negative mother provided a very significant protection against Rh immunization by the fetus. From this observation (expanded in 1958), Levine deduced that when any ABO-incompatible, Rh-positive fetal cells cross the placenta, they are rapidly destroyed by anti-A and-B, before Rh immunization can occur. This proposed mechanism was later used by both American and British workers as an argument in favor of attempting to prevent Rh immunization by injecting Rh-negative mothers with Rh-immune globulin to destroy any Rh-positive fetal cells that might stimulate maternal Rh alloimmunization. Although the actual mechanism of this protection by specific immunoglobulin is much more complex than originally supposed, the great success of Rh-immune prophylaxis is in part attributable to Levine's creative genius.

Another important observation (1955) concerned the aberrant inheritance of ABO and Lewis antigens in a family containing some members of the very rare "Bombay" phenotype. In conjunction with Dr. Ruggiero Ceppellini, Levine proposed a system of inheritance in which the development of normal (H) AB antigens was blocked. The subsequent studies of Walter Morgan and Winifred Watkins showed that this kind of "blockade" was actually due to inheritance from both parents of a very rare allele of the *H* gene, preventing the addition to carbohydrate chains of a fucose residue necessary for the expression of H, the substrate for enzymes that confer A or B specificity by the addition of either N-acetylgalactosamine or galactose.

Levine officially retired from Ortho in 1965, and his research center was renamed the Philip Levine Laboratories. He continued there in emeritus status until 1985, making many more contributions, although the number of his pub

lications declined. For the two years before his death in October 1987, he was confined to a nursing home with far-advanced arteriosclerotic vascular disease. His wife, Hilda, had died in 1975. They are survived by two sons, Mark Levine of Denver and Victor Levine of Madison, and a daughter, Phyllis Klein of New York City.

Philip Levine was a dedicated scientist who prepared his mind to a degree that permitted him to construct major and testable hypotheses from chance observations made in his own laboratory and those of others. He inspired many young investigators to study the immunology and genetics of human red cells at a time when most of the modern techniques of biochemical analysis and molecular biology were unknown. His greatest contribution was describing the pathogenesis of hemolytic disease of the newborn, which led to its treatment by exchange transfusion and later to its prevention by maternal treatment with Rh-specific immunoglobulin.

During his lifetime Levine received many awards, listed below. He was elected to the National Academy of Sciences on April 26, 1966.

HONORS AND DISTINCTIONS

1942 Mead Johnson Award
1944 Fellow of the American College of Physicians
1946 Ward Burdick Award
1946 Lasker Award
1947 Phi Lambda Kappa Grand Award
1951 Passano Foundation Award
1956 A.A.B.B. Karl Landsteiner Award
1956 Townsend Harris Medal, Alumni Association of the City College of New York
1959 Award of Merit of the Netherlands Red Cross
1960 The Johnson Medal for Research and Development
1961 Life membership in the Harvey Society
1964 First Franz Oehlecker Award from German Society for Blood Transfusion
1965 Medal from the German Red Cross
1966 Joseph P. Kennedy, Jr., International Award for Research in Mental Retardation
1966 Elected to the National Academy of Sciences
1966 Clement Von Pirquet Gold Medal from the Seventh Forum on Allergy
1966 Edward J. Ill Award from the Academy of Medicine of New Jersey
1967 Honorary Doctor of Science from Michigan State University
1968 Award of Distinction of the Alumni Association of Cornell University Medical College
1968 Honorary Member of American Academy of Oral Medicine
1969 Distinguished Service Award of the American Association of Blood Banks
1973 Fellow of the Royal College of Physicians
1974 Honorary Fellow of the Truman Library Institute
1975 Norwegian Society of Immunohematology Medal
1975 Bavarian Red Cross Medal
1975 Allan Award from the American Society of Human Genetics
1975 Melvin H. Motolinsky Award from Rutgers University Medical School
1977 Muhlenberg Centennial Medal

1978 Honorary member of the International Society of Blood Transfusion
1978 Honorary life member of the New York Academy of Science
1979 New Jersey Hospital Association Award
1979 Annual McNeil Science Award
1980 Karl Landsteiner Gold Medal from the Netherlands Red Cross
1980 Bronze Medal from the Israel Blood Transfusion Service
1983 Honorary Doctor of Science Degree, University of Wisconsin

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Bruce H Mahan

BRUCE HERBERT MAHAN

August 17, 1930–October 12, 1982

BY IGNACIO TINOCO, JR.

BRUCE MAHAN was born on August 17, 1930, in New Britain, Connecticut, the youngest of three children born to Arthur E. Mahan and Clara Blanche Gray Mahan. He did not reveal much about himself to his colleagues or his students, so there is little information about his early life. It is clear that he did very well in school. His mother told one story about his youth that explains a great deal about his character. His elementary school teacher had told him that his parents must be very proud of him for his good grades. When he said "Not particularly," the teacher called his mother to say that she did Bruce a disservice by not praising him. His mother replied, "I'm happy he is doing well, but it is not necessary to praise him simply for using his God-given gifts to good advantage."

In 1948 he entered Harvard College on a fellowship. He was attracted to chemistry and he distinguished himself rapidly in that subject. He received an A.B. in chemistry in 1952 and as one of the top students he was encouraged to remain there for his graduate work. He decided to carry out his doctoral studies with George Kistiakowsky in physical chemistry. Kistiakowsky had trained with Bodenstein in Berlin, and it was in that tradition that Mahan set out to

pursue his research. It was a pivotal decision, starting him on the track of research in gas phase kinetics that occupied all of his scientific career. He received an A.M. in 1954 and a Ph.D. in 1956. His Ph.D. thesis research was on the photolysis of methyl ketene.

He came to Berkeley as an instructor in 1956 directly from Harvard; his entire career and future life were centered at Berkeley. He immediately started building a vacuum line to continue his research on gas phase photolyses. He was a competent glass blower and as beginning instructors were not allowed to train graduate students, he did all the work himself. This meant he spent long hours in the laboratory. He was very helpful to graduate students in adjoining laboratories, because of his knowledge of physical chemistry and his practical experience with vacuum pumps, seals, and gauges. However, his presence was sometimes inhibiting, as he discouraged the practice of dumping liquid oxygen in the sinks. It seems he had practical experience with an explosion once when liquid oxygen found organic material in the drain trap.

In 1959, three years after arriving at Berkeley, now an assistant professor, he volunteered to teach a new freshman chemistry course described in the catalog as "Lecture and laboratory for students of superior facility and preparation." It ended a long Berkeley tradition of having only one freshman course for all entering students, and it established one of the first beginning chemistry courses that used calculus and the quantitative application of thermodynamics. The course he established and the textbooks he wrote to support it became models for the modern teaching of freshman chemistry in this country. In 1963 *Elementary Chemical Thermodynamics* was published in a general chemistry monograph series; it provides a very clear de

scription of the subject at an elementary level. In 1965 *University Chemistry* was published; this textbook (and its more elementary version *College Chemistry*) was the model for all high-level freshman texts used today. The fact that it was written by a single author instead of the multiauthor texts now common makes it even more impressive. The book went through three editions and sold over half a million copies during Mahan's lifetime. It is now in its fourth edition with Rollie J. Myers as a coauthor. The book has been translated into eight other languages; it has truly had a worldwide impact. Professor Mahan's direct impact on the Berkeley students was also very effective. The students admired and respected him as a demanding, but fair teacher with a very deep understanding of chemistry. He received one of the first campus distinguished teaching awards in 1961.

In 1968 Bruce Mahan became chairman of the chemistry department; he was chairman for three years, from 1968 to 1971. The faculty found him to be a tough but fair administrator. He actually read, understood, and evaluated their publications before making recommendations for promotions and advancements. In a department with more than fifty members, this requires a great deal of knowledge and dedication. Some of the younger faculty found him somewhat intimidating. He was sometimes gruff; he was often abrupt. He expected a great deal and he did not give out a lot of praise; his mother must have taught him this attitude.

Mahan's research interests were on gas phase kinetics and photolysis. He concentrated on molecular collisional processes, especially collisional energy transfers and ion-molecule reactions. He was the first to recognize that the efficient energy transfer from excited polyatomic molecules

was due to frequent events with a small amount of energy transfer rather than from rare events with large amounts of energy transfer. His first independent publication, *The Nature of Collisional Processes in Unimolecular Reactions*, described this theoretical work. His penetrating observation treated the impulsive translational-vibrational energy transfer process correctly for the first time.

State-selective kinetic studies are common now using molecular beams and lasers. However, in the early 1960s Bruce Mahan did pioneering experiments using arc lamps and vacuum systems in the spirit of modern kinetics. By the proper choice of photolyzing wavelengths and reactants, he produced molecules in different electronic states and measured their different reactivities. He was among the first to apply molecular beam systems that provided velocity selection of reactants, and angular and energy analysis of products. Yuan T. Lee, who received his Ph.D. from Mahan in 1965, shared the Nobel Prize in 1986 with Dudley Herschbach for their molecular beam work.

Mahan's main research applications of molecular beams was to reactions of molecules, ion, and electrons. The enormous contributions he made in the field of ion recombination and the dynamics of ion-molecule reactions established him as a world leader in molecular reaction dynamics. His experimental work on angular and energy distributions of the products of reactive ion-molecule reactions are classics. His discovery of specific electronic excitation in inelastic, nonreactive scattering and his original measurements of their angular distributions were a real breakthrough. The research provided direct information about potential energy surfaces not otherwise obtainable. His theoretical insight was of equal importance to his experimental results. He deduced several widely used mod

els for understanding and predicting ion-molecule reactions. The most important are molecular orbital correlation diagrams and energy state correlation diagrams. His simple impulsive models for inelastic and reactive scattering were very helpful to the development of the field.

His research accomplishments were recognized by several awards. He was an Alfred P. Sloan Fellow in 1963–65. He received the gold medal California Section Award of the American Chemical Society in 1968. He was elected to membership in the National Academy of Sciences in 1976.

Professor Mahan provided thorough, sound training to twenty-four graduate students at Berkeley; the first, John Doering, received a Ph.D. in 1961, the last, Fred Grieman, in 1979. Mahan's scientific rigor and his serious personality kept many of his students at a distance. Perhaps this was partly due to his belief that graduate students should take the initiative in pursuing their Ph.D. thesis research and in developing themselves. He was not the type of research director who gave strong and dominating guidance. His way of guiding students during his daily visit to the laboratory always started with, "What's new?" and ended with "What do you plan to do next?" If the answers to these two questions were satisfactory, he would often just nod his head and leave without uttering a word. Many of his students appreciated the way Mahan allowed them to develop early into independent scientists. One of his former students, Yuan T. Lee, attributes his success to the way Bruce chose to train his students.

It was not all work for Bruce Mahan. He was a very shy person who never married, but he did enjoy the company of a few friends. As a graduate student at Harvard he and his housemates continuously renovated a model A to provide a distinguished means of transportation. He was a

very good cook who prided himself in preparing fancy meals for visitors. During his twenty-six years at Berkeley he liked to travel, to photograph, and to listen to opera. He also liked to share his experiences with the morning coffee group at the Faculty Club and with his colleagues at the chemists' table for lunch at the club. This was the family he used to validate his adventures and accomplishments. He would go to Death Valley or to the Arizona desert about once a year. He first drove his Mercedes, but after this car was sand-blasted once in a desert windstorm, he bought a fourwheel drive Bronco. He also bought some rugged land in Mendocino County in northern California and built a shelter on it. He liked to improve the dirt roads and clear brush on the land.

In 1975 Bruce Mahan learned that he had amyotrophic lateral sclerosis, a dreadful disease that slowly but inexorably causes paralysis starting from the periphery of the body and progressing to the center. He went from crutches to a wheelchair to bed and a respirator in about four years. During this time he always remained cheerful and active. He directed his graduate students, worked on the new edition of his book, wrote scientific manuscripts, and studied new areas of science. During the last months he required twenty–four–hour nursing care and could only communicate by his eyes. Even before he became ill he never wasted words; he could demolish a weak argument or explanation just by raising an eyebrow.

Once Mahan made a commitment he never wavered. He had the honesty and integrity and above all the ability to do whatever he said he would do. He would never quit and he would never give an excuse. He faced ALS as he would any other objective. He just kept fighting.

Bruce Mahan's father and older siblings had died long

before he became ill. At first he kept his disease a secret from his mother, but she was called when he contracted pneumonia and his doctor thought he would not last long. He survived for another two years.

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ELLIOTT WATERS MONTROLL

May 4, 1916–December 3, 1983

BY GEORGE H. WEISS

ELLIOTT W. MONTROLL was born on May 4, 1916, to Adolph B. and Esther I. Montroll in Pittsburgh, Pennsylvania. His father, an immigrant from Poland, and his American-born mother encouraged him from an early age to pursue his interests in chemistry, which he did in high school as well as in his undergraduate studies at the University of Pittsburgh. However, after receiving his bachelor's degree in chemistry, Elliot switched fields as a graduate student, receiving his Ph.D. in mathematics at the age of twenty-three. A forerunner of his later interests, Elliot's thesis was on application of the theory of integral equations to the evaluation of integrals that appear in the analysis of imperfect gases.[1] The techniques developed in his thesis were based on linear operator theory and Fourier integrals. These tools were to prove the cornerstone to a significant portion of Elliot's future work.

Following the receipt of his doctorate, Elliott spent three years as a postdoctoral fellow working for a year at Columbia with Joseph Mayer, followed by a year as a Sterling fellow at Yale with Lars Onsager, and finally spending a year with John Kirkwood at Cornell. After this period of study, he accepted an instructorship at Princeton in 1942.

It was at the last of these that Elliott met his future wife, Shirley Abrams, whom he married in 1943. Their marriage was an unusually warm and happy one, producing ten children over the years. Much of Elliott's fertile imagination was devoted to producing new and novel ways to educate his children.

During the war Elliott worked at the Kellex Corporation in New York City as a chief mathematician analyzing problems arising in the production of the atomic bomb. This work also served as a source of techniques that he later developed and applied in other scientific fields. Following the war Elliott briefly held teaching and research positions at Brooklyn Polytechnic Institute and the University of Pittsburgh. He later became the director of physical science at the Office of Naval Research, after which he returned to the world of research, spending a year as a fellow at the Courant Institute in New York City.

In 1951 the Montrolls returned to the Washington area, and Elliott took a position as a research professor at the Institute for Fluid Dynamics and Applied Mathematics at the University of Maryland. During this time he spent a sabbatical period with Ilya Prigogine at the Free University of Brussels, and he held the position of Lorentz Professor at the University of Leiden in 1961. Following this period at the University of Maryland, Elliott decided that he wanted to get a taste of industrial research, several of his doctoral students having gone into industry, and so he left the University of Maryland to become a vice-president in charge of physics research at IBM, a position he held for three years, during which time he also acted as a consultant for the Institute for Defense Analysis. After having been the director of general sciences at IBM, Elliott took on the position of vice-president of the Institute for Defense Analysis.

In 1966 he accepted an offer of an Einstein professorship at the University of Rochester, which he held until 1981 when he returned to the Institute for Physical Science and Technology at the University of Maryland. Subsequent to his appointment he was named a distinguished professor at the university in 1982. This position was held until his death.

The time that Elliott spent at universities produced a large number of doctoral students. His research groups, always extensive, provided a lively intellectual atmosphere and were filled with many junior and senior postdoctoral investigators, all working on a variety of topics as befitted Elliott's wide-ranging research interests. His catholic tastes and interest in topics outside of science proper produced many unusual contributions to disciplines outside of mathematical physics and led to his teaching such courses as "Quantitative Aspects of Social Phenomena" and "The Physical Basis of Modern Technology" at the University of Rochester.

Elliott's scientific style was extremely elegant, producing insight into often difficult physical problems usually by means of very simple calculations. One of his earliest pieces of work resulted in the publication, together with Joseph Mayer, of a technique for the summation of the contribution of the class of ring diagrams in the diagrammatic analysis of the theory of imperfect gases.[2] This seminal contribution proved to be the forerunner of a powerful technique subsequently adapted by many investigators to analyze a variety of problems in both equilibrium and irreversible statistical mechanics. A second, slightly less successful investigation was carried out while Elliot was a postdoc with Lars Onsager into the solution of the Ising model. Elliott developed a technique for solving the partition function of the Ising

model but was only able to solve the one-dimensional case exactly and find high-and low-temperature expansions for the partition function in two dimensions. Onsager, of course, provided an exact solution in two dimensions which, for the first time, showed that the mathematical formalism indeed predicted a phase transition for this model.

Although it was not Elliott who solved the Ising model, his work on it led to other significant contributions. For many years a review article by Newell and Montroll on the Ising model was the most readable and most widely cited introduction to the subject.[3] A second bonus of Elliott's work on the Ising model consisted of some work first published in the *Journal of Chemical Physics* in the context of the Ising model.[4] After the mathematical ideas had been distilled from this work Elliot published an elegant extension of it in the *Annals of Mathematical Statistics*.[5] This later paper contained a general and easily applicable formalism for calculating the probability distribution of functions defined on a Markov chain or a continuous Markov process. The technique will be recognized as starting from the analog of a partition function but proved valuable in making the statistician aware of the extension of the notion of the characteristic function to the domain of Markov processes. Elliott showed that computations based on his technique could be expressed in terms of the properties of certain matrices. These could then be analyzed in terms of eigenfunction expansions of the relevant matrices. Among other benefits available with this technique is the possibility of finding Gaussian approximations as well as corrections to the calculated properties in a straightforward way, in contrast to more formal but somewhat less general techniques used in earlier mathematical literature.[6] This work also contained many of the recurring themes found in Elliott's

later work on stochastic processes and their applications. Elliott was a master of techniques involving applications of the asymptotic analysis of linear operators to problems in the physical sciences. The work described here was a significant contribution to applied probability.

Among Elliott's earliest work were three papers on lattice dynamics, a subject in which he became interested when working as a postdoctoral fellow with J. G. Kirkwood and in which he maintained an interest for many years[7] following.[8-10] Until the time of Elliott's investigation, most of the work on thermodynamic properties of solids used the Debye model for the frequency spectrum of the solid in calculating these properties.[11] This model used the approximation that the frequency spectrum associated with a solid could be calculated from a continuum picture. It had been known since the work of Blackman in the 1930s that the Debye model was inadequate in reproducing much of the experimental data on the specific heat of solids. Blackman's work suggested that one could not neglect the lattice structure of the solid and suggested that the proper starting point for investigating thermodynamic properties of solids was the Born-von Karman model, which pictured the solid as a lattice of discrete atoms connected by springs that obeyed Hooke's law.[12] The question addressed in the first of Elliott's contributions to the subject was how to calculate the frequency spectrum for the Born-von Karman model.8 The first step in the analysis consisted of showing that one could calculate moments in terms of the trace of powers of the dynamical matrix. The second step consisted of an expansion of the frequency spectrum in an infinite series of Legendre polynomials. In this way Elliott was able to reproduce many of the features of the frequency spectrum determined by Blackman by numerical

means. He later returned to the problem of doing exact two-and three-dimensional calculations of the frequency spectrum for simple cubic lattices using the Born-von Karman model, finding the infinite peaks later shown to be a general consequence of symmetry properties of the lattice.[9, 10]

The theory of lattice dynamics proved to be a fertile field for Elliott's combination of techniques and talents for over twenty-five years dating from his initial contribution to this area of physics. As an example of this, Elliott and Renfrew Potts tackled the problem of calculating thermodynamic properties of lattices, particularly lattices with defects.[13, 14] This involves computing sums of the form

$$S = \sum_j g(\omega_j),$$

where $g(\omega)$ is determined by the particular thermodynamic property and the ω_j are the characteristic frequencies of the lattice determined by the solution of the dynamical equation $D(\omega)=0$, where $D(\omega)$ is a determinant whose elements contain all of the physics of the problem. Montroll and Potts solved the problem very neatly by utilizing a representation derived from complex analysis

$$S = \frac{1}{2\pi i}\int g(z)\frac{D'(z)}{D(z)}\,dz$$

in which $g(z)$ is the thermodynamic function, $D'(z)$ is the derivative of the dynamical matrix, and the contour is chosen to surround the zeroes but not the poles of $D(z)$. The effects of lattice defects could be found, using this formalism, by subtracting the contribution of the perfect lattice, which can be calculated in exactly the same way as indicated by the last equation.

Another significant finding contained in this particular series of papers is the technique for calculating the values of vibrational frequencies that may emerge from the con

tinuum of frequencies when defects are present in the lattice. Montroll and Potts showed that when there are n defects in the lattice, a maximum of n frequencies will separate themselves from the continuum of frequencies found in the analysis of translationally invariant lattices. They further showed that the emergent frequencies could be found by the solution of an $n \times n$ determinant whose elements consisted of Green's functions that characterize the lattice. All of the calculations were a demonstration of the elegance of essentially eighteenth-century classical mathematical analysis, of which Elliott was a master. Elliott's mastery of the subject of lattice dynamics led to his coauthorship of *Lattice Dynamics in the Harmonic Approximation* with Alex Maradudin and myself.[15] Somewhat characteristically, the book was originally supposed to have been a review article for *Advances in Solid State Physics*, which Elliott put off writing until there was so much material available that it could only fit into a book.

Aside from the analysis of lattice dynamic problems suggested by applications in solid state physics, Elliott, together with Peter Mazur, studied the properties of Poincaré cycles for an assembly of harmonic oscillators as a simple model for irreversibility in statistical mechanics.[16] This appeared in the first volume of the *Journal of Mathematical Physics*, of which Elliott was the founder and first editor. Because of Elliott's familiarity with the formalism on linear lattice dynamics, it was an easy and revealing tool for the analysis of problems that are quite difficult for physical systems with more complicated interactions. In the publication with Mazur, the authors were able to find precise results for the dynamics as expressed by the Poincaré cycle and the momentum correlation function. They were able to show that the length of the Poincaré cycle for a system of N atoms

goes like exp (aN), the parameter a being positive, which identifies the time during which the system will appear to behave irreversibly.

While engaged in this work on lattice dynamics, Elliott also made fundamental contributions to the theory of unimolecular relaxation as a consultant to the National Bureau of Standards, in collaboration with Kurt Shuler.[17,18] The investigators managed to shed considerable light on an important field through the study of a simple physical model as well as to initiate lines of research in the study of chemical kinetics that have been pursued to the present time. Although the original work consisted of a study of the relaxation and dissociation of a weakly interacting system of harmonic oscillators, the formalism developed has been shown to apply to many other systems. The first step in this area of research was made by Landau and Teller, who calculated the collisional transition probabilities per collision for a system of harmonic oscillators, which subsequently allowed Bethe and Teller to find the average energy of an ensemble of such oscillators as a function of time. Montroll and Shuler first undertook the more exacting task of formulating a theory allowing the calculation of all of the statistical parameters characterizing the relaxation of the system. They did this by using Landau and Teller's form of the rate constants, which allowed them to write a master equation for the set of occupation probabilities of the different energy levels of the system. This system of equations could then be solved by using generating functions. Montroll and Shuler showed that the system of harmonic oscillators has the remarkable property that, if it has an initial Boltzmann distribution, it relaxes to its equilibrium Boltzmann distribution by means of a continuous sequence of Boltzmann distributions. It can be

shown that the harmonic oscillator system is unique in this respect.[19]

Montroll and Shuler made a further significant advance using the harmonic oscillator model by adapting it to study the dynamics of the dissociation of diatomic molecules.[18] The simplifying feature of this model in a quantum-mechanical context is the fact that its energy levels are uniformly spaced. Montroll and Shuler studied the rate at which such a physical system reaches a critical energy of dissociation. In this way the analysis is framed in terms of the theory of first passage times. In this much-cited paper, the authors developed the theory of first passage times for the master equation, demonstrating its applicability to a physically interesting system. This work stimulated considerable further work, both on the mathematical theory of first passage times for master equations and on further applications of the formalism to other problems in chemical kinetics.

Perhaps the area with which Elliott's name is most closely associated is the theory and application of random walks. Elliott pioneered in the study of random walks on a lattice structure as opposed to random walks in a continuum, which had been the subject of most earlier investigations of the subject. This work grew out of Elliott's wartime study of the kinetics of cascades,[20] but it was also intimately related to his interests in solid state physics. A unifying thread throughout his many papers on this subject is the use of many of the same elegant mathematical tools he developed in his analyses of lattice dynamics. In one of his first papers on the subject, he tried to study the excluded-volume problem in polymer physics by analyzing properties of random walks with exclusions that only ranged over a fixed number of steps.[21] It is now known on general grounds

that such a process remains Markovian and that one cannot hope to recover the non-Markovian properties that are characteristic of the excluded-volume random walk (e.g., the fact that the asymptotic mean square displacement of such a random walk varies with the number of steps, n, as n^{α}, where $\alpha \neq 1$). Elliott's first major contribution to the general theory of random walks was made some time later than his first essay into the area of the particular problems posed by the excluded random walk.[22] Most studies of random walk properties in the literature of the physical sciences had focused on random walks in a continuum. No doubt influenced by his work on lattice dynamics, Elliott developed the formalism necessary for the study of random walks on a lattice. Many of the mathematical tools developed in one context could profitably be carried over almost unchanged to the other. In addition, in this early work Elliott showed that Tauberian theorems for power series and Laplace transforms greatly simplified the calculation of many asymptotic properties of random walks. This work was taken up and extended somewhat later in Elliott's most cited paper.[23] A number of results scattered in the mathematical literature were derived in a unified manner by using Tauberian methods, but also a significant new model of lattice random walks was suggested in this paper allowing the notion of such walks in continuous time. In an earlier work, not directly related to random walks, Elliott developed what was essentially a theory of lattice walks in which the intervals between successive steps of the walk were allowed to be random.[24] However, since the distribution of these intervals took a specific form, the resulting random walk retained the Markov property, and there could be no basic difference between the properties of such random walks at very long times and those in which the times

between successive steps are constant. The so-called continuous-time random walk allowed for quite general distributions of interjump times.

Development of the theory of the continuous-time random walk was a purely theoretical one in Elliot's most frequently cited paper.[23] In another paper,[25] Harvey Scher and Elliott demonstrated some of the potentialities inherent in the formalism of the continuous-time random walk by applying it to anomalous dispersion arising in the transport of charge in amorphous solids. It was known at the time that photoconductivity experiments in certain classes of amorphous semiconductors, in which a pulse of light is applied to one face of the solid and a measurement is made of the carriers impinging on the second face, could not be explained in terms of a simple diffusion model. Scher and Montroll showed that the continuous-time random walk model could reproduce all of the peculiar qualitative experimental features observed provided that the probability density of interstep times has the property

$$\psi(t) \sim t^{-(1+\alpha)}, \quad 0<\alpha<1$$

at sufficiently large values of the time. This class of densities has the property of having no finite moments, which induces qualitative differences between such transport processes and ordinary diffusion processes since many of the mobile carriers tend to remain stationary for long periods of time. Somewhat later, Elliott, together with Michael Shlesinger, used related ideas in an attempt to explain the so-called Kohlrausch-Williams-Watt form for the dielectric relaxation function that frequently can be fit to data taken on polymers.[26]

Another area in which Elliott left an indelible mark, and

which is indicative of his wide-ranging and fertile imagination, is in the field of traffic flow. As a consultant to General Motors in the 1950s and early 1960s, Elliott became involved in and indeed was at the forefront of an effort to bring a more scientific approach to the characterization and control of traffic flow that had been initiated by Robert Herman. In a series of joint publications with Herman, Gazis, Rothery, Potts, and Chandler, Elliott developed the linear theory of car-following.[27-29] This theory relates the reaction of a driver in a single lane of traffic to the car in front of him. The simplest version of the theory is embodied in a set of equations for the speeds, $v_j(t)$, of a series of drivers, where $j = 1, 2, 3, \ldots$. These equations have the form

$$v_j(t) = \lambda[v_{j-1}(t - T) - v_j(t - T)],$$

where λ is a control parameter and T is the time for a driver to react to a change in relative speed. Using this greatly oversimplified model, which assumes that changes occur only in reaction to differences in relative speed, Elliott and his collaborators were able to show that for certain ranges in the two parameters, λ and T, a sufficiently long stream of traffic would tend to destabilize, leading to rearend collisions. This is indeed known to occur, for example, in foggy conditions where reaction times tend to be greater than normal. Later, Elliott extended the study of car-following equations by introducing the notion of "acceleration noise," represented by a random term added to the car-following equations written above. It was shown that the conditions leading to an instability in a line of cars also lead to an amplification of the noise. This work, which stimulated a large amount of further research by the traffic community, merited the award of the 1959 Lanchester

Prize for Operations Research for Elliott, together with Chandler, Gazis, Herman, Potts, and Rothery.

This brief account of some of Elliott's work hardly begins to do justice to his wide-ranging interests, which included not only the physical sciences but also all aspects of the world around him. For example, Elliott, together with Robert Herman, wrote a paper on statistical properties of the prices found in Sears Roebuck catalogs over a period of years.[30] His interests in the history of science were legendary, and indeed his last published paper was on the ramifications and interconnections between scientific investigations initiated by nineteenth-century Viennese scientists.[31] Elliott also wrote papers on the denaturation of DNA,[32, 33] model building in the biological and behavioral sciences,34 as well as developing mathematical models to quantify technological development.[35-37] Few aspects of life or science escaped Elliott's attention. Elliott could be characterized as a Renaissance man transplanted into the twentieth century.

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Earl L Muetterties

EARL LEONARD MUETTERTIES

June 23, 1927–January 12, 1984

BY R. G. BERGMAN, G. W. PARSHALL, AND K. N. RAYMOND

EARL MUETTERTIES, Professor of Chemistry at the University of California, Berkeley, died of cancer on January 12, 1984, at the age of fifty-six. He was a major figure in American inorganic chemistry and contributed in almost every area of this discipline. He made important contributions in the structure and bonding of clusters, in reaction dynamics of both main-group and transition-metal compounds, and in both homogeneous and heterogeneous catalysis.

Earl Muetterties was an internationally recognized scientist whose career—first at Du Pont Central Research, later at Cornell, and finally at Berkeley—had a major impact in virtually every area of inorganic chemistry. His work extended into chemical bonding theory, fundamental chemical reaction dynamics, NMR spectroscopy, surface chemistry, applications of topology to chemistry, and stereochemical theory. Because of this wide range of fields in which he made major research contributions, Earl Muetterties emerges as a unique individual who during the last three decades

Reprinted from *Organometallics*, volume 4, no. 1.

had a major impact on the development of modern inorganic chemistry as we know it today.

A hallmark of Muetterties' research was the intellectual elegance of his papers and the rigor of his approach. For example, he was among the first to apply topological arguments to the analysis of intramolecular exchange phenomena and was a pioneer in applying permutation analysis to NMR data in distinguishing reaction pathways. In his organometallic research, he discovered the unique regioselective reduction of aromatic hydrocarbons to give all-cis addition of hydrogen and characterized the mechanistic aspects of this reaction. He demonstrated nucleophilic attack at the carbon atom of coordinated carbon monoxide in metal carbonyls by looking at labeled oxygen exchange between $Re(CO)_6^+$ and ^{18}O-labeled water. In his metal cluster chemistry, Muetterties was among the first to develop and articulate the cluster-surface analogy for surface chemisorption states. He discovered a new class of metal clusters that are coordinately unsaturated and that consequently are extremely active catalysts for hydrogenation reactions. In his coordination chemistry, Muetterties investigated the structural systematics and interrelationships between coordination complexes and clusters. Finally, in his latest field of research, Muetterties had begun a concerted effort to compare the bonding of adsorbed monolayers of molecules on surfaces with the structures of metal clusters. Using adsorbed molecules on crystal surfaces, his approach has promise of producing new advances in our ability to correlate heterogeneous and homogeneous catalytic systems.

Earl was born in Elgin, Illinois, on June 23, 1927. Instead of following his family's wishes that he take over his grandfather's bakery, he earned a bachelors degree in chemistry at Northwestern University in 1949. He did his doc

toral thesis in boron–nitrogen coordination chemistry under Charles Brown and Eugene Rochow. He received his Ph.D. from Harvard in 1952 and joined the Chemical Department, the predecessor of the Central Research Department, at Du Pont. Earl's abilities were soon apparent, and he was promoted to research supervisor extraordinarily rapidly in 1955. He formed a very productive partnership with another rising star, William D. Phillips. Between them, they effectively exploited the new tool of nuclear magnetic resonance spectroscopy for study of dynamic processes in inorganic compounds. In an elegant series of papers, they established the stereochemistry of main-group fluorides such as PF_5.

Earl's research group carried out pioneering work on new processes for synthesis of fluorocarbons and the main-group hydrides, particularly SiH_4 and B_2H_6. The emphasis was on synthesis of these compounds from basic raw materials, such as calcium fluoride, which was explored as a fluorinating agent for chlorocarbons. The hydride synthesis employed aluminum and hydrogen as reducing agents for SiO_2 or B_2O_3 suspended in an aluminum chloride melt.

The boron hydride work led into one of the most exciting periods of Earl's career, the discovery of polyhedral borane anions such as $B_{12}H_{12}^{2-}$. Walter Knoth, who was exploring decaborane chemistry in Earl's group, discovered that the dimethyl sulfide complex $B_{10}H_{12}(SMe_2)_2$ was easily converted to the $B_{10}H_{10}^{2-}$ ion. The most exciting aspect was that $B_{10}H_{10}^{2-}$ displayed a substitution chemistry like that of aromatic hydrocarbons. It was like rediscovering benzene in the richness of its chemistry. A six-to-eight-man task force was assembled to exploit this discovery. Some explored the "aromatic substitution" chemistry and sought practical applications while others attempted direct syn

thesis of $B_{10}H_{10}^{2-}$ from simple reagents like $NaBH_4$ and B_2H_6. The synthesis group uncovered a family of polyhedral borane anions beginning with $B_{11}H_{14}^{-}$ and $B_{12}H_{12}^{2-}$. The work proceeded at a breakneck pace to obtain broad patent coverage. The urgency was maintained by the fact that Fred Hawthorne's research group at the Redstone Arsenal in Alabama had discovered these same materials independently. There were also rumors that Russian scientists were developing high-energy rocket fuels based on boron hydrides, including apocryphal stories of Russian jets belching green flames from their tailpipes.

The late 1950s and early 1960s were a golden era in Earl's group, just as in chemistry as a whole. The intellectual vitality of the group was amazing. Earl led study projects in which the group worked through texts on group theory, ligand field theory, and biochemistry. The study of symmetry and topology stimulated by the polyhedral borane research provided two intellectual themes that persisted throughout Earl's research career, namely, exploration of cluster compounds and delineation of coordination geometries of metal ions. He initiated preliminary attempts to generate polyhedral aluminanes and explored molybdenum cluster chemistry. Even though the results of these programs were disappointing, they laid the foundations for more successful programs in the future.

In addition to the polyhedral borane work, the late 1950s and early 1960s saw the beginning of transition-metal organometallic chemistry in Earl's group. Some pioneering work was done on π-allyl, fluoroalkyl, and boron hydride complexes of the transition metals. Earl's own research diversified to exploration of high coordination number (7-11) complexes.

A major inflection point in Earl's career came in 1965 when he was appointed associate director of the Central

Research Department with a charter to reestablish catalysis as a major discipline in the department. He set up groups in homogeneous and heterogeneous catalysis and in the synthesis and spectroscopy of organometallic compounds. In spite of the administrative responsibility of his new position, he maintained active laboratory research and participated in a variety of new intellectual activities. He edited volume 10 of *Inorganic Syntheses*, published in 1967, and played a major role in revitalizing the *Inorganic Syntheses* organization. Earl edited books on boron chemistry and transition-metal hydrides and wrote a number of reviews on complexes with unusual coordination numbers. Along with Alan MacDiarmid at the University of Pennsylvania and Neil Bartlett, then at Princeton, he set up the Penn-Princeton-Du Pont seminar series that met monthly for discussions of research in inorganic chemistry.

Earl's research interests continued to diversify, even to the extent of research on mammalian pheromones. His technician spent many redolent hours extracting various monkey excretions. The venture into pheromone research was formalized by participation in the Monell Chemical Senses Center of the University of Pennsylvania. His formal academic ties included adjunct professorships in chemistry at Princeton (1967-1969) and at the University of Pennsylvania (1969-1973). He and Alan MacDiarmid shared supervision of a graduate student working in organometallic chemistry.

After a two-month lectureship at Cambridge University in 1972, Earl decided to pursue an academic career. He assumed a professorship in chemistry at Cornell in 1973. A major attraction of Cornell was the potential for interaction with outstanding faculty colleagues. Earl and Roald Hoffmann had a particularly good collaboration during this period when Roald was becoming involved in organome

tallic chemistry. Although Earl continued research in chemical anthropology and in coordination chemistry, his major research theme was organometallic chemistry and homogeneous catalysis. He was associated with some outstanding graduate students and postdoctoral fellows who are now distinguishing themselves in academic and industrial careers—Patricia Watson, David Thorn, Bill Evans, Mary Rakowski, and Marcetta Darensbourg, to name a few. One of the more productive research themes of this period was the exploration of labile allyl and phosphite complexes of cobalt and rhodium that were among the first well-characterized soluble catalysts for the hydrogenation of benzene.

During his years at Cornell (1973-1978) Earl renewed his enthusiasm for cluster chemistry and expounded the analogy between transition-metal cluster compounds and the surface structures of metallic catalysts. A desire to explore this relationship in rigorous fashion was a major driving force for a move to the University of California at Berkeley, which has long been a center of surface science research.

Upon arriving at Berkeley, Earl set up his research in organometallic catalysis and cluster chemistry in the chemistry department at the university and began work on surface science in his new facility at the Lawrence Berkeley Laboratory, which adjoins the Berkeley campus. His perception was that much new understanding of surface-catalyzed reactions could be obtained by applying the principles and ideas of inorganic solution chemistry to this area. He liked to describe his heterogeneous catalysis work as experiments on the coordination chemistry of metal surfaces, but he also focused attention on reactive surface-bound organic species. During this period his organometallic group synthesized and studied the chemistry of a number of in

teresting complexes, such as reactive carbide clusters and very temperature-and air-sensitive anionic dinuclear rhodium complexes. They also uncovered a reaction in which a dinuclear complex reduces an alkyne with specifically trans stereochemistry. At the same time his surface science group was applying Earl's earlier findings on arene activation to his heterogeneous work. They obtained important information about how aromatic organic molecules are bound to surfaces and how carbon–hydrogen bonds are broken in reactions of these molecules. He combined his major areas of research especially well in his parallel studies of the reactions of small coordinating molecules such as CH_3CN and CH_3NC with metal surfaces, metal cluster compounds, and monomeric metal complexes.

Earl's establishment of these parallel efforts had a major impact on the nature of research and the intellectual atmosphere at Berkeley. Because of his conviction that the fundamental chemical processes in heterogenous and homogeneous metal-based chemistry were closely related, the presence of his group did a great deal to increase the interaction between surface scientists and inorganic chemists at Berkeley. This trend fit in well with Earl's growing conviction that chemistry departments in general were too divisionalized and interdisciplinary research was likely to be of growing importance in the future. This was an attitude that undoubtedly germinated at Du Pont and was reinforced by Earl's experience in the small, interactive department at Cornell. He believed strongly that if the Cornell-style interactive atmosphere and the physical and intellectual resources of the university and Lawrence Berkeley Laboratory could be combined, his new environment could be truly unique and scientifically powerful. He worked hard—and successfully—to establish that combination.

Earl's dedication to all phases of the education process were evident early in his career, when he played a major role in the establishment of the ACS journal *Inorganic Chemistry*. After moving to Berkeley, he perceived a need for a focused journal in the area of organometallic chemistry. He worked hard to determine whether there was a solid demand for such a journal and, after being convinced of this, played a singularly effective role in getting the new journal *Organometallics* established. He was instrumental in attracting Dietmar Seyferth and Richard Schrock to their current editorial positions at the journal. Educational policies and processes, at both the graduate and undergraduate levels, were also an important part of Earl's vision of Berkeley's growing excellence in inorganic chemistry. His terms as graduate inorganic advisor were marked by successful efforts to provide students with new flexibility in designing their course programs. Shortly after arriving at Berkeley he instituted a new advanced inorganic course, emphasizing modern structural and mechanistic principles, and taught the course himself for several years. Dedicated to attracting the best faculty and graduate students to the department, he expended much effort explaining his goals and ideas to potential students and faculty. At the time of his death, he was chairing a committee charged with revising the first-year chemistry curriculum. The committee continued his work on this project, and several of Earl's ideas have been incorporated into a new freshman chemistry program that was instituted this year.

Earl's personality reflected and reinforced much of the character of his scientific work. He gave the impression of being rather reserved, placing great importance on interacting with others with calm and dignity; he almost never raised his voice or became outspoken in public. However,

his friends, family, and colleagues realized that he was a deeply caring and emotional person and understood the powerful drive and intensity that motivated him. This intensity affected everyone who knew him. Although in some cases his work provoked controversy, everyone acknowledged his dedication to research and education, the unique breadth of his scientific vision, and the major contributions he made to chemistry during his lifetime.

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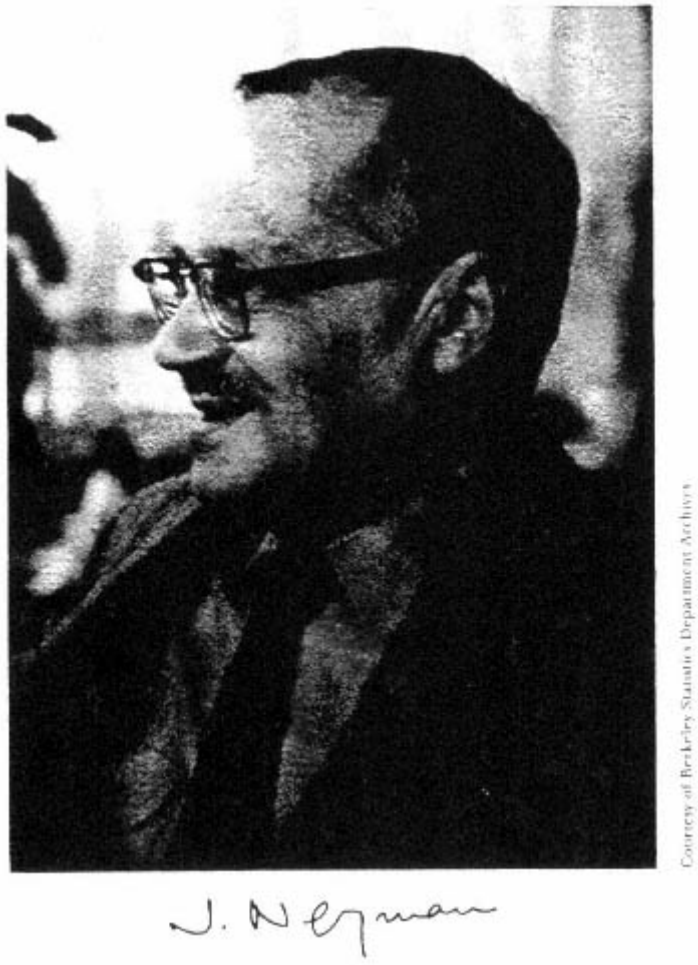

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J. Neyman

JERZY NEYMAN

April 16, 1894–August 5, 1981

BY E. L. LEHMANN

DURING THE 1930s Jerzy Neyman developed a new paradigm for theoretical statistics, which derives optimal statistical procedures as solutions to clearly stated mathematical problems. He applied these ideas to the theories of hypothesis testing, estimation by confidence intervals, and survey sampling. During the following decades this became the dominant approach to theoretical statistics. In addition to his scientific work, Neyman was a far-seeing and highly efficient administrator who in the decade 1945–55 created in Berkeley a substantial Department of Statistics of international stature. Starting in 1945 he also established a Berkeley series of Symposia on Mathematical Statistics and Probability, meeting at five-year intervals, which for the next twenty-five years became the principal series of international meetings in statistics.

Neyman's long life was dominated by his work, of which he took a comprehensive view encompassing its academic, administrative, and social aspects.

Adapted from a biographical article written for the *Dictionary of Scientific Biography*, Supplement II. I am grateful to the American Council of Learned Societies for permitting the use of this material.

EARLY YEARS

Jerzy Neyman was born in Bendery (Russia) to parents of Polish ancestry. His full name with title—Splawa-Neyman—the first part of which he dropped at age thirty, reflects membership in the polish nobility. Neyman's father Czeslaw, who died when Jerzy was twelve, was a lawyer and later judge and an enthusiastic amateur archeologist. Since the family had been prohibited by the Russian authorities from living in Central Poland, then under Russian domination, Neyman grew up in Russia: in Kherson, Melitopol, Simferopol, and (after his father's death) Kharkov, where in 1912 he entered the university.

At Kharkov, Neyman was first interested in physics, but because of his clumsiness in the laboratory he abandoned it in favor of mathematics. On reading Lebesgue's "Leçons sur L'integration et la Recherche des Fonctions Primitives," he later wrote (in a Festschrift in honor of Herman Wold [1970]): "I became emotionally involved. I spent the summer of 1915 at a country estate, coaching the son of the owner. There were three summer houses on the estate, filled with young people, including girls whom I found beautiful and most attractive. However, the involvement with sets, measure and integration proved stronger than the charms of young ladies and most of my time was spent either in my room or on the adjacent balcony either on study or on my first efforts at new results, intended to fill in a few gaps that I found in Lebesgue." A manuscript on Lebesgue integration (500 pp., handwritten) that Neyman submitted to a prize competition won a gold medal.

One of his mentors at Kharkov was Serge Bernstein who lectured on probability theory and statistics (including application of the latter to agriculture), subjects that did not particularly interest Neyman. Nevertheless, he later ac

knowledged the influence of Bernstein from whom he "tried to acquire his tendency of concentrating on some 'big problem'." It was also Bernstein who introduced him to Karl Pearson's *Grammar of Science*, which made a deep impression. After the first World War, Poland regained its independence but soon became embroiled in a war with Russia over borders. Neyman, still in Kharkov, was jailed as an enemy alien. In 1921, in an exchange of prisoners, he finally went to Poland for the first time at the age of twenty-seven.

In Warsaw he established contact with Sierpinski, one of the founders of the journal *Fundamenta Mathematicae*, which published one of Neyman's gold medal results (1923, vol. 5, pp. 328–30). Although Neyman's heart was in pure mathematics, the statistics he had learned from Bernstein was more marketable and enabled him to obtain a position as (the only) statistician at the Agricultural Institute in Bydgoszcz (formerly Bromberg). There, during 1921–22, he produced several papers on the application of probabilistic ideas to agricultural experimentation. In light of Neyman's later development, this work is of interest because of its introduction of probability models for the phenomena being studied, particularly a randomization model for the case of a completely randomized experiment. (A key section was translated and published with an introduction by Speed and comments by Ruben in *Statistical Science*, vol. 5, 1990, pp. 463–80.) He had learned the philosophy of such an approach from Karl Pearson's book, where great stress is laid on models as mental constructs the formulation of which constitutes the essence of science.[1]

In December 1922 Neyman gave up his job in Bydgoszcz to take charge of equipment and observations at the State Meteorological Institute, a change that enabled him to move

to Warsaw. He did not like the work and soon left to become an assistant at the University of Warsaw and Special Lecturer in mathematics and statistics at the Central College of Agriculture; he also gave regular lectures at the University of Krakow. In 1924 he obtained his doctorate from the University of Warsaw with a thesis based on the papers he had written at Bydgoszcz.

Since no one in Poland was able to gauge the importance of his statistical work (he was "sui generis," as he later described himself), the Polish authorities provided an opportunity for him to establish his credibility through publication in British journals. For this purpose they gave him a fellowship to work with Karl Pearson in London. He did publish three papers in *Biometrika* (based in part on his earlier work), but scientifically the academic year (1925–26) spent in Pearson's laboratory was a disappointment. Neyman found the work of the laboratory old-fashioned and Pearson himself surprisingly ignorant of modern mathematics. (The fact that Pearson did not understand the difference between independence and lack of correlation led to a misunderstanding that nearly terminated Neyman's stay at the laboratory.) So when, with the help of Pearson and Sierpinski, Neyman received a Rockefeller fellowship that made it possible for him to stay in the West for another year, he decided to spend it in Paris rather than in London.

There he attended the lectures of Lebesgue and a seminar of Hadamard. "I felt that this was real mathematics worth studying" he wrote later, "and, were it not for Egon Pearson, I would have probably drifted to my earlier passion for sets, measure and integration, and returned to Poland as a faithful member of the Warsaw school and a steady contributor to *Fundamenta Mathematicae*."

THE NEWMAN-PEARSON THEORY

What pulled Neyman back into statistics was a letter he received in the fall of 1926 from Egon Pearson, Karl Pearson's son, with whom Neyman had had only little contact in London. Egon had begun to question the rationale underlying some of the current work in statistics, and the letter outlined his concerns. Correspondence developed and, reinforced by occasional joint holidays, continued even after the end of the Rockefeller year when Neyman returned to a hectic and difficult life in Warsaw. He continued to lecture at the university (as docent after his habilitation in 1928), at the Central College of Agriculture, and at the University of Krakow. In addition, he founded a small statistical laboratory at the Nencki Institute for Experimental Biology. To supplement his meager academic income, and to provide financial support for the students and young co-workers in his laboratory, he took on a variety of consulting jobs. These involved different areas of application, with the majority coming from agriculture and from the Institute for Social Problems, the latter work being concerned with Polish census data.

Neyman felt harassed, and his financial situation was always precarious. The bright spot in this difficult period was his work with the younger Pearson. Trying to find a unifying, logical basis that would lead systematically to the various statistical tests that had been proposed by Student and Fisher was a "big problem" of the kind for which he had hoped since his student days with Bernstein.

In 1933 Karl Pearson retired from his chair at University College, London, and his position was divided between R. A. Fisher and Egon Pearson. The latter lost no time, and, as soon as it became available, in the spring of 1934 offered Neyman a temporary position in his laboratory. Neyman

was enthusiastic. This would greatly facilitate their joint work and bring relief to his Warsaw difficulties.

The set of issues addressed in the joint work of Neyman and Pearson between 1926 and 1933 turned out indeed to be a "big problem," and their treatment of it established a new paradigm that changed the statistical landscape. What concerned Pearson when he first approached Neyman in 1926 was the ad hoc nature of the small sample tests being studied by Fisher and Student. In his search for a general principle from which such tests could be derived, he had written to Student. In his reply Student suggested that one would be inclined to reject a hypothesis under which the observed sample is very improbable, "if there is an alternative hypothesis which will explain the occurrence of the sample with a more reasonable probability" (E. S. Pearson in *Research Papers in Statistics*, F. N. David, ed., 1966). This comment led Pearson to propose to Neyman the likelihood ratio criterion, in which the maximum likelihood of the observed sample under the alternatives under consideration is compared to its value under the hypothesis. During the next year Neyman and Pearson studied this and other approaches, and worked out likelihood ratio tests for some important examples. They published their results in 1928 in a fundamental two-part paper, "On the Use and Interpretation of Certain Test Criteria for Purposes of Statistical Inference." The paper contained many of the basic concepts of what was to become the Neyman-Pearson Theory of Hypothesis Testing, such as the two types of error, the idea of power, and the distinction between simple and composite hypotheses.

Although Pearson felt that the likelihood ratio provided the unified approach for which he had been looking, Neyman was not yet satisfied. It seemed to him that the likelihood

principle itself was somewhat ad hoc and had no fully logical basis. However, in February 1930 he was able to write Pearson that he had found "a rigorous argument in favour of the likelihood method." His new approach consisted of maximizing the power of the test, subject to the condition that under the hypothesis (assumed to be simple) the rejection probability has a preassigned value (the level of the test). He reassured Pearson that in all cases he had examined so far this logically convincing test coincided with the likelihood ratio test. A month later Neyman announced to Pearson that he now had a general solution of the problem of testing a simple hypothesis against a simple alternative. The result in question is the "Fundamental Lemma," which plays such a crucial role in the Neyman-Pearson theory.

The next step was to realize that in the case of more than one alternative there might exist a uniformly most powerful test that would simultaneously maximize the power for all of them. If such a test exists, Neyman found, it coincides with the likelihood ratio test, but in the contrary case—alas—the likelihood ratio test may be biased. These results, together with many examples and elaborations, were published in 1933 under the title, "On the Problem of the Most Efficient Tests of Statistical Hypotheses." While in the 1928 paper the initiative and insights had been those of Pearson, who had to explain to Neyman what he was doing, the situation was now reversed, with Neyman as leader and Pearson a somewhat reluctant follower.

The 1933 paper is the fundamental paper in the theory of hypothesis testing. It established a framework for this theory[2] and states the problem of finding the best test as a clearly formulated, logically convincing mathematical problem that one can then proceed to solve. Its importance transcends the theory of hypothesis testing since it also pro

vided the inspiration for Wald's later, much more general, statistical decision theory.

SURVEY SAMPLING AND CONFIDENCE ESTIMATION

The following year Neyman published another landmark paper. An elaboration of work on survey sampling he had done earlier for the Warsaw Institute for Social Problems, it was directed toward bringing clarity into a somewhat muddled discussion about the relative merits of two different sampling methods. His treatment, described by Fisher as "luminous," introduced many important concepts and results and may be said to have initiated the modern theory of survey sampling.

The year 1935 brought two noteworthy events. The first was Neyman's appointment to a permanent position as reader (associate professor) in Pearson's department. Although at the time he was still hoping to eventually return to Poland, he in fact never did except for brief visits. The second event was the presentation at a meeting of the Royal Statistical Society of an important paper on agricultural experimentation in which he raised some questions concerning Fisher's Latin square design. This caused a break in their hitherto friendly relationship and was the beginning of lifelong disputes. (Fisher, who opened the discussion of the paper, stated that "he had hoped that Dr. Neyman's paper would be on a subject with which the author was fully acquainted, and on which he could speak with authority, as in the case of his address to the Society last summer. Since seeing the paper, he had come to the conclusion that Dr. Neyman had been somewhat unwise in his choice of topics.")

Neyman was to remain in England for four years (1934–38). During this time he continued his collaboration with

Egon Pearson on the theory and applications of optimal tests, efforts that also included contributions from graduate and postdoctoral students. To facilitate publication and to emphasize the unified point of view underlying this work, Neyman and Pearson set up a series, "Statistical Research Memoirs," published by University College and restricted to work done in the Department of Statistics. A first volume appeared in 1936 and a second in 1938.

Another central problem occupying Neyman during his London years was the theory of estimation: not point estimation in which a parameter is estimated by a unique number, but estimation by means of an interval or more general set in which the unknown parameter can be said to lie with specified confidence (i.e., probability). Such confidence sets are easily obtained under the Bayesian assumption that the parameter is itself random with a known probability distribution, but Neyman's aim was to dispense with such an assumption that he considered arbitrary and unwarranted.

Neyman published brief accounts of his solution to this problem in 1934 and 1935 and the theory in full generality in 1937 in "Outline of a Theory of Statistical Estimation Based on the Classical Theory of Probability." He had first submitted this paper to *Biometrika*, then being edited by Egon Pearson, but to his great disappointment Pearson rejected it as too long and too mathematical.

Neyman's approach was based on the idea of obtaining confidence sets $S(X)$ for a parameter θ from acceptance regions for the hypotheses that $\theta = \theta_o$ by taking for $S(X)$ the set of all parameter values θ_o that would be accepted at the given level. This formulation established an equivalence between confidence sets and families of tests and enabled him to transfer the test theory of the 1933 paper lock, stock, and barrel to the theory of estimation. (Unbe

knownst to Neyman, the idea of obtaining confidence sets by inverting an acceptance rule had already been used in special cases by Laplace, in a large-sample binomial setting, and by Hotelling).

In his paper on survey sampling, Neyman had referred to the relationship of his confidence intervals to Fisher's fiducial limits, which appeared to give the same results, although derived from a somewhat different point of view. In the discussion of the paper, Fisher welcomed Neyman as an ally in the effort to free statistics from unwarranted Bayesian assumptions. He went on to say that "Dr. Neyman claimed to have generalized the argument of fiducial probability, and he had every reason to be proud of the line of argument he had developed for its perfect clarity. The generalization was a wide and very handsome one, but it had been erected at considerable expense. . . . " He then proceeded to indicate the disadvantages he saw in Neyman's formulation, of which perhaps the most important one (revealing the wide difference between their interpretations) was nonuniqueness. The debate between the two men over their respective approaches continued for many years, usually in less friendly terms; it is reviewed by Neyman in "Silver Jubilee of My Dispute with Fisher" (*Journal of the Operation Research Society of Japan*, 1961, pp. 145-54).

STATISTICAL PHILOSOPHY

During the period of his work with Pearson, Neyman's attitude toward probability and hypothesis testing gradually underwent a radical change. In 1926 he tended to favor a Bayesian approach[3] in the belief that any theory would have to involve statements about the probabilities of various alternative hypotheses and hence an assumption of prior probabilities. In the face of Pearson's (and perhaps

also Fisher's) strongly anti-Bayesian position, he became less certain, and in his papers of the late 1920s (both alone and jointly with Pearson) he presented Bayesian and non-Bayesian approaches side by side. A decisive influence was von Mises's book *Wahrscheinlichkeit, Statistik und Wahrheit* (1928) about which he later wrote (in his Author's Note to *A Selection of Early Statistical Papers of J. Neyman*) that it "confirmed him as a radical 'frequentist' intent on probability as a mathematical idealization of relative frequency." He remained an avowed frequentist and opposed any subjective approach to science for the rest of his life.

A second basic aspect of Neyman's work from the 1930s on is a point of view, that he formulated clearly in the closing pages of his presentation at the 1937 Geneva Conference ("L'estimation statistique traitée comme un problème classique de probabilité," *Actualites Scientifiques et Industrielles*, no. 739, pp. 25–57). He states that his approach is not based on inductive reasoning but on the concept of "comportement inductif" or inductive behavior. That is, statistics is to be used not to extract from experience "beliefs" but as a guide to appropriate action.

He summarized his views in a paragraph in a paper presented in 1949 to the International Congress on the Philosophy of Science ("Foundations of the General Theory of Estimation," *Actualites Scientifiques et Industrielles*, 1951, No. 1146, p. 85).

> "Why abandon the phrase 'inductive reasoning' in favor of 'inductive behavior'?" As explained in 1937,[4] the term inductive reasoning does not seem appropriate to describe the new method of estimation because all the reasoning behind this method is clearly deductive. Starting with whatever is known about the distribution of the observable variables X, we deduce the general form of the functions f(X) and g(X) which have the properties of confidence limits. Once a class of such pairs of functions is found, we formulate some properties of these functions which may be considered

> desirable and deduce either the existence or non-existence of an "optimum" pair, etc. Once the various possibilities are investigated we may decide to use a particular pair of confidence limits for purposes of statistical estimation. This decision, however, is not 'reasoning'. This is an act of will just as the decision to buy insurance is an act of will. Thus, the mental processes behind the new method of estimation consist of deductive reasoning and of an act of will. In these circumstances the term 'inductive reasoning' is out of place and, if one wants to keep the adjective 'inductive', it seems most appropriate to attach to it the noun 'behavior'.

In other writings (e.g., *Reviews of the International Statistical Institute*, 1957, vol. 25, pp. 7–22), Neyman acknowledges that a very similar point of view was advocated by Gauss and Laplace. It is, of course, also that of Wald's later general statistical decision theory. On the other hand, this view was strongly attacked by Fisher (e.g., JRSS (B), 1955, vol. 17, pp. 69-78) who maintained that decision making has no role in scientific inference and that his fiducial argument provides exactly the mechanism required for this purpose.

MOVING TO AMERICA

By 1937 Neyman's work was becoming known not only in England and Poland but also in other parts of Europe and in America. He gave an invited talk about the theory of estimation at the International Congress of Probability in 1937 in Geneva, and in the spring of 1937 he spent six weeks in the United States on a lecture tour organized by S. S. Wilks. The visit included a week at the Graduate School of the Department of Agriculture in Washington arranged by Edward Deming. There he gave three lectures and six conferences on the relevance of probability theory to statistics and on his work in hypothesis testing, estimation, sampling, and agricultural experimentation as illustrations of this approach. These "Lectures and Con

ferences on Mathematical Statistics," which provided a coherent statement of the new paradigm he had developed and exhibited its successful application to a number of substantive problems, were a tremendous success. A mimeographed version appeared in 1938 and was soon sold out. Neyman published an augmented second edition in 1952.

After his return from the United States, Neyman debated whether to remain in England, where he had a permanent position but little prospect of promotion and independence, or to return to Poland. Then completely unexpectedly, in the fall of 1937, he received a letter from an unknown, G. C. Evans, chairman of the Mathematics Department at Berkeley, offering him a position in the department. Neyman hesitated for some time. California and its university were completely unknown quantities to him, while the situation in England, although not ideal, was reasonably satisfactory and stable. An attractive aspect of the Berkeley offer was the nonexistence there of any systematic program in statistics, so that he would be free to follow his own ideas. What finally tipped the balance in favor of Berkeley was the threat of war in Europe. Thus, in April 1938 Neyman decided to accept the Berkeley offer and emigrate to America, with his wife Olga (from whom he later separated) and his two-year-old son Michael. He had just turned forty-four, and he would remain in Berkeley for the rest of his life.

THE BERKELEY DEPARTMENT OF STATISTICS

Neyman's top priority after his arrival in Berkeley was the development of a statistics program, that is, a systematic set of courses and a faculty to teach them. He quickly organized a number of core courses and began to train some graduate students and one temporary instructor in

his own approach to statistics. Administratively, he set up a statistical laboratory as a semiautonomous unit within the Mathematics Department. However, soon America's entry into World War II in 1941 put all further academic development on hold. Neyman took on war work, and for the next several years this became the laboratory's central and all-consuming activity. The work dealt with quite specific military problems and did not produce results of lasting interest.

The building of a faculty began in earnest after the war, and by 1956 Neyman had established a permanent staff of twelve members, many his own students, but also including three senior appointments from outside (Loève, Scheffé, and Blackwell). Development of a substantial faculty, with the attendant problems of space, clerical staff, summer support, and so on, represented a major sustained administrative effort. A crucial issue in the growth of the program concerned the course offerings in basic statistics by other departments. Although these involved major vested interests, Neyman gradually concentrated the teaching of statistics within his program, at least at the lower division level. This was an important achievement both in establishing the identity of the program and in obtaining the student base that alone could justify the ongoing expansion of the faculty. In his negotiations with the administration, Neyman was strengthened by the growing international reputation of his laboratory and by the increasing postwar importance of the field of statistics itself.

An important factor in the laboratory's reputation was the series of international "Symposia on Mathematical Statistics and Probability" that Neyman organized at five-year intervals during 1945–70, and the subsequent publication of their proceedings. The first symposium was held in

August 1945 to celebrate the end of the war and "the return to theoretical research" after years of war work. The meeting, although rather modest compared to the later symposia, was such a success that Neyman soon began to plan another one for 1950. In later years the symposia grew in size, scope, and importance and did much to establish Berkeley as a major statistical center.

The spectacular growth Neyman achieved for his group required a constant struggle with various administrative authorities, including those of the Mathematics Department. To decrease the number of obstacles, and also to provide greater visibility for the statistics program, Neyman, soon after his arrival in Berkeley, began a long effort to obtain independent status for his group as a Department of Statistics. A separate department finally became a reality in 1955, with Neyman as its chair. He resigned the chairmanship the following year (but retained the directorship of the laboratory to the end of his life). He wrote in his letter of resignation that "the transformation of the old Statistical Laboratory into a Department of Statistics closed a period of development . . . and opened a new phase." In these circumstances he stated that "it is only natural to have a new and younger man take over."

There was perhaps another reason. Much of Neyman's energy during his nearly twenty years in Berkeley had gone into administration. His efforts had been enormously successful—a first-rate department, the symposia, and a large number of grants providing summer support for faculty and students. It was a great accomplishment and his personal creation, but now it was time to get back more fully into research.

APPLIED STATISTICS

Neyman's theoretical research in Berkeley was largely motivated by his consulting work, one of the purposes for which the university had appointed him and through which he made himself useful to the campus at large. Problems in astronomy, for example, led to the interesting insight (1948, with E. L. Scott) that maximum likelihood estimates may cease to be consistent if the number of nuisance parameters tends to infinity with increasing sample size. Also, to simplify maximum likelihood computations, which in applications frequently became very cumbersome, he developed linearized, asymptotically equivalent methods—his BAN (best asymptotically normal) estimates (1949), which have proved enormously useful.

His major research efforts in Berkeley were devoted to several large-scale applied projects. These included questions regarding competition of species (with T. Park), accident proneness (with G. Bates), the distribution of galaxies and the expansion of the universe (with C. D. Shane and particularly Elizabeth Scott, who became a steady collaborator and close companion), the effectiveness of cloud seeding, and a model for carcinogenesis. Of these perhaps the most important was the work in astronomy, where the introduction of the Neyman-Scott clustering model brought new methods into the field that "were remarkable and perhaps have not yet been fully appreciated and exploited." (*Peeble: Large Scale Structure of the Universe*, Princeton University Press, Princeton, N.J., 1979).

Neyman's applicational work, although it extends over many different areas, exhibits certain common features, which he made explicit in some of his writings and which combine into a philosophy for applied statistics. The following are some of the principal aspects:

1. *The studies are indeterministic*. Neyman pointed out that the distinction between deterministic and indeterministic studies lies not so much in the nature of the phenomena as in the treatment accorded to them ("Indeterminism in Science and New Demands on Statisticians," *Journal of the American Statistical Association*, 1960, vol. 55, pp. 625–39). In fact, many subjects that traditionally were treated as deterministic are now being viewed stochastically. Neyman himself contributed to this change in several areas.
2. *An indeterministic study of a scientific phenomenon involves the construction of a stochastic model*. In this connection, Neyman introduced the important distinction between models that are interpolatory devices and those that embody genuine explanatory theories. The latter he describes as "a set of reasonable assumptions regarding the mechanism of the phenomena studied," while the former "by contrast consist of the selection of a relatively ad hoc family of functions, not deduced from underlying assumptions, and indexed by a set of parameters" ("Stochastic Models and Their Application to Social Phenomena," coauthored by W. Kruskal and presented at a joint session of the IMS, ASA, and the American Sociological Society, Sept. 1956). The distinction was discussed earlier, and again later, in Neyman's paper in *Annals of Mathematical Statistics* (1939, vol. 10, pp. 372–73) and in *A View of Biometry*. Siam. (Philadelphia, 1974, pp. 185–201).

   Neyman's favorite example of the distinction between the two types was the family of Pearson curves, which for a time was very popular as an interpolatory model that could be fitted to many different data sets, and Mendel's model for heredity. "At the time of its invention," he wrote about the latter in the *Journal of the American Statistical Association* (1960, vol. 55, pp. 625–39), "this was little more than an

interpolatory procedure invented to summarize Mendel's experiments with peas," but eventually it turned out to satisfy Neyman's two criteria for a model of genuine scientific value, namely (i) broad applicability (i.e., in Mendel's case not restricted to peas) and (ii) identifiability of details (the genes as entities with identifiable location on the chromosomes).

Most actual modeling, Neyman pointed out, is intermediate between these two extremes, often exhibiting features of both kinds. Related is the realization that investigators will tend to use as building blocks models that "partly through experience and partly through imagination, appear to us familiar and, therefore, simple." (with E. L. Scott, "Stochastic Models of Population Dynamics," *Science* 1959, vol. 130, pp. 303–8).

3. *To develop a "genuine explanatory theory" requires substantial knowledge of the scientific background of the problem.* When the investigation concerns a branch of science with which the statistician is unfamiliar, this may require a considerable amount of work. For his collaboration with Scott in astronomy, Neyman studied the astrophysical literature, joined the American Astronomical Society, and became a member of the Commission on Galaxies of the International Astronomical Union. When he developed an interest in carcinogenesis, he spent three months at the National Institutes of Health to learn more about the biological background of the problem.

Neyman summarized his own attitude toward this kind of research in the closing sentence of his paper, "A Glance of My Personal Experiences in the Process of Research" (in *Scientists at Work*, Almquist and Wicksell, Uppsala, Sweden, 1970): "The elements that are common… seem to by my susceptibility to becoming emotionally involved in

other individuals' interests and enthusiasm, whether these individuals are sympathetic or not, and, particularly in the more recent decades, the delight I experience in trying to fathom the chance mechanisms of phenomena in the empirical world."

An avenue for learning about the state of the art in a field and bringing together diverse points of view, which Neyman enjoyed and of which he made repeated use, was to arrange a conference. Two of these (on weather modification in 1965 and on molecular biology in 1970) became parts of the then-current symposia. In addition, in 1961, jointly with Scott, he arranged a "Conference on the Instability of Systems of Galaxies." In 1973 he edited for the National Academy of Sciences a volume in celebration of the five-hundredth anniversary of the birth of Nicholas Copernicus: *The Heritage of Copernicus: Theories Pleasing to the Mind*. The volume presents revolutionary changes that occurred, respectively, in astronomy and cosmology, biology, chemistry and physics, mathematics, technology, and in the thinking in mathematics and science brought about by the introduction of chance mechanisms. Finally, in July 1981, jointly with Le Cam and on very short notice, Neyman arranged an interdisciplinary cancer conference.

EPILOGUE

A month after the cancer conference, Neyman died of heart failure at age eighty-seven on August 5, 1981. He had been in reasonable health up to two weeks earlier and on the day before his death was still working in the hospital on a book on weather modification.

Neyman is recognized as one of the founders of the modern theory of statistics, whose work on hypothesis testing, confidence intervals, and survey sampling has revolutionized

both theory and practice. His enormous influence on the development of statistics is further greatly enhanced through the large number of his Ph.D. students. These are:

From Poland: Kolodziejczyk, Iwaszkiewicz, Wilenski, Pytkowski.

From London: Hsu, David, Johnson, Eisenhart, Sukhatme, Beall, Sato, Shanawany, Jackson, Tang.

From Berkeley: Chen, Dantzig, Lehmann, Massey, Fix, Chapman, Eudey, Gurland, Hodges, Seiden, Hughes, Taylor, Jeeves, Le Cam, Tate, Chiang, Agarwal, Sane, Read, Singh, Borgman, Marcus, Buehler, Kulkarni, Davies, Clifford, Samuels, Oyelese, Ray, Grieg, Green, Tsiatis, Singh, Javitz, Darden.

Neyman was completely and enthusiastically dedicated to his work, which filled his life—there was no time for hobbies. Work, however, included not only research and teaching but also their social aspects, such as traveling to meetings and organizing conferences. Pleasing his guests was an avocation; his hospitality had an international reputation. In his laboratory he created a family atmosphere that included students, colleagues, and visitors, with himself as paterfamilias.

As administrator, Neyman was indomitable. He would not take "no" for an answer and was quite capable of resorting to unilateral actions. He firmly believed in the righteousness of his causes and found it difficult to understand how a reasonable person could disagree with him. At the same time, he had great charm that often was hard to resist.

High on Neyman's list of values were his opposition to injustice and his sympathy for the underdog. Two illustrations must suffice. In 1946, as a member of the allied

mission to supervise the Greek elections, his feeling for fairness and justice led him to disobey orders of his superiors, with the consequence of his services being abruptly terminated. The details are given by Constance Reid (*Neyman—from Life*, Springer, New York, 1982, pp. 201–8). This book also describes (pp. 262–68) how deeply Neyman was affected, when in 1963 as a visiting lecturer for the Mathematical Association of America, he came into firsthand contact with segregation in the South. This led him to various efforts that culminated in the establishment at Berkeley of a special scholarship program to help prepare talented underprivileged young people for a university education.

On a personal level, the characteristic that perhaps remains above all in the minds of his friends and associates is his generosity—furthering the careers of his students, giving credit and doing more than his share in collaboration, and extending his help (including financial assistance out of his own pocket) to anyone who needed it.

NOTES

1. "One of my favorite ideas," Neyman later wrote in 1957 (*Rev. Int. Stat. Inst.* 25:8), "learned from Mach via Karl Pearson's 'Grammar of Science,' is that scientific theories are no more than models of natural phenomena."

2. Its role in today's statistical climate is discussed by Lehmann, "The Neyman-Pearson theory after 50 Years" (In *Proceedings of the Berkeley Conference in Honor of Jerzy Neyman and Jack Kiefer*, vol. 1 [Wadsworth, 1985]:1–14).

3. In "Frequentist Probability and Frequentist Statistics" (*Synthese* 36[1977]:97–131, Neyman states, "I began as a quasi-Bayesian. My assumption was that the estimated parameter (just one!) is a particular value of a random variable having an unknown prior distribution."

4. Loc. cit.

HONORS AND DISTINCTIONS

HONORARY DEGREES

1959

D.Sc., University of Chicago

1963

LL.D., University of California, Berkeley

1964

Ph.D., University of Stockholm, Sweden

1974

D.Sc., University of Warsaw, Poland

1974

D.Sc., Indian Statistical Institute

MEMBERSHIPS

1963

U.S. National Academy of Sciences

1963

Royal Swedish Academy

1966

Polish National Academy

1979

Royal Society (London)

AWARDS

1958

AAAS Newcomb Cleveland Prize

1966

U.K. Royal Statistical Society Guy Medal in Gold

1969

U.S. National Medal of Science

1973

Copernicus Society of America, Medal and Award

SELECTED BIBLIOGRAPHY

I. ORIGINAL WORKS

A complete bibliography of Neyman's work is given at the end of David Kendall's memoir (*Biographical Memoirs of Fellows of the Royal Society*, vol. 28, 1982).

Some of the early papers are reprinted in the two volumes, *A Selection of Early Statistical Papers of J. Neyman* and *Joint Statistical Papers of J. Neyman and E. S. Pearson* (University of California Press).

Neyman's letters to E. S. Pearson from 1926 to 1933 (but not Pearson's replies) are preserved in Pearson's estate.

An overall impression of Neyman's ideas and style can be gained from his book, *Lectures and Conferences on Mathematical Statistics and Probability*, Second Revised and Enlarged Edition (Graduate School, U.S. Department of Agriculture, Washington, D.C., 1952). The following partial list provides a more detailed view of his major theoretical contributions.

A. Paradigmatic Papers

1928 With E. S. Pearson. On the use and interpretation of certain test criteria for purposes of statistical inference. *Biometrika* 20A:175–240, 263–94.

1933 With E. S. Pearson. On the problem of the most efficient tests of statistical hypotheses. *Philos. Trans. R. Soc. Lond. Ser. A* 231:289–337.

1934 On the two different aspects of the representative method. *J. R. Stat. Soc.* 97:558–625 (A Spanish version of this paper appeared in *Estad. J. Inter-Am. Stat. Inst.* 17:587–651.)

1937 Outline of a theory of statistical estimation based on the classical

theory of probability. *Philos. Trans. R. Soc. Lond. Ser. A* 236:333–80.
1937 'Smooth' test for goodness of fit. *Skand. Aktuar. Tidskr.* 20:149–99.
1939 On a new class of 'contagious' distributions, applicable in entomology and bacteriology. *Ann. Math. Stat.* 10:35–57.
1948 With E. L. Scott. Consistent estimates based on partially consistent observations. *Econometrica* 16:1–32.
1949 Contribution to the theory of the chi–square test. In *Proceedings of the Berkeley Symposium on Mathematical Statistical Probability*, ed. J. Neyman, pp. 239–73. Berkeley: University of California Press.
Optimal asymptotic tests of composite statistical hypotheses. In *Probability and Statistics*, Harald Cramér Volume, ed. U. Granander, pp. 213–34. Uppsala, Sweden: Almquist & Wiksells.

Neyman's position regarding the role of statistics in science can be obtained from the following more philosophical and sometimes autobiographical articles.

1951 Foundation of the general theory of statistical estimation. *Actual. Sci. Ind.* 1146:83–95.
1955 The problem of inductive inference. *Commun. Pure Appl. Math.* VIII:13–45.

1957 'Inductive behavior' as a basic concept of philosophy of science. *Rev. Inst. Int. Stat.* 25:7–22.
1959 With E. L. Scott. Stochastic models of population dynamics. *Science N.Y.* 130:303–8.
1970 A glance at some of my personal experiences in the process of research. In *Scientists at Work*, ed. T. Dalenius, G. Karlson and S. Malmquist, pp. 148–64. Sweden: Almquist & Wiksells.
1971 With E. L. Scott. Outlier proneness of phenomena and of related distributions. In *Optimizing Methods in Statistics*, ed. J. S. Rustagi, pp. 413–30. New York: Academic Press.
1977 Frequentist probability and frequentist statistics. *Synthèse* 36:97–131.

The most important source for Neyman's life and personality is Constance Reid's *Neyman—from Life* (Springer, New York, 1982), which is based on Neyman's own recollections (obtained during weekly meetings over a period of more than a year) and those of his colleagues and former students and on many original documents. A useful account of his collaboration with E. S. Pearson was written by Pearson for the Neyman Festschrift, *Research Papers in Statistics* (F. N. David, ed., Wiley, New York, 1966). Additional accounts of his life and work are provided by the following papers.

1974 L. Le Cam and E. L. Lehmann. J. Neyman—on the occasion of his 80th birthday . *Ann. Stat.* 2:vii–xiii.

1982 D. G. Kendall, M. S. Bartlett, and T. L. Page. Jerzy Neman, 1894–1981. In *Biographical Memoirs of Fellows of the Royal Society*, vol. 28, pp. 379–412.
1982 E. L. Lehmann and Constance Reid. In memoriam–Jerzy Neyman, 1894–1981. *Am. Stat.* 36:61–62.
1985 E. L. Scott. Neyman, Jerzy. *Encycl. Stat. Sci.* 6:214–23.

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John H. Northrop

JOHN HOWARD NORTHROP

July 5, 1891–May 27, 1987

BY ROGER M. HERRIOTT

JOHN HOWARD NORTHROP, trained in chemistry and introduced to general physiology by Jacques Loeb, proved that the enzymes pepsin and trypsin are proteins. The pattern of investigation that he used in this work was followed by his associates in isolating and examining other enzymes. The success of these studies led to the general acceptance of the view that enzymes are proteins. The importance of this work earned Northrop a share in the Nobel Prize in chemistry in 1946.

John H. Northrop was an eighth-generation Yankee, a descendant of Joseph Northrop, who arrived in Milford, Connecticut, in 1630. His forebears included men of influence and accomplishment. Three of them were the Reverend Thomas Hooper 1631; the Reverend Jonathan Edwards, president of Princeton College in 1738; and Frederick C. Havemeyer, founder of the American Sugar Refining Company. The Havemeyer family provided Columbia University with a huge chemistry building in his name.

John's parents were Alice Rich Northrop and John Isaiah Northrop. His father received a Ph.D. from Columbia's School of Mines in 1888 and was appointed "tutor" in the new Zoology Department under Professor Henry Fairfield

Osborne. His mother had been an instructor in the Normal (later Hunter) College of New York City.

A tragic explosion and fire in the Zoology Museum took the life of John Isaiah Northrop just two weeks before his son was born in Yonkers, New York. Despite this devastating accident to her husband, Mrs. Northrop maintained a close association with both Columbia's Zoology Department and Hunter College while rearing her son. She was a botanist and naturalist and helped introduce nature studies into the curriculum of the New York City schools. She also prepared most of the manuscript of a book entitled *Through Field and Woodland*, which was later edited by Oliver P. Medsger and published in 1925 after her untimely death in 1922 when her car was struck by a train.

Young John's earliest recollection[1] of his mother is of her sitting at her desk correcting proof of "A Naturalist in the Bahamas,"[2] a report of a collecting trip his mother and father had made in 1889.

With a devoted mother interested in nature, it is not surprising that John was reared with a deep understanding of the natural world. Both John and his mother took long walks, going with ease over rough terrain for long distances.

John was educated in the public schools of Yonkers, New York, and recalled excellent teachers of mathematics (Mr. Graves) and chemistry (Dr. Metzger). The latter aroused an interest in chemistry that continued throughout his life. John attended Columbia College, where he was an outstanding member of the championship rifle and revolver team and the intercollegiate championship fencing teams. He received his B.S. in 1912 and proceeded directly to Columbia's graduate program in chemistry, earning a master's degree in 1913. He thought the following were exceptional teachers: F. C. Chandler, J. M. Nelson, and M. T.

Bogart in chemistry; T. H. Morgan, E. B. Wilson, and Calkins in zoology; and Carlton Curtiss in botany. Student associates were Michael Heidelberger, George Scatchard, Herman Muller, A. H. Sturtevant, and Calvin Bridges—quite a galaxy of future scientists.

John's doctoral studies were supervised by Professor John M. Nelson, a man of broad interests. The subject of John's thesis was "The Essentiality of Phosphorus in Starch." In 1915 the award of his Ph.D. was accompanied by the W. Bayard Cutting Travelling Fellowship, but the turmoil in Europe and Jacques Loeb's acceptance of John to work at the Rockefeller Institute for Medical Research led him to forego the fellowship. This was an important decision because John retained an association with the Rockefeller Institute (later University) for 70 years.

On June 26, 1917, John Northrop and Louise Walker were married. Louise was a graduate of Barnard College, where she was elected president of her freshman class. She earned a master's degree in zoology at Columbia University and was working on her doctorate. This work took her to Woods Hole in the summer for studies at the Marine Biological Laboratory. It was there she met John. They lived in Mt. Vernon, New York until about 1925, when John, who strongly disliked commuting into New York City, became interested in offers from other institutions. He was persuaded by W. J. V. Osterhout to try working at the Rockefeller Institute's Animal Pathology Laboratory outside of Princeton, New Jersey, where he could walk to the laboratories. John's Princeton house looked out on Lake Carnegie, a great improvement over conditions in New York. He also became a member of several sporting clubs in New Jersey.

Mrs. Northrop gave up her professional studies and de

voted herself to John's interests and the rearing of their two children, Alice Havemeyer and John. She did manage to maintain an interest in music and art in Princeton.

During the hot and humid Princeton summers, the family went to Maine and later to their house near Cotuit, Massachusetts. In the latter place, Northrop could maintain laboratory work in nearby Woods Hole and they all could enjoy playing tennis and the cool sea breezes.

Alice married Dr. Frederick C. Robbins in 1948. They presently live near Cleveland, Ohio, where Robbins is university professor emeritus of Case Western Reserve University. He has had a most distinguished career. In 1954 he shared with Drs. John F. Enders and Thomas H. Weller of Harvard the 1954 Nobel Prize in physiology and medicine for discovering and developing the growth of the polio virus in tissue culture, which led to the vaccines that have been so effective since 1955. He was elected to the National Academy of Sciences and was president of the Academy's Institute of Medicine from 1981–85. He also was dean of Case Western Medical School from 1966 to 1980. The Robbins have two daughters, Alice Christine Robbins Hamlin and Louise Enders Robbins.

Alice's brother John obtained his collegiate education at Princeton and his doctorate at Hawaii and is a program manager at the Naval Ocean Systems Center in San Diego. He married Barbara Mason, and they have three grown children, John H. Northrop II, Geoffrey Mason Northrop, and Helen Haskel Northrop. John H. Northrop II has a daughter, Emma Louise Northrop.

Throughout most of his life Northrop was a strong individual physically. Paul de Kruif admired Northrop's ability to pole a canoe up fast-flowing streams to favorite fishing areas in New Brunswick and Newfoundland. He excelled

in sailing, hunting, marksmanship, and even horseback riding. He trained bird dogs and loved using them in his fall excursions after pheasants, quail, and partridge, yet he avoided research involving animals for he found that distasteful.

A double mastoid operation following an infection during his undergraduate days made Northrop sensitive to certain climatic conditions. He attributed his deafness to exposure to low levels of mustard gas that he worked with during World War II. He avoided scientific meetings in part because of this.

Although he devoted virtually his entire career to laboratory research, Northrop had his moments of interest in other endeavors. He so enjoyed hunting and fishing that he sought ventures that would allow him time for these pleasures. In 1913 he and a friend tried farming near Newburgh, New York, which ended when a fire destroyed their buildings. He next turned to prospecting for gold along the Colorado River where today is Lake Mead. World War I put a stop to that. For seven years after moving to Princeton he joined with a plant pathologist in raising seed potatoes, in the summer months in Aroostook County, Maine. His work was selecting varieties or sources of potatoes that were not infected with disease agents, as judged by whether they produced lesions on tobacco plants. This work also allowed him time to fish for salmon in the Miramachi, Tobrique, or Serpentine rivers of New Brunswick. He reported that the Miramachi River drops 2,000 feet in 80 miles and that he and friend Cheney ran the rapids several summers. "It always afforded us plenty of excitement and plenty of salmon."

Northrop's influence on his associates was by example or casual comment. He was liberal in his acceptance of manuscripts as long as the evidence warranted the conclu

sions. He was associated with the *Journal of General Physiology* for nearly 70 years as contributor, editor, and honorary editor.

EARLY RESEARCH, 1915-25

Jacques Loeb soon found John Northrop a responsive worker, thoroughly grounded in physical principles and unprejudiced about biological processes. The two quickly developed a strong regard for each other. John recognized and often commented to me later about Loeb's ingenious design of experiments to obtain answers to specific questions. Stimulated by the work on fruit flies of T. H. Morgan at Columbia, Dr. Loeb and John examined some of the effects of environmental factors on heredity. John grew *Drosophila* aseptically by freeing the eggs of contaminating organisms and cultivating them on a sterile mixture of yeast extract and banana. These may well have been the first animals grown free of microorganisms. With such fruit flies, Loeb and Northrop showed that there was a temperature coefficient for the duration of life and suggested several mechanisms for such control. John undermined the existing theory of life duration being fixed by an *energy limit* , for he found that carbon dioxide output, a measure of energy expended, was greater at 15°C than at 22°C, yet at 15°C the flies lived longer than at the higher temperature. John also found that inbreeding of aseptic drosophila for 230 generations in the dark had no discernable effect on their life duration, fecundity, or resistance to harmful bacteria.

John's work with Loeb was halted by America's entry into World War I in Europe. Many important chemicals were found to be in short supply, and assistance was requested of many laboratories in developing methods of

producing these chemicals. John had remembered an acetone odor emanating from flasks containing potato discs. He investigated this with the production of acetone in mind and found an organism that yielded acetone in appreciable quantities. He was commissioned a captain in the U.S. Army Chemical Warfare Service and carried the process through the first stage of plant development for Commercial Solvents Corporation of Terra Haute, Indiana. He succeeded in converting 8 percent of "black strap" sugar to acetone and 22 percent to ethanol.

In this connection Northrop recalled that in England the basic explosive "cordite" manufacture depended on the use of acetone, which was in very short supply. Weizman developed an effective means of preparing acetone and saved the day for England. The British government in turn rewarded Weizman by establishing Israel as he wished.

After the war Northrop returned to the Rockefeller Institute and studied a variety of phenomena. These included heliotropism in which he and Loeb found that the horseshoe crab *Limulus* responded to light like a photo cell. Exposed to multiple light sources, the crabs oriented themselves so the product of the intensity of the light, the time of exposure, and the cosine of the angle of incidence at the surface of the photosensitive organ were equal for each light source. In other work he studied Donnan equilibria; the kinetics of osmosis; the swelling of cells; and, with Moses Kunitz, the micellar nature of gelatin. With Paul de Kruif and Jules Freund, he studied the agglutination of bacteria and red cells. Northrop also devoted considerable effort to kinetic studies of the action of pepsin and trypsin and the inhibitor effect of some digestion products. In a paper he published with R. B. Hussey is a comment so characteristic of Northrop's reasoning that I must quote it. In com

menting on the adsorption theories of enzymes held by some European enzymologists, they noted, "In as much as it is possible to account for enzyme reactions on the basis of the laws of general chemistry, there seems to be no theoretical reason to disregard this fact and seek explanations in adsorption theories."

Northrop found that "living cells have a peculiar membrane which is very selective about passage of material through it. The selective process is destroyed once the cell is dead. I found that neither pepsin nor trypsin are taken up by living organisms, whereas as soon as the organisms die, the enzyme rapidly digests them. Live fish or worms may live in the presence of pepsin or trypsin strong enough to digest the dead organism in a few hours."

Jacques Loeb's sudden death in 1924 brought to a close an important period in Northrop's life. For nearly a decade Northrop had been nurtured by one of the great experimentalists and given the freedom to explore a variety of systems. Promotion of Northrop to member of the Rockefeller Institute soon followed. After his move to the Rockefeller Institute laboratory in Princeton, where the Department of Animal Pathology was directed by Theobald Smith, Northrop gathered a small group beginning with Moses Kunitz, who had been on Loeb's staff and with whom Northrop had collaborated. The respect each member of the group had of the others' qualities led to a highly productive relationship. Mortimer L. Anson joined them and initially developed with Northrop the simple but useful cintered glass disc cell for measuring diffusion constants of substances. In 1929 Albert Krueger, joined the group and studied the bacteriophage infection of *Staphylococcus aureus*. Krueger's return to California in 1931 left an opening that I was privileged to fill from 1932 to 1948.[3]

PROOF THAT PEPSIN IS A PROTEIN

Northrop had isolated swine pepsin in 1920 using a method described earlier by Pekelharing, but when the enzyme failed to crystallize he put the problem to one side. Professor James B. Sumner's success in crystallizing urease in 1926 stimulated Northrop to return to pepsin, especially since the European enzymologists took exception to Sumner's conclusion that urease is a protein. By 1929 Northrop had crystallized swine pepsin from crude commercial preparations, and his paper with the extensive evidence of its protein nature was published a year later. His evidence consisted of a number of attempts to separate the enzymic activity from the protein, all of which failed. He fractionated crystalline pepsin by recrystallization, salt fractionation, pH, heat, or radiation inactivation in which initial and final fractions were assayed for their enzymic activity per milligram of protein. In no case was there a significant change in this measure, a result expected if the enzyme is a protein.

The solubility studies that Northrop and Kunitz developed especially to detect inhomogeneity in pepsin were probably his strongest evidence. S. P. L. Sørensen, the Danish chemist who first used the term pH, showed how to measure it, and who had also made earlier solubility studies of crystalline proteins, was unable to find a crystalline protein that was homogeneous by this test.

The solubility method is relatively simple and is applicable to any substance. It has a solid theoretical basis in the Gibbs Phase Rule. Briefly, it predicts that the quantity of a *pure* compound dissolved in a given volume of solvent increases until a saturation concentration is reached. Further addition of the solid compound will not alter the concentration of the dissolved material. When the starting

material is made up of two or more substances, the results will deviate from those of an ideal single substance. An early solid phase may persist before saturation is near, or the soluble phase may increase after the quantity of added material is in excess.

Northrop made a number of solubility studies of crystalline pepsin, varying the pH and/or the nature of the salt used in the solvent. In general, these solubility curves were close to that of a pure single substance. He also examined all fractions for shifts in enzyme activity per milligram of protein which would indicate the possible separation of the enzyme from the protein. He found no change in this measure in any of the fractions. In his cautious manner he acknowledged that his studies could not rule out the case of pepsin being two closely related proteins but then he noted, "It seems reasonable to conclude from these experiments that the possibility of a mixture must be limited to a mixture of proteins, so that the conclusion seems justified that pepsin itself is a protein."

In 1933 workers in two European laboratories reported adsorbing peptic activity onto melon seed proteins. One writer interpreted this as a transfer of the "active group" of pepsin to the seed protein, as expected from their view of enzymes. Although this interpretation was in conflict with his experiments, Northrop recognized that he could not exclude such an interpretation. He therefore carefully repeated their protocols and found that crystals of mellon seed proteins mixed with pepsin under their conditions did bind some peptic activity. However, he carried the study one step further. He dissolved the crystalline seed protein carrying peptic activity in dilute acid. The seed protein was quickly digested by the pepsin, and Northrop crystallized the pepsin out in its usual bipyrimidal form.

This pepsin had the same chemical and catalytic properties as all his pepsin preparations. This proved that the so-called "active group" of pepsin had *not* been shifted to the seed protein but rather that the pepsin protein had formed a weak link with the melon protein, an inconsequential observation as it related to the chemical nature of pepsin.

While Northrop was studying pepsin, Kunitz was struggling with the isolation of trypsin in the adjoining room. Daily discussions with Northrop finally led to its isolation in crystalline form. Similar fractionation and solubility studies failed to separate the tryptic activity from the protein. Northrop investigated the reversible heat denaturation of crystalline pure trypsin and showed that the level of tryptic activity throughout the heating and restoration paralleled the level of native protein, strong evidence that trypsin is a protein. As reported elsewhere, Kunitz[4] later isolated a number of enzymes and precursors and applied the same criteria as used for pepsin and trypsin. In all instances the enzymes proved to be proteins.[5]

Northrop suggested that earlier workers failed to find protein in their purified preparations because they frequently diluted the preparations back to the same level as initially found and as the impurities were removed the tests for protein were not sensitive enough.

Northrop's influence on associates was by example or casual comment. He seldom worked directly in the laboratory with us. The exception was in the fractionation of pepsin in 1939, when Victor Desreux and I found active fractions of differing solubility. Northrop saw this clearly as a case of solid solutions and carried out experiments showing this.

Northrop was generous in helping others when help was sought. He would correct one if a principle was in viola

tion, but otherwise he seldom intruded into one's work. He had known Kunitz so long, trusted him implicitly, and gave him free rein. I doubt it they ever had important differences. They both were tolerant and respected the opinions of the other.

Northrop's son John reported to me that his father had strong prejudices. They must have been reserved for the family's ears, for he did not reveal them to me in our long and, at times, close contact. I never heard him speak ill of anyone.

In one of his few talks, via radio, to the general public, Northrop described with great clarity the difference in approach of some chemists and biologists to the solution of a few key biological problems. In that talk he applied "Occam's razor"[6] to remove nonessential features (evidence). It was an insight into the nature and depth of the reasoning that guided him for over half a century.

John H. Northrop was highly effective in designing a variety of instruments and methods of considerable importance. In addition to the diffusion cell and the solubility diagram procedures, he designed electrical panels for close temperature control of incubators and water baths. He produced micro and macro cataphoresis equipment. During World War II he developed excellent portable equipment for sampling and assaying airborne toxic agents. He also developed a chemostat for continuous growth of cell cultures.

John H. Northrop was a loner in many respects. He kept to himself and yet he had friends in many fields of endeavor. His sporting friends called him "Jack" as did a few scientists, but those of us who worked in his group for many years never spoke of him, let alone addressed him, in that familiar manner. This was not by arrangement or

request. It just did not seem to fit our relationship. After he moved to California and I to Johns Hopkins, we corresponded frequently and his letters were always signed "Jack." I felt honored.

John H. Northrop was elected to the National Academy of Sciences in 1934.

VIRUSES

Northrop's interest in viruses began early in his career. Perhaps it was when André Gratia, one of the early bacteriophage investigators from Bordet's laboratory, worked for a period at the Rockefeller Institute from 1919 to 1922 and developed a lasting friendship with Northrop. Northrop published a paper on potato mosaic virus with Peter Olitsky in 1925. He also built a greenhouse in Princeton to study tobacco mosaic virus, but he relinquished his plan upon learning that a department of plant pathology was to be added in 1932, with the isolation of tobacco virus as one of its areas of investigation.

Between 1929 and 1931 Albert Krueger and Northrop made kinetic analyses of the action of bacteriophage infections of Staphylococcus cultures, and they developed a dynamic method of assaying the phage.

Upon Krueger's return to California in 1931 and Northrop's concentration on pepsin, the phage work lagged. However, in an environment in which his colleague R. E. Shope was demonstrating the viral nature of the cause of swine influenza and Wendall Stanley was crystallizing tobacco mosaic virus, Northrop returned to study the chemical nature of Staphylococcus bacteriophage in 1936. He precipitated the phage from 200 liter quantities of lysate, followed by salt fractionation and solubility studies of the phage. Northrop found nucleic acid in his purest phage preparations, a finding

also made by M. Schlesinger only a year or two earlier on centrifuged coli phage. These independent observations of nucleic acid in phages and Bawden and Pirie's discovery of RNA in tobacco mosaic virus were only highly suggestive at the time, since the function of nucleic acids was not understood then. This gap in the knowledge of the function of nucleic acids led Northrop, unfortunately, to suggest that phage, like pepsin and trypsin, may be derived from precursor protein in the host cells.

CRYSTALLINE ANTIBODIES

After his arduous task of purifying phage, Northrop turned to antibodies. They had not been isolated, and, like enzymes, they had high specificity for the antigen with which they reacted. Northrop chose diphtheria antitoxin, for there were large supplies of it in a nearby pharmaceutical company. He precipitated the antitoxin by the addition of the toxin, and after recovery of the precipitate he digested away the toxin with the protease trypsin under special conditions of pH. This liberated the antitoxin. Solubility studies of the released antitoxin indicated that further salt fractionation was needed. Eventually he obtained protein crystals derived from the crude antitoxin that were more than 90 percent precipitated by the toxin and that had at least 700 units per milligram of protein nitrogen by both floculation and protection tests. Northrop recognized from sedimentation measurements that his crystalline material was a partially degraded antitoxin.

Some seven years later Northrop and W. Goebel at Rockefeller purified Type I pneumococcal polysaccharide antibody. Although this crystalline product was homogeneous by centrifuge and electrophoresis studies, there was

more than a single component by the solubility test. In this paper it was again noted that tryptic digestion had split diphtheria antitoxin in their earlier study but that pneumococcal antibody was not split by trypsin.

WORLD WAR II

Northrop's services for research on problems of interest to the Defense Department were sought before Pearl Harbor. He responded by giving the request his full attention. He developed highly sensitive chemical and animal methods of detecting toxic chemicals. In 1948 he was awarded a presidential citation for these contributions to the Defense Department. Northrop reported what may have been a coincidence but was a very important development. Even before our entrance into the war, Northrop conceived the notion that in place of combating enemy bombers with antiaircraft guns, the use of small explosives suspended from small parachutes might be more effective. He passed this notion on to Dr. J. A. V. Butler, an English scientist in his laboratory, who later became the British scientific representative in Washington. This was passed to the British defense which in due time replied with a polite "thank you for your valuable suggestion" and nothing more. After the war Northrop read in one of Churchill's books, "There will be no more mass bombing raids, since a defense has been found: small explosive charges suspended from small parachutes."

POSTWAR ACTIVITIES

In the years following World War II a number of events were to influence John H. Northrop. In the fall of 1946 recognition of his contributions to the field of enzymology was made by awarding him a share in the Nobel Prize in

chemistry along with James B. Sumner of Cornell University and Wendall M. Stanley of Rockefeller. This was the first Nobel award for work done, in part, at the Rockefeller Institute.

Research had resumed in Northrop's laboratory after this well-deserved recognition, when the decision was announced to close the Rockefeller laboratory in Princeton in 1951. No explanation for the closing was offered to the staff, but in George Corner's *History of the Rockefeller Institute*, financial exigency was given as the reason.[7] This surprising turn of events broke up a highly productive group. Northrop and Kunitz had worked together for over twenty-five years and Anson had been with Northrop for about twenty years. I was approaching my sixteenth year with him. Northrop did not wish to return to New York City, nor did I. He was offered a professorship in the Bacteriology and Biophysics Department at the University of California at Berkeley without relinquishing his association with the Rockefeller Institute. He accepted this arrangement and moved to California in 1949.

In California, Northrop's interest returned to bacteriophage. By 1949 the field had developed far beyond that which he had left in 1940 to help the war effort. He became intrigued with the nature of the cellular changes in lysogenic *B. megatherium* that induced phage production. He found that phosphate in the medium inhibited induction and magnesium ion promoted it. He also confirmed de Jong's 1931 report that spores of this organism heated to 100°C for five minutes still yielded cells upon germination that were lysogenic, that is that carried the phage gene. I am surprised that Northrop did not make more of de Jong's experiment. However, in the closing sentence of one of his late papers, Northrop correctly suggested the nature

of bacteriophage, a nature later proved by Alfred Hershey. He wrote, "The nucleic acid may be the autocatalytic part of the molecule, as in the case of the transforming principle of pneumococcus, and the protein portion may be necessary only to allow entrance to the host cell."

In the last years of his scientific career, Northrop with the technical assistance of Marie King, examined the origin of bacterial viruses. It was known that uninfected (lysosensitive) cells could be infected with phage and, depending on conditions, a fraction of the cells would survive and carry the virus in a silent noninfectious (lysogenic) form. It was also known from Lwoff's work that mutagenic agents such as radiation or certain chemicals induced phage development in these lysogenic cells. Northrop devoted many months of research to showing that the rate of induction of lysogenic cells to form phage was comparable to the rates of mutation of these cells to antibiotic or phage resistance. He and Kunitz found that his data conformed to the theoretical expression developed for the formation of mutants. I wonder why he did not examine the formation of mutant cells in the system in which he had found that phosphate-inhibited phage induction and magnesium ions promoted it, for these agents were not known to affect mutagenesis.

Little attention has been given to this work of Northrop, perhaps because it merely quantified Lwoff's earlier finding or because it did not establish the origin of phage. The problem of the origin of phage is a bit like the chicken and the egg: which came first? Recombination as the origin was not considered.

RETIREMENT

Officially, retirement came in 1962, but Northrop con

tinued his laboratory work and publications until 1968. In this period Mrs. Northrop became ill, and he cared for her for several years. However, the Berkeley climate was not kind to his sensitive respiratory system, like the dry climate of the desert was. In 1971 Mrs. Northrop went to live with the Robbins in Ohio. She died April 21, 1975.

Dr. Northrop moved to a house a mile outside of Wickenberg, Arizona, where he walked his dog, practiced his shooting, gardened, fed birds, and read books. Until 1980 he made annual fishing trips with his son, John, to the interior of Wyoming or Montana. I visited him just before his ninetieth birthday and found him active and mentally alert. He complained that his legs were getting weaker. As he approached his ninety-sixth birthday, he must have viewed his future with concern. He presumably felt that he was becoming an unfortunate burden to his family and friends and decided to avoid such a future. He took his life on May 27, 1987. To me his action was quite in keeping with his character.

CONCLUSION

John H. Northrop was a clear-thinking scientist who made significant contributions in several different fields, but his best-known study was in the field of enzymes. As John Edsall wrote "John Northrop probably did more than any one other individual to establish that pure enzymes are indeed proteins." In view of the involvement of enzymes in virtually all biological reactions, establishing their chemical nature was a scientific contribution of the first magnitude. The power of Northrop's reasoning and experiments combined with his quiet, modest presentation attracted the attention and admiration of investigators everywhere.

I am indebted to Mrs. Frederick Robbins and Dr. John Northrop for information about the family. Special thanks go to Dr. John T. Edsall for his careful review and suggestions about the manuscript, which vastly improved it. To Marie King goes my appreciation for volunteering to loan me one of the very few copies of Northrop's unpublished autobiography.

NOTES

1. John H. Northrop, *Just for the Fun of It*, unpublished autobiography, 1968.

2. John I. Northrop, *A Naturalist in the Bahamas* (New York: Columbia Press, 1910).

3. I worked for my doctorate at Columbia's Chemistry Department under Professor John M. Nelson, as did Dr. Northrop. My thesis dealt with the reversal of denaturation of the enzyme invertase. I was delayed in getting my degree in 1931 by Northrop's publication that spring on the reversal of denaturation of pepsin. Professor Nelson generously wrote Northrop of my interest in working with him, and after he visited us at Columbia an offer was made to me in 1932.

4. "Moses Kunitz, 1887-1976," In: *Biographical Memoirs*, vol. 58, (Washington, D.C.: National Academy Press, 1989):304-17.

5. The discovery in 1982-83, by Thomas Cech and Sidney Altman, that certain RNAs have catalytic properties modifies the generally held belief that all enzymes are proteins.

6. Material in this talk was expanded and published in the *Annual Review of Biochemistry* 30(1961):1–10.

7. George W. Corner, *A History of The Rockefeller Institute, 1901-1953* (New York: Rockefeller Institute Press, 1964):331, 454-59.

HONORS

1931

The Stevens Prize of the College of Physicians and Surgeons of Columbia

1932

Walter C. Alvarez Lecture, American Society of Gastroenterologists

1934

Election to the National Academy of Sciences

1936

The Charles Frederick Chandler Medal

1936

Honorary Sc.D. degree, Harvard University

1937

Honorary Sc.D. degree, Columbia University

1937

Honorary Sc.D. degree, Yale University

1937

De La Mar Lecture, Johns Hopkins School of Hygiene and Public Health

1938

Jessup Lecture, Columbia University

1939

The Daniel Giraud Elliot Medal of the National Academy of Sciences

1939

The Hitchcock Lectures, University of California (Berkeley)

1939

Honorary LL.D. degree, University of California

1940

Honorary Sc.D. degree, Princeton University

1941

Honorary Sc.D. degree, Rutgers University

1946

Nobel Prize in Chemistry, shared with James B. Sumner and Wendell M. Stanley

1948

The President's Certificate of Merit

1949

Columbia University Lion Award Alumni Club of Essex County

1961

The Alexander Hamilton Award, Columbia University

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Julia Robinson

JULIA BOWMAN ROBINSON

December 8, 1919–July 30, 1985

BY SOLOMON FEFERMAN

One of my earliest memories is of arranging pebbles in the shadow of a giant saguaro . . . I think I have always had a basic liking for the natural numbers. To me they are the one real thing. We can conceive of a chemistry which is different from ours, or a biology, but we cannot conceive of a different mathematics of numbers. What is proved about numbers will be a fact in any universe.

(From The Autobiography of Julia Robinson by Constance Reid)

As A MATHEMATICIAN, Julia Bowman Robinson will long be remembered for her many important contributions to questions of algorithmic solvability and unsolvability of mathematical problems, in particular for her part in the negative solution of Hilbert's "Tenth Problem." And, despite her expressed wish, she will be remembered as the first woman to be elected to the mathematical section of the National Academy of Sciences, as well as the first woman to be president of the American Mathematical Society. By those who knew her personally she will be remembered for her rare qualities of idealism, integrity, modesty, openness, and generosity, and for her appreciation and encouragement of the work of others.

She was born Julia Bowman on December 8, 1919, in St. Louis, Missouri, the second of two daughters, to Helen Hall Bowman and Ralph Bowers Bowman. Her mother died when she was two years old, and her father retired not long after, having lost interest in his machine tool and equipment business. Ralph Bowman remarried a few years later to Edenia Kridelbaugh, and the family moved first to Arizona and then to San Diego; a third daughter, Billie, joined Constance and Julia a few years later. As a child, Julia was said to be stubborn and slow to talk, but she exhibited a precocious liking for the natural numbers, as evidenced by her earliest reported memories.

At the age of nine, Julia was stricken first with scarlet fever, and then with rheumatic fever, which, after several relapses, forced her to spend a year in bed. As a result, she lost more than two years of school, and there were more serious, lifelong consequences for her health.

Julia returned to school after a year of tutoring, during which she went through the state syllabuses for the fifth, sixth, seventh, and eighth grades. Shy and out of the swim socially, she took to her studies and found herself especially attracted to mathematics. Moving on in high school through the standard courses of algebra, trigonometry, and plane and solid geometry, she stood out as the only girl in the advanced mathematics and physics courses. She graduated from high school with awards in all the sciences (except chemistry, which she had not taken) and a special medal (the Bausch-Lomb) for all-round excellence in mathematics and science.

Following in the footsteps of her older sister Constance, Julia entered San Diego State College (now University) in 1936. It was common for students there to attend State for a couple of years and then transfer to UCLA or the Univer

sity of California at Berkeley; those who remained generally obtained teaching credentials. Julia majored in mathematics because she liked it and was good at it, but she had no idea that there was such a thing as being a mathematician. When she came across the book *Men of Mathematics* by E. T. Bell, she became very excited at the intellectual vistas that opened up and she was determined to transfer to UCLA or Berkeley to learn some real mathematics. Finances were strained due to the suicide in 1937 of her father, whose retirement savings had been wiped out by the 1929 crash and the subsequent depression. However, with the assistance of an aunt and her older sister, in 1939 she managed finally to transfer to U.C.B. as a senior. It happened to be a particularly fortuitous time to enter the mathematics program at Berkeley, as the noted chairman, Griffith C. Evans, had been building up the department with outstanding researchers and teachers. In her first year at Berkeley, Julia took five mathematics courses, including one in number theory taught by Raphael M. Robinson. She was extremely happy at Berkeley, finding herself among so many students and faculty excited by and talking about mathematics.

Julia received her A.B. degree in 1940 and, at the urging of Raphael Robinson, continued on with graduate studies at Berkeley. She also managed to obtain a part-time position as an assistant to Professor Jerzy Neyman for his work on statistics. During this period, Julia and Raphael developed a personal friendship that blossomed into a courtship, and they married in December 1941. The relationship with Raphael was also to have major significance for Julia's development as a mathematician; he was an excellent teacher, both in class and in one-to-one discussions, and he had a deep knowledge of many parts of classical

and modern mathematics. Julia counted Raphael Robinson as one of her two most important scientific influences, the second one being the famous logician Alfred Tarski, who joined the Berkeley faculty in 1942.

Unfortunately, her marriage to a faculty member was to limit Julia's employment opportunities in Berkeley, since there was at that time (and for many years after) a nepotism rule in the U.C. system that prevented members of the same family from working in the same department. This did not affect her at first, since she had already received a teaching assistantship in mathematics for the second year of her graduate studies. Julia had wanted to teach calculus, but Jerzy Neyman pushed her to teach statistics, which she didn't like as much. The connection was useful, though, as Neyman was to employ her in his "Stat Lab" later during the war, and her work there would result in her first published paper.

From the beginning of their marriage, the Robinsons wanted and expected to have a family, and though Julia continued to audit mathematics courses, her preoccupations shifted more toward their home life. She became pregnant but, unfortunately, lost the baby a few months later; then, shortly afterward, on a visit home to San Diego, she contracted viral pneumonia. A doctor there was the first to recognize that there was substantial scar tissue in the mitral valve of the heart, a residue of her early bout with rheumatic fever, and he strongly advised her against becoming pregnant. He also told her mother in private that Julia would be lucky to live to age forty.

Julia was deeply depressed for a long time over not being able to have children, but, encouraged by Raphael, she returned eventually to the rewards of mathematics. She attended the first seminar that Tarski conducted at Berke

ley and soon provided an ingenious solution to a definability problem in number theory that had been posed by Tarski's former student Andrzej Mostowski. The question was whether addition can be defined in terms of the successor operation and multiplication. Tarski was impressed by her positive solution to this problem and viewed it as suitable thesis material. It, and other similar work, was eventually to be incorporated as a relatively minor part of her thesis, the major part of which is to be described below.

During the immediate postwar period, Tarski was building a school in mathematical logic at Berkeley. One of the two most important logicians of the 20th century (the other being Kurt Gödel), he was a very systematic yet intense and charismatic lecturer with extensive research programs and a wealth of good problems to match. Tarski's main subjects of interest were metamathematics, set theory, model theory, universal (abstract) algebra, and algebraic theory. During a period of thirty-odd years following the war, he directed the doctoral work of a series of outstanding students, of whom Julia Robinson was one of the first.

Except for two papers, all of Robinson's work is concerned with the *effective solvability* and *unsolvability* of various mathematical problems, as well as with the characterization of various notions of effectiveness. The exceptions were her very first paper (1948), on a topic in sequential analysis, which came out of her work in the U.C.B. Stat Lab during World War II, and a paper (1951) on the theory of games. The latter resulted from her work during a year (1949–50) spent at the RAND Corporation in Santa Monica, where game theory was at the time a topic of intense investigation. Robinson succeeded there in solving in the affirmative a "prize" problem that had been posed by George W. Brown, whether a certain iterative method of play al

ways leads to the value of a two-person zero-sum game; that result has been considered a very significant contribution to the subject.

To return to the main topic of Robinson's work: the informal idea of *effective solvability* (or *decidability*) of a class of mathematical problems of the form—Is *P(a)* true? (where *a* ranges over a given set *S*)—is that provided by an *algorithm*, i.e., a completely determined finitely described procedure which, given any element (or "input"), leads step-by-step to a definite conclusion as to the truth or falsity of the predicate $P(a)$. Similarly an operation (function) f on elements of S to S is said to be *effectively computable* if there is an algorithm which, given any element $a \in S$ as argument, leads to the value (or "output") b of $f(a)$, for which $f(a) = b$. (We here use $\in$ for the membership relation and read "a in S" for "$a \in S$".) The elements of the set S must themselves be presented in finite form as a finite sequence of symbols. Using any one of the standard systems of representation, these notions thus apply to predicates and operations on the set Z of *integers* and its subsets N^+ of *positive integers* and N of *non-negative integers* (*natural numbers*), i.e., to $Z = \{\ldots, -3, -2, -1, 0, 1, 2, 3, \ldots\}$, $N^+ = \{1, 2, 3, \ldots\}$ and $N = \{0, 1, 2, 3, \ldots\}$. The notions extend directly to the set Q of all rational numbers, i.e., all fractions n/m with $n, m \in Z$ and $m \neq 0$. Furthermore, if $A = \{\alpha_1, \ldots, \alpha_k\}$ is any finite alphabet, we can apply the notions of effectiveness to predicates and functions on the set $S = W(A)$ of all finite expressions (or "words") $\alpha i_1 \ldots \alpha i_m$ with letters from A. Finally, if effectiveness is meaningful for predicates and operations on S, the same holds for the set S^n of all n-tuples $(a_1, \ldots, a_n)$ where we deal with n-ary relations $P(a_1, \ldots, a_n)$ and operations $f(a_1, \ldots, a_n) = b$.

It should be noted that the notion of effectiveness for

predicates and relations can be reduced to that for operations, using distinct elements t_1, $t_0 \in S$ (e.g., 1 and 0) to represent *truth* and *falsity*, respectively. By the *characteristic function* of P (an n-ary relation between elements of S), is meant the operation f_P defined on S^n by $f_P(a_1, \ldots, a_n) = t_1$ if $P(a_1, \ldots, a_n)$ is true and $f_P(a_1, \ldots, a_n) = t_0$ otherwise. Then, clearly, P is effectively decidable if and only if f_P is effectively computable.

Since the beginning of abstract mathematics in antiquity, many algorithms have been presented for various specific mathematical problems and operations. In each case it was verified that the algorithm does the required work by following through its application to see that it gives the appropriate answer for an arbitrarily given argument as input. No general notion of effectiveness was required for such verifications, i.e., the informal conception of effectiveness sufficed. However, if one is to show that a problem of the form—Is $P(a)$ true? (for $a \in S$)—is *effectively undecidable*, i.e., that *no possible algorithm* can serve to effectively determine the truth or falsity of $P(a)$ for each $a \in S$, we must have a completely general and precise definition of effective decidability, so that its extent can be sharply delimited. The same applies to the task of showing that a given operations f is *not* effectively computable. By the remark above, once the general notion of effectively computable function is made precise, the same applies to that of effectively decidable predicate or relation.

Several independent proposals for a general, mathematically precise definition of effectively computable function on the natural numbers N (or N^+) were made in the 1930s, and before long all were shown to be equivalent. Among the first was that made by Alonzo Church who advanced, for this, calculability in a certain restricted symbolism for

functions called the λ-*calculus*. Independently, and around the same time (using a suggestion of Jacques Herbrand), Kurt Gödel proposed the class of *general recursive functions* as a candidate for the algorithmically computable functions. Before this, in his famous 1931 paper on the incompleteness of *Principia Mathematica* and other formal axiomatic systems concerning the natural numbers, Gödel had made heavy use of a subclass of these, called the *primitive recursive functions*. In 1936, Church's student Stephen C. Kleene proved the equivalence of the λ-definable and general recursive functions; in the same year Church first proposed in print to identify the algorithmically computable functions with either one of these (coextensive) classes, and this proposal was subsequently dubbed *Church's Thesis*. Unaware of the preceding work, Alan Turing in 1937 proposed a notion of mechanically computable functions, where the calculations are carried out by an idealized machine (subsequently dubbed *Turing machines*) without limitation on storage or time. When Turing learned of Church's Thesis, he established the equivalence of the λ-calculable functions with his own mechanically computable functions. All these (and related) contributions bolstered the arguments for Church's Thesis, which has since gained practically universal acceptance; in particular, Turing's notion is considered to be one of the most faithful to the informal concept of a step-by-step finite mechanical procedure. His definition also extends directly to that of effective computability on any set of expressions generated from a finite alphabet.

The systematic development of the theory of effectively computable functions, assuming Church's Thesis, was initially due to Kleene; in particular, working with the Herbrand-Gödel definition, he showed how the general recursive functions can be obtained from the primitive recursive functions,

themselves generated by some relatively perspicuous schemata, by the adjunction of one new scheme embodying the construction "do . . . until . . . " It became convenient to work with Kleene's schemata as a means for verifying various properties of the effectively computable functions. As a result of this, the subject of effective computability (both for positive and negative results) came to be called *recursive function theory*. One mildly complicating feature, though, of Kleene's schemata is that they pass through functions of arbitrarily many arguments in order even to obtain the functions of one argument (the unary functions). The problem thus arose of finding a simple set of schemata for generating the unary general recursive functions. An important step in this direction had been made by Raphael Robinson, who obtained a simple set of schemata for the unary primitive recursive functions; he suggested to Julia the problem of extending this to a characterization of the unary general recursive functions. After several years' work, she succeeded in obtaining an elegant solution in 1948, which was published in a paper (1950). She returned to this problem in a later paper (1968, 1) with an even more elegant characterization of the class of unary general recursive functions as the least class containing the zero and successor functions and closed under composition and a new special scheme of general recursion. Related to these papers is her note (1955) on primitive recursive functions. Somewhat in the same spirit, but for other classes of functions or sets, are her papers (1967; 1969, 1; 1973, 2) (in the last, within an axiomatic setting). Of these, one (1967) is noteworthy for its beautifully simple and direct exposition of the theory of hyperarithmetical functions, a class originally obtained by a complicated transfinite iteration of the "jump" process associated with general recursion in

a relativized form. These papers comprise one of three main areas of Robinson's contributions to the theory of effective computability.

For an explanation of Julia Robinson's dissertation work with Tarski and her later work on the Diophantine problem, we consider two further notions from recursive function theory. Suppose S is a set to which the notion of effectively computable (*alias* general recursive) function is applicable, either directly or by an effective enumeration of S by N. A subset D of S is said to be *decidable* (or *recursive*) if its characteristic function f_D on S is effectively decidable (or *recurvsive*) if its characteristic function f_D on S is effectively computable; in other words, D is decidable if its membership problem is effectively decidable. A subset E of S is said to be *effectively* (or *recursively*) *enumerable* if it is the range of a recursive function f from N to S, i.e., if E is the set of values $f(0), \ldots, f(n), \ldots$ for $n \varepsilon N$; for simplicity, the empty set is also counted as being effectively enumerable. It is not hard to see that D is decidable if and only if both D and its complement $S - D$ are effectively enumerable.

Of special interest in modern logic are the sets $S = WFF(L)$ of well-formed formulas in a formal Language L, which are special kinds of expressions generated from a finite symbolism. In the first-order predicate calculus these are generated from one or more basic relations $R(x_1, \ldots, x_n)$ by closure under $\wedge$ ("and"), $\vee$ ("or"), $\neg$ ("not"), $\rightarrow$ ("if . . . then . . . "), $\forall x$ ("for all x, . . . "), and $\exists x$ ("there exists x, . . . "). In the following we consider the special case where the basic relations are $x = y$, $x + y = z$, and $x \cdot y = z$. We define $x \neq y$ by $\neg (x = y)$, $x = 0$ by $x + x = x$, $x = 1$ by $(x \cdot x = x) \wedge (x \neq 0)$, etc. In this language we can speak of firstorder properties of the structures of the natural numbers

N, the integers *Z*, as well as of the rational numbers *Q*, the real numbers *R*, and the complex numbers *C*.

A formula *A* of *L*, such as $\exists x \forall y\ (xy = y)$, is said to be *closed* if it contains no free variables. For any mathematical structure $(M, R_1, \ldots, R_m)$ in which the basic relations of *S* are interpreted in a definite way (with $x = y$ interpreted as equality) each closed formula *A* of *S* has a definite truth value in *M*. By the *theory of M*, in symbols $Th(M, R_1, \ldots, R_m)$, is meant the set *T* of closed well-formed formulas which are true in *M* under this interpretation. This theory is said to be *decidable* if *T* is a decidable subset of *S*, otherwise *undecidable*. One of the basic consequences of the work of Gödel and Church is that the theory of the natural number systems, $Th(N, +, \cdot)$ is undecidable, and the same applies to $Th(Z, +, \cdot)$ since *N* is definable in the latter theory by: $x \varepsilon N$ if and only if $\exists y \exists z \exists u \exists w (x = y^2 + z^2 + u^2 + w^2)$ (according to a famous theorem of Lagrange). On the other hand, it was known from earlier work of M. Presburger (1930) that $Th(Z, +)$ and $Th(N, +)$ are decidable; note that the product relation $x\ y = z$ is *not* included in these structures.

One of Tarski's main long-term programs, beginning in the 1930s in Warsaw and continuing over into his Berkeley period, was the systematic investigation of the *decision problem* for first-order theories associated with mathematical structures met in practice. Tarski's most famous result in this direction, first announced in 1931 but not published in full until 1948, was his decision procedure for the elementary (first-order) theory of real numbers, i.e., $Th(R, +, \cdot)$; moreover, this was shown to be the same as the theory of any real-closed field $(M, +, \cdot)$, including the countable field of real algebraic numbers, i.e., the real number solutions of polynomial equations over *Q*. Tarski had also shown

(what was easier) that the elementary theory of the complex number field $Th(C, +, \cdot)$ is decidable and that any algebraically closed field $(M, +, \cdot)$ of characteristic zero has the same theory.

This is where things stood when Julia Robinson took up, at Tarski's suggestion (via Raphael Robinson), the question of definability of the set N in $Th(Q, +, \cdot)$. The status of the decision problem for the theory of the field of rational numbers was at that point the big unknown between the undecidable theory of integers $Th(Z, +, \cdot)$ and the decidable theory of real numbers $Th(R, +, \cdot)$. Robinson's exceptional achievement in her thesis work was to show that the set Z (and hence N) *is* first-order definable in $Th(Q, +, \cdot)$, and hence that the latter theory is also undecidable. It was far from obvious how to do this. Her first breakthrough came with the realization that if r is a rational number and r is expressed as a quotient of integers a/b in lowest terms, then b is odd if and only if $(\exists x_1\ \exists x_2\ \exists x_3)\ (7r^2 + 2 = x_1^2 + x_2^2 + x_3^2)$ is true in Q. Thus one ternary quadratic form can be used to "eliminate" 2 as a factor from the denominator of a rational number. Robinson then found other ternary quadratic forms to eliminate in turn all the other prime numbers from denominators. The final problem that she overcame was to combine these infinitely many different quadratic forms into a finitely described class of forms which would succeed in eliminating all (and only) denominators of fractions in lowest terms and thus in characterizing the integers Z as exactly the rationals satisfying a first-order property in $(Q, +, \cdot)$. Among the important consequences of this deep and difficult work were the result that the axiomatic theory of fields is undecidable; this is a corollary using some general results of Tarski on undecidable theo

ries. Robinson received her Ph.D. in 1948, and the results of the thesis were published soon after in the paper (1949).

In a later paper (1959, 1), Robinson extended her thesis work to algebraic fields $(F, +, \cdot)$ of finite degree over the rationals (subfields of the complex numbers C). Here she showed that N is definable in the ring $(A, +, \cdot)$ of algebraic integers of F and that A is in turn definable in the field F, so that both $Th(A, +, \cdot)$ and $Th(F, +, \cdot)$ are undecidable. The papers (1962, 2) and (1965) contain further related results of interest.

We can now finally return to the third main area of Robinson's mathematical preoccupations, that of existential definability in arithmetic, also called *Diophantine definability*. The background to this problem is as follows.

In the third century A.D., the Greek mathematician Diophantus worked on solving equations with arbitrary integer coefficients, for integer values. The general linear Diophantine equation in two variables is $ax + by = c$ where a, b, c are arbitrarily given integers. An algorithm to determine whether or not there are $x, y \in A$ satisfying $ax + by = c$ makes use of an algorithm, due to Euclid, for finding the greatest common divisor of two integers: provided $a \neq 0$ or $b \neq 0$, the equation has a solution $x, y \in Z$ if and only if the greatest common divisor d of a and b is a divisor of c; then if there is a solution at all, we have a further algorithm for finding all possible solutions. Another classical algorithm, to find all possible $x, y, z \in N^+$ satisfying $x^2 + y^2 = z^2$, connects number theory with geometry; the solutions of this equations such as 3, 4, 5 and 5, 12, 13, provide all possible right triangles with each side of integer length. The famous Fermat problem concerns the existence of integer solutions, if any, of $x^m + y^m = z^m$, with $x, y, z \neq 0$ and $m > 2$.

The general Diophantine equation in n variables $x_1, \ldots$

. ,x_n is given by an equation $P_1(x_1, \ldots, x_n) = P_2(x_1, \ldots, x_n)$ where P_1, P_2 are polynomials with integer coefficients. By subtraction this can always be brought to the form $P(x_1, \ldots, x_n) = 0$, where P is again such a polynomial, i.e., P is a finite sum of terms of the form $ax_1^{k_1} \ldots x_n^{k_n}$ where a is in Z and the exponents k_i are in N. The statement that (or question whether) there exist integer solutions at all to this equation is symbolized by $(\exists x_1 \ldots x_n \in Z)\ [P(x_1, \ldots, x_n) = 0]$. Closely related questions are whether there exist natural number solutions $(\exists x_1 \ldots x_n \in N)\ [P(x_1, \ldots, x_n) = 0]$ or positive integer solutions $(\exists x_1 \ldots x_n \in N^+)\ [P(x_1, \ldots, x_n) = 0]$.

Interest in Diophantine problems lay mostly dormant until the 17th century, when they were taken up by the outstanding amateur mathematician Pierre de Fermat, who solved many individual Diophantine problems, often challenging others to do the same without revealing his methods. Subsequently the subject was pursued by such great mathematicians as Euler, Lagrange, Gauss, Dirichlet, Dedekind, and others through the 19th century. This work brought to bear many ingenious and difficult arguments, which were organized by various techniques; however, no general theory emerged.

Faced with this situation at the turn of the 20th century, David Hilbert proposed the following decision problem for arbitrary Diophantine equations: *To devise a process according to which it can be determined by a finite number of operations whether the equation is solvable in integers.*[1] This problem was the tenth on his famous list of twenty-three problems in a wide variety of fields, which Hilbert dramatically presented as a challenge in his address to the International Congress of Mathematicians in 1900. Hilbert's optimism about finding a general algorithm for deciding all questions of the

form $(\exists x_1, \ldots, x_n \in Z)\ [P(x_1, \ldots, x_n) = 0]$ with P an integer polynomial was in line with his proclaimed optimism about the eventual solvability of all mathematical problems, but flew in the face of the fact that Diophantine equations were known to be exceptionally resistant to general methods of solution. Indeed, for classifications according to degree, an algorithm was subsequently provided by Carl Ludwig Siegel only for the general problem of Diophantine equations of degree 2 and arbitrarily many unknowns. (The degree of $P(x_1, \ldots, x_n)$ is the maximum of the sums of the exponents $k_1 + \ldots + k_n$ of its terms $ax_1^{k_1} \ldots x_n^{k_n}$; the general polynomial of degree 2 in two variables is thus of the form $ax_1^2 + bx_1x_2 + cx_2^2 + dx_1 + ex_2 + f$.) On the other hand, in classifications according to the number n of variables, some progress has been made in recent years only for $n = 2$ and here only for a wide class of equations of degree higher than 2.[2] Even now, practically nothing systematic is known for nonquadratic equations in more than two variables.

With the emergence in the 1930s of the theory of recursive functions and the demonstrated effective unsolvability of some logical and mathematical problems, it became possible to consider giving a *negative* solution to Hilbert's Tenth Problem. In fact, there were already related negative results due to Gödel in his famous 1931 paper on incompleteness of formal systems of arithmetic. He there associated with each consistent axiom system T containing a sufficient amount of arithmetic, a true statement not provable in T, of the form $\forall\, "x(f(x) \neq 0)$ where f is primitive recursive. Then he succeeded in showing that the relation $f(x) = y$ is definable over N in the form:

$$(1) \qquad f(x) = y \leftrightarrow (Q_1 z_1) \ldots (Q_m z_m)\ [P(x, y, z_1, \ldots, z_m) = 0]$$

where each Q_i is either the universal quantifier "$\forall$" or the existential quantifier "$\exists$", and P is a polynomial with integer coefficients. Somewhat later (1950), Martin Davis succeeded in showing that one can choose in place of the right-hand side of (1), a definition in which all but one of the Q_i are existential, and where the universal quantifier is "bounded," so that f is definable in the form:

$$(2) \qquad f(x) = y \leftrightarrow (\exists u)(\forall w \leq u)(\exists z_1 \ldots z_m) [P(x,y,u,w,z_1,\ldots,z_m) = 0]$$

for a suitable polynomial P. Hence elimination of the bounded universal quantifier would give a negative solution to Hilbert's Tenth Problem. For, by the work of Church, Turing, and Kleene:

(3) (a) Every non-empty recursively enumerable set A of natural numbers is definable in the form

$$x \in A \leftrightarrow \exists y[f(y) = x]$$

with f primitive recursive; and

(b) one can construct a recursively enumerable set A which is not recursive and hence not effectively decidable.

Thus, elimination of the bounded universal quantifier in the form (2) for such A would eventually give

$$(4) \qquad x \in A \leftrightarrow (\exists z_1 \ldots z_m)\ [P(x,z_1,\ldots z_m) = 0]$$

for a suitable integer polynomial P, and this would show that there is no general algorithm for deciding whether a Diophantine equation has any solutions at all in the natural numbers.

A set A of natural numbers is called *Diophantine* if it is definable in the form (4) with the variables "z_i" ranging over N. This is equivalent to its being definable in purely

existential form in the structure $(N, +, \cdot)$. Julia Robinson's work here started with the specific question, posed by Tarski, whether the set $\{2, 2^2, \ldots, 2^n, \ldots\}$ of powers of 2 is Diophantine. At first she tried to establish Tarski's conjecture that the answer would be negative, but failing in that, she began to consider the opposite conjecture, and before long was led to the general problem of the Diophantine definability of arbitrary recursively enumerable sets. In her paper (1952) Robinson reported her first results in this direction. She showed there if R is any binary relation in the natural numbers of *roughly exponential* growth in the sense of (5) next, then the relation x *Pow* y (x is some power of y) is existentially definable in the structure $(N, +, \cdot, R)$, where:

$$(5)\quad (a)\quad \exists n\ \forall x\ \forall y\ [R(x,y) \rightarrow y < x^{\cdot^{\cdot^{x}/n}}],\ \text{and}$$
$$(b)\quad \neg\exists k\ \forall x\ \forall y\ [R(x,y) \rightarrow y < x^k].$$

Furthermore, she showed that

(6) The relations $x^y = z$, $(x/y) = z$ and $x! = y$ are all existentially definable in terms of *Pow*, hence in terms of any R of roughly exponential growth.

The full significance of Robinson's 1952 results was not to emerge for close to a decade. During that period she continued to work hard on the general problem of Diophantine definability without substantial progress, though, as described above, she was able to obtain very satisfying results in her other two main areas of interest.

Around 1960, Julia received the draft of a paper by Martin Davis and Hilary Putnam in which they showed that if the famous hypothesis that there exist arbitrarily long arithmetic progressions containing only prime numbers were true, then every recursively enumerable (r.e.) set would be exponen

tial Diophantine, i.e., existentially definable in $(N, +, \cdot, Exp)$, where $Exp(x, y) = x^y$. She quickly succeeded in eliminating that hypothesis (still unproved) and also simplified their arguments in many other respects. This led to the joint publication (1961) with Davis and Putnam in which the main result is that every r.e. set A is the set of all x for which a Diophantine equation $P(x, z_1, \ldots, z_m) = 0$ with *variable exponents* has solutions $z_1, \ldots, z_m$ in N. The Davis, Putnam, Robinson paper (1961) also featured the "J. R. Hypothesis," that some relation R of roughly exponential growth is Diophantine. By her 1952 results and this joint paper, the J. R. Hypothesis implies that every r.e. set is Diophantine. But, once more, matters would rest without essential progress for almost a decade.

Julia Robinson's doctor had told her mother in 1941 that she would be lucky to live to age forty. In 1961, when she was forty-one, her heart was functioning so poorly that the only alternative to a life of invalidism was an operation, by a technique then in its pioneering stage, to remove the built-up scar tissue. Her health improved dramatically, and one month after surgery, Julia took up bicycling as a new form of exercise. Over the following years, she bought a half dozen increasingly better bicycles and thereby enjoyed many outings and cycling trips in the U.S. and elsewhere, including The Netherlands. Raphael Robinson sometimes complained that "while other men's wives buy fur coats and diamond bracelets, [my] wife buys bicycles." (*Autobiography*, p. 18.)

Julia continued to work hard on Hilbert's 10th Problem throughout the 1960s. Then in 1970 the news came from the U.S.S.R. that a twenty-two-year old mathematician in Leningrad named Yuri Matijasevi had succeeded in establishing the J. R. Hypothesis. He showed that the sequence

of even Fibonacci numbers, known to be of exponential growth, formed a Diophantine relation. This work involved elementary properties of the so-called Pell (Diophantine) equation $x^2 + (a^2 - 1)\, y^2 = 1$ for $a > 0$. As it happens, Robinson had used the same equation in her 1952 paper and was very familiar with its properties. In retrospect, she realized that she had herself been very close to the solution of Hilbert's 10th Problem. Nevertheless, she was very excited and pleased to see the long effort capped by Matijasevi 's achievement, and she immediately sent her generous congratulation:" . . . now I know it is true, it is beautiful, it is wonderful. . . . If you really are 22, I am especially pleased to think that when I first made the conjecture you were a baby and I just had to wait for you to grow up." (*Autobiography*, p. 19.) In 1971, the Robinsons visited Leningrad and had the pleasure of meeting Matijasevi and his wife.

Capitalizing on the breakthrough, Julia Robinson and Yuri Matijasevi subsequently collaborated on three papers, (1974), (1975), and (1976), the last of these jointly with Martin Davis. In the 1975 paper Robinson and Matijasevi succeeded in reducing to 13 the number m of unknowns in the representation (4). In later work (by Matijasevi alone), this number was further reduced to 9. There is still a wide gap between the positive information on algorithmically solvable Diophantine equations in two unknowns mentioned above and the negative results for 9 and more unknowns. The most challenging open problem currently in this direction is whether there is a general algorithm for deciding the solvability of Diophantine equations in three unknowns.

The paper of Davis, Matijasevic, and Robinson (1976) provides a beautifully exposed yet concisely presented sur

vey of these results on Hilbert's 10th Problem, together with a series of new "positive" applications, such as the Diophantine representation (i.e., as the range of positive values of a polynomial) of the set of prime numbers, and the equivalence of many famous problems—including the Riemann Hypothesis—with statements of the form $(\forall\ z_1 \ldots z_m)\ [P(z_1, \ldots, z_m) \neq 0]$; the paper also presented a number of further interesting open problems. This work was solicited for the Proceedings of the 1974 *Symposium on Mathematical Developments Arising from Hilbert Problems* (ed. Browder, 1976). Other papers that Robinson wrote herself on the subject of Hilbert's 10th Problem, both before and after the 1970 breakthrough, are (1962, 1), (1969, 1, 3, 4), and (1973, 1).

In recognition of her various outstanding contributions and, in particular, of her central role in the work leading to the solution of Hilbert's 10th Problem, Julia Robinson was elected in 1975 to the mathematical section of the National Academy of Sciences, the first woman to be so honored. In the same year, the University of California at Berkeley offered her a full professorship in the Department of Mathematics with a special arrangement permitting her to serve quarter-time since, although her health had improved greatly as a result of the operation mentioned earlier, she still did not feel that she could take on a full teaching load. In the past she had on occasion taught classes in the Department of Mathematics, but this was her first appointment as a regular member of the faculty at Berkeley since her receipt of the Ph.D. there in 1949.

Other signal honors followed in the next decade. Robinson was chosen as the colloquium lecturer at the 84th Summer Meeting of the American Mathematical Society in 1980; her lectures covered the main areas of her interests between logic and number theory, and the notes for these

constitute her last writings, though they were not in final form for publication. In 1982, she was nominated for the presidency of the American Mathematical Society (for the years 1983–84), again the first woman to be so honored. Uncertain whether to take on the position because of her limited energies, she finally decided that, in the words from her *Autobiography* (pp. 20–21):" . . . as a woman and as a mathematician I had no alternative but to accept. I have always tried to do everything I could to encourage talented women to become research mathematicians. I found my service as President of the Society taxing but very, very satisfying." In 1983, Julia Robinson received a MacArthur Fellowship with its substantial award for a five-year period. And, in 1985, she was chosen as a member of the American Academy of Arts and Sciences.

While she was presiding over the summer A.M.S. meeting in Eugene, Oregon, in 1984, it was discovered that she was suffering from leukemia. After prolonged treatment and hospital stays, she enjoyed a remission of several months in the spring of 1985. But then the disease returned, and she died on July 30, 1985 at the age of sixty-five. She is survived by her husband, Raphael Robinson, and two sisters, Constance Reid and Billie Comstock.

One of Julia's last requests was that there be no funeral service and that those wishing to make a gift in her memory contribute to the Alfred Tarski Fund, which she had been instrumental in setting up in honor of her late teacher, friend, and colleague. Modest to the end, she let her character and achievements speak for themselves.

I AM INDEBTED to Constance Reid, as well as to John Addison, Leon Henkin, and Raphael Robinson of the University of California at Berkeley for materials on the life, work, and career of Julia Robinson. From published sources I have drawn most heavily on *The Autobiog*

raphy of Julia Robinson by Constance Reid, and *Julia Bowman Robinson (1919–1985)* by Constance Reid with Raphael M. Robinson. Other valuable biographical material and personal impressions are listed in the references which follow.

NOTES

1. See Browder (1976), pp. 17–18, for the translation from the original German. I have omitted the adjective "rational" before "integers" to avoid confusion below.

2. For the result on Diophantine equations of degree 2, see Siegel (1972); the work mentioned on Diophantine equations in two variables of degree > 2 is due to Baker (1968).

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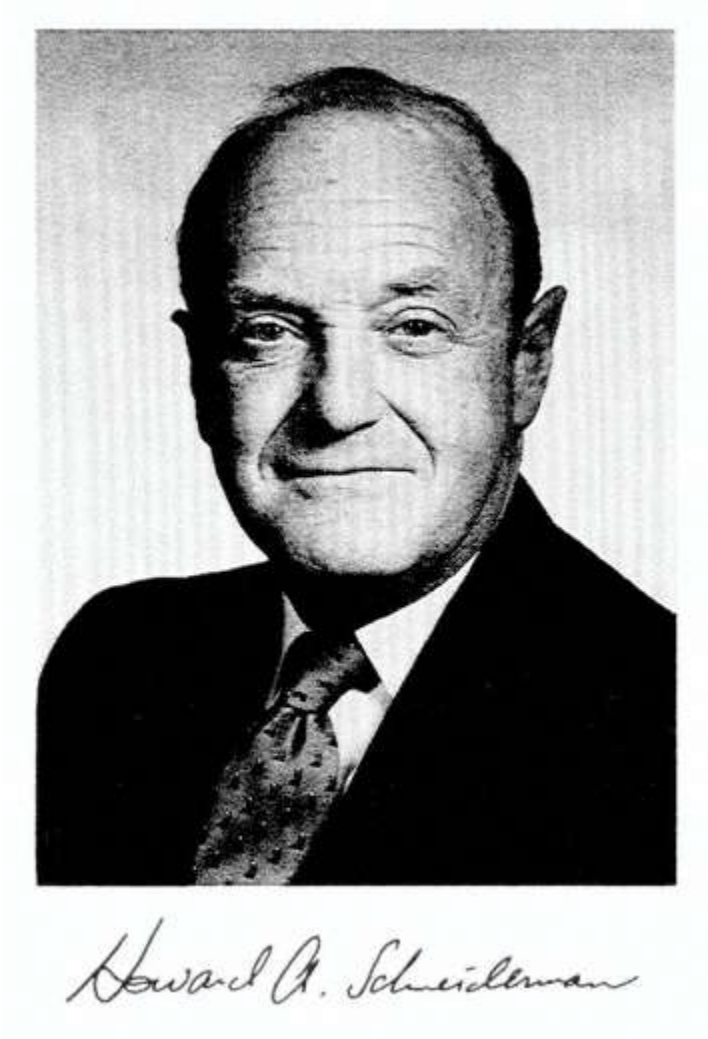

HOWARD A. SCHNEIDERMAN

February 9, 1927–December 5, 1990

BY LAWRENCE I. GILBERT

HOWARD SCHNEIDERMAN passed away on December 5, 1990. His loving wife Audrey was at his side when he lost his courageous two-year battle against leukemia. Dr. Schneiderman, an eminent developmental biologist, academician, and university administrator, was, at the time of his death, chief scientist and senior vice-president for research and development at the Monsanto Corporation. Dr. Schneiderman was the epitome of a master teacher. His contagious enthusiasm elicited the very best from undergraduates, graduate students, and postdocs, many of whom have become world leaders in science. Several months after his death two memorial services celebrated his life; one took place at Washington University in St. Louis and the other at the University of California at Irvine. The conclusion reached by all who knew Howard well agreed with my personal feelings: Howard Schneiderman was a "mensch." According to the *American Heritage Dictionary*, a mensch is "a person having admirable characteristics, such as fortitude and firmness of purpose." It is a word derived from the Yiddish and middle high German and certainly one that pays tribute to his personality.

Howard was born in Brooklyn, New York, to Louis and

Anna Schneiderman, Anna being director of education for the American Jewish Congress when she died in 1950. In 1953 his father remarried, and in Howard's own words, "I acquired three attractive stepbrothers." Howard Schneiderman adored his father and looked back on his childhood with fond memories. As a young boy he enjoyed the same frivolities in Brooklyn as I did in the Bronx, namely playing stick ball, stoop ball, and ringaleevio, and went through the same Hebrew lessons that ended with a bar mitzvah at the age of thirteen.

Howard attended the Brooklyn Ethical Culture School, since both of his parents had been associated with the Ethical Society. Although it was a financial burden to his parents, Howard enjoyed the school with its small class sizes, and both his intellect and imagination prospered. During eighth grade all students were expected to write a small book, and, as if prophetic of his future, Howard chose the topic of life and evolution. He spent many days at the American Museum of Natural History in New York compiling data for his book and came to know the works of Lamarck, Cuvier, and Darwin. He attacked the problem of obtaining the information for this project in a manner later typical of his preparation of a research project. As he describes it in his unpublished autobiography, "When I first went to the museum, I would look at an entire hall. The exhibits were often arranged in the halls by periods in evolutionary history. I had only about three hours to spend at the museum on any day and so I was selective about the material. I examined the 30 or so items in an entire hall and picked out 5 or 6 that I wanted to discuss in the book. I tried to select the ones that seemed most important, based on the amount of space that the museum devoted to it. I took all the notes, made sure that the pages were num

bered, and identified the items that I wanted to include by making marks along the edge of each page. If I was uncertain about a word, I would look it up and, if possible, use a simpler word. I did my best to make my chapters brief because I had to write each page of the final book in my own hand." My own memories of Howard as a scientist indicate that these habits he developed at the age of thirteen formed the basis of his research philosophy as an adult, since he was one of the most meticulous thinkers I have ever known.

During the last several years of his life, when he was suffering with leukemia and had undergone chemotherapy, radiation, and a bone marrow transplant, Howard put his life in order. Among his most cherished items was his stamp collection, which he cataloged with his home computer during those last months. His interest in stamp collecting began when he was about seven years old, and as an adult he used a similar paradigm in expanding his collection as he did in his science and in his eighth-grade writing project. "I picked a particular group of countries or a particular group of stamps in which I was especially interested and put together as complete a collection as I could afford. I tried to obtain stamps in beautiful condition and constantly tried to improve the quality of my collection. I kept close track of what I bought over the years and made a detailed inventory of every purchase since 1961. It is about 180 pages long, 30 lines to a page, and lists all of the stamps, collections and auction lots that I have obtained." His collection was more than simple collecting as most of us envision it. "My stamp collection is like a time machine for me. I sit down and look at it, see all the notations, some from childhood, a few from my father. I feel a sense of continuity. It has been a most rewarding

and intellectually stimulating hobby." Knowing Howard Schneiderman was a most rewarding and intellectually stimulating experience for those of us who were lucky to have him as a friend.

The high school Howard attended—the Fieldston School in Riverdale, New York—also was an Ethical Culture Society school. Although he did not take biology in high school because he had learned high school biology on his own, he did take chemistry and physics as well as four years of math. In addition to academics, he joined the football team and learned to fence. His Quaker math teacher recommended Swarthmore College, and he followed her advice and entered Swarthmore in the summer of 1944. Eight months later he joined the Navy and entered Columbia University as a midshipman in the Navy V-12 Program. Howard looked back on those days with great pleasure and felt that the most exciting courses he took at Columbia were those given by Professor Nagel in symbolic logic. He was discharged from the Navy in mid-1946 and returned to Swarthmore that fall with a deep interest in the classics, but during his junior year he entered an honors program in math and natural sciences with emphasis on biology. He studied embryology with Ruth Jones; comparative physiology with Knut and Bodil Schmidt-Nielsen and Per Scholander; and evolution and systematics at the Philadelphia Academy with Ruth Patrick, George Gaylord Simpson, Theodosius Dobzhansky, and H. Ratcliffe Roberts, among others.

In the summer of his junior year, Howard went to Arizona with Knut and Bodil Schmidt-Nielsen to study the water metabolism of desert animals. That summer was the start of his lasting love of the desert. The time he spent in the desert resulted in his first publication in 1948 and a lifetime of wearing those strange leather ties (bolas) and

boots—the cowboy look. This was Howard's first experience as a research scientist. Working with the Schmidt-Nielsen, who investigated how desert animals such as kangaroo rats and pocket mice manage to go their entire lives without drinking water, was an experience he recalled fondly. Many times he said that he learned how to conduct science by watching people who knew how to do science. "By listening to the questions they asked each other and by asking a lot of questions myself, I learned about the desert and desert animals from people who worked at the experimental station and who were deeply informed about the desert."

Howard Schneiderman was always a great observer of both nature and people, and during his time as an undergraduate he came to know a great deal about the ecology of the desert, as well as the physiology of mammals inhabiting that niche. He always had a great intellectual curiosity, and one of the wonderful things about him was his ability to expound on various subjects of biology, including ecology and evolution, as well as his major emphasis on physiology and developmental biology. After graduating from Swarthmore in 1948, he studied the parasites of large and small animals in the Grand Teton National Park and thus began his interest in that area of the country. It was during that summer that he established "a lifelong love for the Tetons," and it was with great happiness that he reflected on his backpack trips with his wife and two children, Anne and John.

Howard Schneiderman began graduate school at Harvard University in 1948 and conducted his doctoral dissertation research under the direction of Professor Carroll Williams. He finished his doctorate in four years, presented a thesis entitled "The Metabolism of Metamorphosis in the Cecro

pia Silkworm," and spent an additional year as a postdoctoral fellow in Williams' laboratory, working on the discontinuous respiration of silkworms. During that five-year period he wrote a number of interesting and important papers in the area of insect biochemistry, but no incident in the research laboratory was as momentous and important to Howard Schneiderman as was his meeting with Audrey MacLeod in 1949; they were married in 1951 at the Brooklyn Ethical Culture School.

Howard and Audrey had a wonderful relationship over a period of about four decades, and, in the opinion of this writer, Audrey was a vital force in Howard's success as a scientist and administrator. As he put it, "Audrey is a talented writer, enormously intelligent, endowed with fantastic common sense, sensitive and empathetic yet strong and single-minded. She hasn't an unkind bone in her body and has been a wonderful companion and fantastic help to my career over the years." Having known Audrey Schneiderman for 35 years I can only say that, if anything, the above is an understatement. While on a personal tack, it should be noted that the Schneiderman’s had two children. Anne, who received her Ph.D. in neurobiology from Harvard Medical School, completed postdoctoral work at Yale, and is presently an assistant professor at Cornell University. (This is coincidental since, as will be noted subsequently, Cornell was the first institution at which Howard Schneiderman held an academic position.) Their son John was an undergraduate at the University of California at Irvine and received a master's degree there. John is a professional lutist, a lecturer in the Early Music Program at the University of California at Irvine, and instructs students in the guitar, lute, and banjo.

Howard Schneiderman began his professional academic

career as assistant professor of zoology at Cornell University in 1953, where he taught comparative physiology and cellular physiology. His studies in those early years were on insect respiration and insect spiracles, as well as wound healing and some aspects of developmental biology of the giant silkworm, *Hyalophora cecropia*. It was at this stage of his career that I was privileged to meet him in the spring of 1955. I was a prospective graduate student after spending four years in the Navy and had decided to attend either Princeton or the University of California at Berkeley for my doctoral studies. I walked into his office at Cornell, where he was removing the brains of giant silkworm pupae, and he looked up at me with his captivating smile. We talked about biology, and he enticed me with his contagious enthusiasm for his research, academics, and life in general. This enthusiasm never left Howard Schneiderman, even during the last years. I didn't know anything about insects, didn't really want to do my doctoral dissertation on insects, but, in the end, accepted a teaching assistantship at Cornell after turning down full fellowships at Berkeley and Princeton. It was a personal decision because of the man Howard was, and I have never regretted that decision!

His closest colleagues and friends at Cornell at that time were Marcus Singer, a world authority on amphibian regeneration, and F. C. Steward, who had pioneered plant tissue culture. Naturally, both served as members of my doctoral committee when I began my studies at Cornell in the fall of 1955. One of the things I remember so vividly about those years at Cornell other than going with Howard Schneiderman into the woods to "bag" trees to raise silkworms, was the fantastic effect he had on undergraduates. They were highly motivated, worked all hours of the night,

and were among the brightest young scientists I ever met. They included Robert I. Levy, who at one time was head of the National Heart Institute; Judith Willis, who is currently chair of the Department of Zoology at the University of Georgia; Mordecai Blaustein, a prominent physiologist in the Department of Physiology at the University of Maryland Medical School; Charles Kurland, professor of molecular biology in Sweden; and many others. Over the past three decades I have never met another faculty member who approached Howard Schneiderman's ability to train and motivate undergraduates. During those years at Cornell, Howard and I worked on the insect juvenile hormone, and we continued to collaborate after I left in 1958 to take a faculty position at Northwestern University.

During his tenure at Cornell, Howard became imbued with the spirit of the Marine Biological Laboratory at Woods Hole and taught the invertebrate zoology course. He was a meticulous lecturer both there and in the university classroom, preparing every lecture in the most methodical manner and with every word on the pages before him. However, when Howard Schneiderman lectured either in class or at professional functions, one always had the feeling of spontaneity and excitement. Since I was his teaching assistant at Cornell, I know that he was one of the finest teachers of undergraduate and graduate students in the country. It is of interest that he taught in the invertebrate biology course at Woods Hole since he had taken that course in the late 1940s, and he considered it one of the great achievements of his career to be selected to teach there. Later he became a trustee of the Marine Biological Laboratory when James Ebert was head, and his professional life was influenced to a great degree by the lab and the people he met there. From 1959 to 1960 he worked with Sir Vincent

Wigglesworth at Cambridge. It was during that period that Howard Schneiderman, as a young scientist, became acquainted with some of the most respected and influential scientists in Europe, including Sir James Gray, Lord Victor Rothschild, Max Perutz, David Keilin, Joseph Needham, and Sir Richard Southwood. In addition, he noted, "I also had memorable dinners at various Cambridge colleges with C. P. Snow, E. M. Forster, and C. S. Lewis."

In 1961 Howard moved to Western Reserve University to assume the chair of the Department of Biology, where his administrative abilities came to the fore. He developed the Department of Biology into one of the most outstanding in the United States by recruiting such individuals as Boris and Harriet Ephrussi, Bodil Schmidt-Nielsen, and Michael Locke. During the summer of 1965, while at Woods Hole, he spent some time with Ernst Hadorn of the University of Zurich and learned the new methodology developed by Professor Hadorn for the in vivo culture of *Drosophila* imaginal discs. At about this time he converted his research emphasis from silkworms to the fruitfly *Drosophila melanogaster* . He continued to work on silk moth hormones during this period at Western Reserve but also published an important paper with Peter Bryant on the use of x-ray-induced mitotic recombination, which permitted the clonal analysis of cell lineage, growth, and determination of the imaginal leg disc of *Drosophila*. This was an important experimental paradigm, and Howard Schneiderman and his colleagues used this clonal analysis to analyze cell lineage, growth, and determination in all of the imaginal discs of *Drosophila*. Indeed, a later paper with his student Cliff Poodry, on the ultrastructure of the developing leg imaginal discs of *Drosophila*, became a Citation Classic. His work with John Postlethwait, another of his graduate students, on pattern

formation and determination in the antenna of the homeoeotic mutant of *Drosophila* was also extremely well cited.

His development of the Department of Biology was made possible by a million-dollar grant from the Ford Foundation, another example of Howard Schneiderman's willingness to place his personal research aspirations second to those of the organization he served. To his scientific disciples, this was an important lesson in selflessness. The Ford Foundation application was to set the stage for many analogous projects during his career. Perhaps a few quotes from Professor Schneiderman regarding his strategy for the Ford Foundation grant will further illustrate his personality and ability. "I called up various people who had previously dealt with the Ford Foundation and learned from them what was important in an application. I got various colleagues to prepare drafts of specific sections. To obtain consensus, I calmly had lunch with colleagues who were anxious to be part of the proposal. After all the spade work was done, I put the proposal together, wrote it out, used scissors and scotch tape to glue sections together and had a secretary type it. In this process, I would first write a detailed outline of what I wanted to accomplish. All the time I was preparing the proposal, I was thinking about the people who would read it. What kinds of things can I put in the proposal that everybody else and his brother won't put down also? What can I put that's different, that's unique?" Interestingly, the grant from the Ford Foundation was ultimately an important parameter leading to the merger of Case Institute and Western Reserve University into Case Western Reserve University.

After eight years in Cleveland, the Schneiderman's moved to the University of California at Irvine, where Howard became head of the Department of Organismic Biology,

later called the Department of Developmental and Cell Biology. Three months after his arrival Howard became the third dean of the School of Biological Sciences. Only after a great deal of work involving the faculty and administration did the Developmental Biology Center become a reality. It was modeled after the Developmental Biology Center that Howard and Marc Singer had established at Western Reserve. The center at Irvine was almost totally concerned with *Drosophila*, amphibians, and *Hydra*. At Irvine, Howard continued to attract excellent postdocs and graduate students. Both Peter and Susan Bryant had moved with him from Case Western Reserve University; Peter Bryant presently directs the Developmental Biology Center. Others included the Madhavans and a number of individuals from Ernst Hadorn's laboratory.

During his time at Irvine, Howard Schneiderman was personally involved with a series of publications on the dynamics of cell growth and determination in various imaginal discs of *Drosophila*. Especially noteworthy was the series of papers with Peter Bryant, John Postlethwait, and Cliff Poodry on various aspects of this topic. He and Peter Bryant published a very useful review in *Nature* in 1971 on the genetic analysis of development mechanisms. Together with Mary Bownes and Thomas Cline, the Irvine group demonstrated the rescue of a female lethal maternal effect mutant, "daughterless," by cytoplasmic transplantation into embryos. Meticulous studies on the role of abdominal histoblasts with Madhavan and Roseland answered some basic questions regarding the role of these cells in the development of the pupal and adult abdomen of *Drosophila*. During his time at Irvine, Howard Schneiderman became deeply interested in the ethical and social implications of advances in life sciences. Until becoming ill, he lectured extensively on the

moral dilemmas posed by such questions as whether our genes are private, the responsibilities of insurance companies in insuring individuals with a high-risk disease, and the ownership of rare genes.

In 1975 Howard Schneiderman was elected to both the National Academy of Sciences and the American Academy of Arts and Sciences. Two activities with the National Academy of Sciences were particularly important to him. The first was his 1984–88 service on the Council and Executive Committee of the Government-University-Industry Roundtable, and the second was as chairman of Working Group III. The latter was organized to promote new research alliances among universities, industry, and government. These activities became a large part of Howard Schneiderman's life, but as far as activities with the Academy are concerned, he took great pleasure in playing what he considered to be a small role in persuading Donald Bren to donate $6 million worth of land for the Western Center of the National Academy of Sciences—the Arnold and Mable Beckman Center. It is appropriate that this important edifice is situated directly adjacent to the University of California at Irvine, which was so important to Howard for many years. During his time at Irvine as dean of the School of Biological Sciences, Howard recruited a large number of very bright researchers and planned curricula to educate undergraduate majors in the breadth and modern aspects of biology, but he was always interested in the entire university as well as the School of Biological Sciences. He played a vital role in having the university require that all undergraduate majors in biology take two years of humanities courses. Howard always believed that an individual was not truly educated unless he or she had a breadth of knowledge and did not specialize solely in one segment of higher education.

We who hold academic administrative offices know that the fun is in building and developing a department or school by recruiting the very best scholars and teachers and taking delight when the job is almost done and one can harvest the incredible but intangible rewards. At that time, new challenges may beckon. I feel that Howard Schneiderman chose a new challenge when he left Case Western Reserve in 1969 at a time when the reputation of the Department of Biology and the Developmental Biology Center was at its zenith. Later he decided to accept the offer from the Monsanto Company in 1979 as senior vice-president for research and development and chief scientist as another, different sort of challenge. It was not without a great deal of soul searching and discussion with his closest friends that he accepted the position at Monsanto. I remember clearly the conversations I had with him when he complained that some of his colleagues thought it was close to a traitorous act to desert academia for industry. My reply was that the scientific community needed people like Howard Schneiderman to interface between universities and industry and who, indeed, have some power to ensure that cooperative projects are initiated. I like to think that my thoughts on the matter helped influence his move to Monsanto, because his years there were among the most productive of his career and, I think, among the happiest of his life.

His contributions at the University of California-Irvine were summarized succinctly by Chancellor Peltason at the March 1991 celebration of Howard Schneiderman's life when he said "Howard Schneiderman was an intellectual beacon for UCI. The fruits of his energy, enthusiasm and leadership are still very present on this campus." The comments at the December 1990 celebration of his life at Washington

University by his colleagues at Monsanto echoed a very similar theme. His intellectual brilliance and enthusiasm were certainly noted by everybody with whom he had contact.

At Monsanto he was able to convince management that the company must enter the age of molecular biology and recombinant DNA technology. Howard Schneiderman basically engineered the new Life Sciences Research Center (known around the company as "the house that Howard built") that Monsanto built in 1984 at a cost of about $200 million, a structure that houses more than 1,000 young scientists. The biotechnology program involving plants and animals is one of the best in the world, and by 1990 Monsanto had one of the most efficient internal biotechnology capabilities of any commercial company. A central focus of his interest was the potential advantages that biotechnology might bring to developing—and developed—countries, in terms of health care and a safer, reliable, and sustainable agriculture to feed an inevitably growing world population. In a speech in 1985 to the National Research Council's Agency for International Development, he concluded that "genetic engineering and its handmaiden, biotechnology, have initiated a profound revolution in science with enormous technological and social consequences. I suspect that we underestimate its pending impact on society and its durability as a scientific tool in the service of humanity. Indeed, we can argue persuasively that genetic engineering may be the most significant scientific and technological discovery ever made. . . . We, using nature's own methods, will have learned to persuade her to be a full partner in humanity's major enterprise, civilization." Although some of the fruits of the biotechnology advances at Monsanto have yet to be reaped, due to federal regulations, it is of

interest that recently the bovine somatotropin has been endorsed for use by the European equivalent of the Food and Drug Administration. A National Institutes of Health panel has already approved it, and it is simply a matter of time before this product and others are utilized by the benefactors of what Howard always termed "the second Industrial Revolution."

Another project close to his heart involved research in the area of pharmaceuticals. Howard Schneiderman was influential in the establishment of a health care division at Monsanto and eventually in the acquisition of the G. D. Searle Company in 1985. However, he realized that Monsanto could not develop a drug-discovery reputation internally. Therefore, he began discussions with the Washington University School of Medicine's administration, the goal being a collaborative research program. He investigated every aspect of Washington University School of Medicine and had a small Monsanto task force meet with university representatives. He worked with the faculty at Washington University to initiate a proposal that he felt would be acceptable to both the university and his colleagues at Monsanto. He did a complete rewrite and insisted that the venture be a real partnership, with the executive committee of the joint program being composed of equal numbers of Monsanto and Washington University personnel.

More difficult was selling the entire idea to the management of Monsanto, but, in his usual enthusiastic manner and with all the possible data one could command, Howard obtained the support of each of the influential individuals at Monsanto. In 1982 Monsanto and Washington University signed the initial five-year $23 million agreement, which is exemplary among university/industry collaborations and continues to the present. When commenting on the suc

cess of the program, he noted, "To be sure there was scientific excellence; that was necessary but not sufficient. What was also necessary was mutual respect and trust. In discussions between the two institutions, the social contract took precedence over the legal contract. There was a willingness to work for a durable relationship rather than for a quick fix."

Even after this historic program was initiated, Howard Schneiderman continued to develop close research collaborations between Monsanto and other universities such as Oxford and Rockefeller universities. He became one of the leading and most vocal advocates of alliances between university and industry, and he presented exciting, compelling, and intellectually tantalizing lectures at many institutions, including my own, on the virtues of such relationships. He emphasized the fact that the government must be involved in some way or we were going to lose the "second Industrial Revolution" to foreign countries. I know that his lecture in Chapel Hill inspired all of us. It wasn't long afterwards that he became ill and fought the great battle against leukemia.

Howard Schneiderman himself summarized, to my mind, the key to his success at Monsanto and, indeed, to his success in his university positions and as a human being. The single element according to him was "truth in packaging." He told it as it was. His views on various issues were well known and easily understood because, as he notes, "I use declarative sentences, not the future less-vivid conditional!"

Howard Schneiderman was an individual honored in many ways. He was elected to office, was appointed to editorial boards, presented memorial lectures, was elected to both Academies, was a member of the National Science Board by presidential appointment, held several honorary doctor

of science degrees, and held an endowed chair. In 1990, just a few months before his death, he was the recipient of the prestigious Gregor Mendel Gold Medal, presented to him by his old friend and colleague Frantisek Sehnal on behalf of the Czechoslovakian Academy of Science. The legacy he left, however, was much greater than the awards he received. He instilled in those of us who worked with him a zest for science, a curiosity about nature, a love of life and family, and courage during adversity. In our discussions he noted many times that if he had his life to live over he wouldn't live it any other way. The scientific community will forever have a void in its core because of the loss of Howard Schneiderman. All of us who were fortunate enough to have known this extraordinary man have gained a great deal. We will always miss him.

MUCH OF THE MATERIAL in this memoir was taken from an unpublished autobiography written by Howard Schneiderman during the last two years of his life. He knew that he was dying and, in his own inimitable way, got "his affairs in order." He wrote a 45-page autobiography, cataloged his beloved stamp collection on the computer, and helped to recruit his successor at Monsanto. An incredible individual!

I thank Audrey Schneiderman and Doris Gilbert for their superb editorial work on drafts of this memoir.

HONORS AND DISTINCTIONS

1975 Member, National Academy of Sciences
1975 Fellow, American Academy of Arts and Sciences
1975 D.Sc. (Honorary), La Salle College
1982 D.Sc. (Honorary), Swarthmore College
1984 D.Sc. (Honorary), University of Toledo
1986 D.Sc. (Honorary), University of Massachusetts at Amherst
1989 D.Sc. (Honorary), Washington University at St. Louis
1989 LL.D. (Honorary), Clemson University
1989 UCI Medal, University of California, Irvine
1990 Gregor Mendel Gold Medal, Czechoslovakian Academy of Science
1966–69 Jared Potter Kirtland Distinguished Professorship, Case Western Reserve University
1973 Distinguished Faculty Award, UCI Alumni
1983 Founders Memorial Award, Entomological Society of America
1988 Distinguished Leadership Award, Marine Biological Laboratory, Woods Hole, Massachusetts

SERVICE (SELECTED)

1964–66 President, Society for Developmental Biology
1966–72 Trustee, Marine Biological Laboratory, Woods Hole, Massachusetts
1975–81 Member, Assembly of Life Sciences, National Academy of Sciences
1980–86 Member, Expert Committee on Biotechnology, Organization for Economic Cooperation and Development
1981–90 Member of Board, International Society of Developmental Biologists
1981–90 Member, Board of Trustees, Missouri Botanical Garden
1984–88 Member, Council of Government-University-Industry Research Roundtable, National Academy of Sciences
1987–92 Member, National Science Board, by Presidential Appointment and Senate Confirmation
1988–90 Member, Board of Trustees, Carnegie Institution of Washington
1988–90 Member, Board of Directors, Life Sciences Research Foundation

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With C. A. Poodry and P. J. Bryant. The mechanism of pattern reconstruction by dissociated imaginal discs of *Drosophila melanogaster. Dev. Biol.* 26:464–77.

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1975 With P. Simpson. Isolation of temperature sensitive mutations blocking clone development in *Drosophila melanogaster*, and the effects of a temperature sensitive cell lethal mutation on pattern formation in imaginal discs. *Wilhelm Roux' Arch. Entwicklungsmech. Org.* 178:247–75.

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THOMAS KILGORE SHERWOOD

July 25, 1903–January 14, 1976

BY HOYT C. HOTTEL

THOMAS KILGORE SHERWOOD was, by any standards, one of America's great chemical engineers. His scholarly work on mass transfer under molecular and turbulent-flow conditions made him a world authority in the area. He was the author of five books, two of which had enormous influence on the teaching and practice of chemical engineering. Taking strong stands on the problems of engineering education was one of his hallmarks. In the early stages of World War II he was the finder of talent for military research in chemical engineering; in the war's late period he was in Europe gathering intelligence. He was one of the founders of the National Academy of Engineering. He was respected and admired by his peers; countless numbers of them called him friend. He had warmth, charm, orderliness, and a conscience that drove him to use his talents to the fullest to advance chemical engineering in theory and practice. The world has his number—the Sherwood Number.

Thomas Kilgore Sherwood was born to Milton Worthington Sherwood and Sadie Tackaberry Sherwood on July 25, 1903, in Columbus, Ohio, but spent most of his early youth in Montreal. With a B.Sc. degree from McGil University, in

1923 he came to M.I.T. for graduate work in chemical engineering. Upon receiving his M.Sc., he became an assistant to W. H. McAdams in distillation and heat transfer. The next year he began research on his S.D. thesis under W. K. Lewis on a subject which—and under a man who—would have a lifelong effect on his career. The drying of solids sounds prosaic, but it touches on all the phenomena, some recondite and chemically controlled, related to transport of a vapor or liquid through and between phases. For Sherwood that was the first step in a lifelong dedication to mass transfer in chemically related systems. A two-year appointment as assistant professor at Worcester Polytechnic Institute was followed by one in chemical engineering at M.I.T., where he completed his doctorate in 1931. He became a professor in 1941 and was appointed the first professor of chemical engineering to the Lammot du Pont chair in 1966. When the time for retirement came, he left M.I.T. for California to become, from 1970 to his death, a visiting professor in chemical engineering at the University of California, Berkeley.

Though Sherwood's early papers showed his inclination to move frequently from research to industrial practice—papers on heat transfer, rubber vulcanization, wet-bulb hygrometry, optimization of ammonia condensers, plate-column entrainment and flooding are examples—his dominant research up to World War II was in mass transfer, papers on Drying of Solids I-VII, absorption, extraction, packed-tower and bubble-cap column performance. But his most important contributions to chemical engineering in that prewar period were two books exerting far-reaching influence on chemical engineering teaching. *Absorption and Extraction* (1937) was the first significant book in that area. The second, *Applied Mathematics in Chemical Engineering*, (1939),

written with C. E. Reed, began as a graduate subject. Sherwood would have been the first to deny any claim to being a mathematician. But any mathematical defects in the book were far more than offset by the many stimulating examples of application to industrial practice; the book influenced chemical engineering curricula throughout the world. A much-revised edition, prepared chiefly by H. S. Mickley, appeared in 1957.

By 1940 it was clear that the United States might be involved in war. At the instigation of Vannevar Bush the National Defense Research Committee was set up, and Sherwood was appointed a technical aide. His job was to line up chemical engineers who would be available for military research if war came. He later became section chief for Miscellaneous Chemical Problems in NDRC's Division 11 and a consultant to the Baruch Committee concerned with synthetic rubber development. Under his supervision were such diverse problems as new hydraulic fluids for use at very high and very low temperatures, antifouling coatings for ship bottoms, the inerting of gas spaces in aircraft fuel tanks, the development of large screening-smoke generators, and the production of concentrated hydrogen peroxide. In addition to supervising NDRC contracts, Sherwood had his own research programs at M.I.T., the drying of penicillin, evaporation of falling drops, mixing in commercial reactors, and the manufacture of formaldehyde for making RDX.

In 1944 Sherwood was made a member of the first of two successive committees to assess the status of jet propulsion in the United States, the so-called Whitman Committee. That fall, as an expert consultant of the War Department, he was made one of a small group of scientists operating in Europe behind the Allied lines, charged with gathering

scientific intelligence on German technical developments, particularly in the nuclear and rocket areas.

When World War II ended, Sherwood returned to M.I.T. for teaching and research. The next year, however, he was appointed dean of engineering. In that position he had the difficult task of seeing the institute through its period of postwar adjustment. Although his research, directed particularly to the area of heat, mass, and momentum transfer in turbulent flow systems, did not stop, he showed an increasing tendency to address problems outside his area of technical expertise. Papers and lectures on science in education, teacher development, research in education, creative accomplishment, and new frontiers in science were characteristic of that period. But his preference for research, teaching, and the organization of parts of chemical engineering science in book form pulled him out of administration after six years as dean, to return to his scientific and technological interests. A quote from a paper given years later at a symposium on mass transfer and diffusion measures him:

> We have much more concern with complex physical phenomena, and we have not yet arrived at a point where all can be left to the computer. In a way I hope we never will, for chemical engineering is so much more fun when we don't know very much.

Despite his coauthoring a book on mathematics, he had a strong preference for physical and chemical phenomena over theory. A study of interfacial phenomena in liquid-liquid extraction produced some exciting results. For example, the rate of water-extraction of acetic acid from its solution in isobutyl alcohol (immiscible with water) may be expected to be affected by addition of a base to the water phase. Then-existing theory predicted a maximum twofold increase in rate of extraction. Instead, the rate

climbed tenfold with increased base concentration, and violent interfacial turbulence showed up, even forming submerged droplets. Completion of the study of this phenomenon, important in determining the size of extraction equipment used by chemical industry, was left to others. Sherwood went on, continuing to mix scholarly research with such practical problems as mechanical draft cooling towers, vacuum dehydration using liquid absorbents, separation of hydrocarbons with an adsorbent slurry, and desalination by freezing or by reverse osmosis.

Two of Sherwood's books have been mentioned. The second edition of *Absorption and Extraction*, revised with R. L. Pigford, appeared in 1952. Then came *Properties of Gases and Liquids*, coauthored with R. C. Reid; a *Course in Process Design; The Role of Diffusion in Catalysis*, coauthored with C. N. Satterfield; and a much-expanded and far more comprehensive edition of his first book, with title changed to *Mass Transfer*, coauthored with R. L. Pigford and C. R. Wilke. Sherwood's talent for organizing, for identifying the most significant defects of a technical scheme, process, or design and for designing an experiment to supply the most needed new knowledge caused him to be sought out for many organizing activities. He was technical adviser to the Office of Saline Water of the U.S. Department of the Interior from 1952 to 1961; in 1960 he chaired a planning committee for the Research Study at Woods Hole on Salt Water Conversion. He was a member at large of NRC's Division of Engineering and Industrial Research (1962–65). He was a founding member of the National Academy of Engineering (1964). At M.I.T. he chaired the Committee on Staff-Administration (1964). In 1967, when NAS–NRC again went with intensity into desalination, he chaired a planning committee for the Desalination Research Con

ference. That year he was also chairman of the Long-Range Planning Committee for M.I.T. libraries and a trustee of the M.I.T. Pension Association. From 1967 to 1969 he was chairman and then a two-year member of the NAE Committee on Air Quality Membership, and in 1974 a member of the NAE Task Force on Energy.

Sherwood's later-life associates think of his avocation as having been mountaineering, particularly in the Canadian Rockies. Personal experience suggests a postscript to that: A year after the death of his first wife, Betty, Tom, Reg Wynn—Tom's closest Montreal high school associate—and I spent an idyllic month in the Tetons. On a Grand Teton climb (up by the exciting Glenn Exom route; the Grand Teton was America's Matterhorn, and Exom had climbed the Matterhorn solo at age seventeen), our guide chose Tom to be the first, on our way down, to make a 110-foot rappel down a cliff. As he prepared for the back-jump off the cliff, leaning out to prevent his chin from hitting the edge as he dropped, his foot caught in a crevice and in pain he dropped his rappel rope! But his belaying rope, monitored by the guide, saved him. So I was elected to make the first rappel. Waiting at the end of my 120-foot rope and speculating on whom the guide would send down next, I saw Tom in a few moments, inching his way down the curved cliffside. When he joined me, still whitefaced, he said, "Hoyt, I am never going to climb a mountain again." But the next year he married Virginia, and she made him into a mountaineer.

Outstanding among the many invited lectures given by Sherwood were the Priestley Lecture at Pennsylvania State, the King Lecture at Johns Hopkins University, and a comprehensive review of his fifty years of interaction with his special interest, "The Development of Mass Transfer Theory,"

presented in 1973 at a University of Houston symposium. His many memberships and honors are listed below; outstanding among the latter were honorary doctorates, from Northeastern University, from his first alma mater McGill University, and from the Technical University of Denmark. He was honored by his colleagues by having a dimensionless number used in scientific literature in relation to mass transfer—previously called ambiguously the Nusselt number for mass transfer or the reciprocal of one of the Taylor numbers—renamed the Sherwood Number, a nomenclature now almost universally accepted. Sherwood was one of the giants of twentieth-century chemical engineering.

HONORS AND DISTINCTIONS

MEMBERSHIPS

National Academy of Sciences (Chairman, Section of Engineering, 1962–65)
National Academy of Engineering (Founding member)
National Academy of Arts and Sciences
American Society of Engineering Education
American Chemical Society
American Institute of Chemical Engineers (Councillor, 1947–49)
American Society of Mechanical Engineers
Sigma Xi, Tau Beta Pi, Alpha Chi Sigma
Chemical Institute of Canada (Honorary Life Member)

AWARDS AND HONORARY DEGREES

1941
William H. Walker Award, A.I.Ch.E.
1947
Doctor in Engineering, Northeastern University
1948
United States Medal for Merit
1951
Doctor of Science, McGill University
1963
Founders Award, American Institute of Chemical Engineers
1972
Warren K. Lewis Award, A.I.Ch.E.
1972
E. V. Murphree Award, Industrial and Engineering Chemistry
1974
Doctor of Science, Technical University of Denmark

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1936 Air drying of solids. *Trans. A.I.Ch.E.* 32:150.
1937 *Absorption and Extraction*. New York: McGraw-Hill.
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