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ALFRED GILMAN

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A Biographical Memoir by
MURDOCH RITCHIE

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Alfred Sloan

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BY MURDOCH RITCHIE

ALFRED GILMAN, AN INTERNATIONALLY renowned pharmacologist who died on January 13, 1984, will be remembered by countless scholars for his coauthorship of the seminal textbook on the pharmacological basis of therapeutics, by generations of medical students for his brilliant and inspiring lectures, and by his many friends for his warmth and concern for their personal problems. As for his scientific achievements, he played a key role in our understanding of how the ionic milieu of the body is maintained and he pioneered the first clinical trial that established the use of chemotherapy in the treatment of cancer.

Alfred Gilman was born in Bridgeport, Connecticut, on February 5, 1908. He graduated in 1928 from Yale College and remained as a graduate student in the Department of Physiological Chemistry, as many departments of biochemistry were called at that time. In 1931 for his dissertation on "Chemical and Physiological Investigations on Canine Gastric Secretion," he was awarded a Ph.D. degree in biochemistry. Although his heart was set on taking a medical degree to become a research clinician, the exigencies of the Great Depression led him to postdoctoral fellowships at Yale, first in the Department of Biochemistry for a year in 1931 and

subsequently in the Department of Pharmacology. Thus, a career that changed the face of pharmacology was started.

The switch from biochemistry to pharmacology was one of those fortuitous events that was of no apparent significance at the time. G. R. Cowgill, Gilman's mentor in the biochemistry department, was studying the osmotic relations between blood and gastric juice. The main instrument used for this at the time, which depended on the depression of the freezing point, had a limited resolution and accuracy. By chance the young Gilman heard a seminar given by a visiting professor from Britain (A. V. Hill, Nobel prizewinner for his work on the mechanism of muscle contraction) in which was described the use of an extremely sensitive vapor-pressure method for determining the osmolality of very small volumes of fluid. Gilman soon arranged for A. V. Hill's technician in London (A. C. Downing) to make for him the sensitive thermopile and galvanometer that was needed, and then used the method with great success. It happened that the chairman of pharmacology at the time (H. G. Barbour) was also interested in osmotic changes in blood and body fluids that resulted from various procedures. As a result (at least according to Gilman) Barbour had little hesitation in offering this postdoctoral fellow in biochemistry with his state-of-the-art methodology, first a postdoctoral fellowship and subsequently an assistant professorship in pharmacology. He remained in pharmacology for the rest of his career.

While still a postdoctoral fellow in pharmacology Gilman first met Louis S. Goodman, who had just completed an internship in medicine at Johns Hopkins University School of Medicine. Both had a compelling interest in pharmacology, which they began teaching jointly. It soon became clear to them both that the textbooks of the time were outmoded and inadequate for the teaching of medical students. They

were either poorly written for the needs of medical students or else failed to reflect the latest findings in drug therapy—or sinned on both counts. By now assistant professors, the two young lecturers decided to write a text originally for the use of Yale students. Their aim was to correlate pharmacology with related medical sciences, to reinterpret the action and uses of drugs in the context of the important advances in medicine that were being made at the time, and to emphasize the application of pharmacodynamics to therapeutics—a momentous change to be undertaken by two junior faculty members, both barely thirty years old. Hearing of their project, John Fulton, professor of physiology, introduced the young authors-to-be to the Macmillan Publishing Company; the rest is history.

The editors at Macmillan, expecting a book of about 450,000 words, were aghast at the size of the manuscript that Gilman and Goodman submitted; it was nearly a million words long, all written in longhand. Despite heated discussion the young authors refused to make any cuts in the text; and, after a day of arguing, Macmillan agreed to publish the manuscript as submitted at the then unheard of price of $12.50 per copy (most medical books at that time sold for about $8.00). Needless to say, it became an immediate best-seller. It has remained so through nine editions.

Despite its length the book published in 1941 was not a compendium of drug data. Rather, it was the reinterpretation of the actions and uses of well-established therapeutic agents in light of recent advances in the medical sciences; and the time was ripe. The sulfa drugs had already been introduced, and over a hundred pages were devoted to them in the first edition. Modern chemotherapy had been born, to be followed by (and described in subsequent editions)

the antibiotics, the antimalarials, and a host of chemotherapeutic agents that were specific against particular diseases.

The book was explicitly written as a textbook for physicians and medical students; and this was made clear in the first edition's subtitle. Emphasis throughout the book was clinical. Medical students, they believed, must be taught pharmacology from the standpoint of the actions and uses of drugs in the prevention and treatment of disease; and the practicing physician must be offered an opportunity not only to keep abreast of recent advances in therapeutics but also to acquire the basic principles necessary for the rational use of drugs in daily practice.

The book was an immediate success. Within three years 28,000 copies had been sold and by the time the second edition appeared in 1955 the first edition had sold more than 86,000 copies—a record for a pharmacology textbook. Subsequent editions have continued to enjoy record-breaking sales. Within a few years of the first edition, however, it became clear to the authors that the Blue Bible (after the color of its cover) needed thorough revision. The drug revolution was underway. Steroids, CNS compounds, new antimalarials, and antihistamines had been introduced, and the antibiotic era had been started with the introduction of penicillin. Any immediate revision, however, was prevented by the intervention of the Second World War so that the second edition did not appear until 1955. Much of the reason for the further delay after end of the war was the breakneck speed at which pharmacology and therapeutics were moving. Each time the last of the chapters had been rewritten, the earlier chapters were already out of date and had to be revised. By the time the new second edition eventually came off the press, it had become clear to both authors that the whole field of therapeutics had become too extensive and too specialized for two men to encompass all areas

appropriately. The 1955 edition, therefore, was to be the last edition written by themselves alone. Two decisions were made: first, to revise the book every five years (a goal they met), and second, to call on other coauthors (forty-two in all) preeminent in their fields of specializations, most of whom were current or former associates of Gilman or Goodman. The fact that the book from the third edition on had multiple authors did not mean that either Gilman or Goodman abrogated their responsibilities. If the book was to maintain its readability, cohesiveness, organization, and most essentially, its philosophy and objective, strict editing by them was mandatory. This requirement was rigorously met; and, equally important, the timetable was kept. New editions appeared regularly every five years; in 1995 it was in its ninth edition. Gilman died before the seventh edition appeared (1985). Goodman relinquished his role prior to the eighth edition; Gilman's son, Alfred Goodman Gilman, who became the senior editor at the time of the sixth edition, will continue as the Blue Bible's consultant editor.

Gilman could not, from the very beginning, hide his obvious love affair with teaching and the responsiveness of those he taught, whether medical students or professional physicians. At Columbia University's College of Physicians and Surgeons in New York, which succeeded Yale as Gilman's academic home, the Department of Medicine had weekly staff conferences (grand rounds) always attended by the full faculty with the chairman of the department together with the senior professors in the front row and then behind them in due hierarchical structure, the associate professors, the assistant professors, the instructors, the house staff, as well as the senior and junior medical students in the rows behind. Discussion of patients' medical problems ranged from the commonest to the most perplexing and esoteric. Into this impressive arena Alfred Gilman appeared in 1946.

Not only appeared, but became a leading participant, commenting on all issues of pathophysiology and pharmacotherapy. He was soon counted on to add to the educational importance of these weekly meetings.

Wherever he taught he had tremendous impact, not just on the graduate students but also (and most particularly) on the much larger numbers of medical students. His lecturing style was leisurely. The facts and "information bits" presented during the hour were small in number, and they were often presented in the context of humor. But these "bits" had been carefully selected as the cardinal points at issue; and twenty years after such a lecture the students (by now practicing physicians or academic faculty) would still remember. As a lecturer Gilman was superb. He had an exceptional combination of modesty, good sense, and humor. For example, he gave the acid-base lectures in pharmacology. For this topic he would make sure to get to the lecture room well ahead of the students and fill the blackboard with the mathematical derivation of the Henderson-Hasselbalch equation. When the students arrived their jaws would drop visibly on seeing what they thought was in store for them. Gilman would then start his lecture by announcing that he was not going to go into the derivation of the equation, at which point he would erase most (but not all) of the blackboard. He would then continue with an hour of applied pharmacology, all beautifully illustrated by the final equation itself which had remained untouched. He taught the students how to *use* the equation rather than just how to derive it. What Gilman liked was actually teaching, not just talking about it, whether formally in a lecture or informally in a seminar. His office was always rather small and on the main corridor, and the door was always open, both literally and figuratively. Students would often drop in for a

brief visit just to get something straightened out and the house staff would wander in just "to see what Gilman thinks."

In his teaching Gilman guided his students through the maze of pharmacology by selecting and emphasizing key issues and letting the unimportant ones take care of themselves. As John Kemeny, president of Dartmouth, said on the occasion at which Gilman was awarded an honorary degree, "Far more than an isolated exercise in pharmacology, your book has provided for generations of students and practitioners the essential but difficult bridge between the basic medical sciences and the practice of medicine. Indeed it could be said that long before the concept of an integrated curriculum became a popular educational philosophy in medical schools, it was a reality in the form of your textbook."

During the Second World War Gilman left Yale for army service as chief of the Pharmacology Section in the Medical Division at Edgewood Arsenal, Maryland, with the rank of major. These war years were largely spent in trying to develop antidotes for the nerve gas organophosphates and for the nitrogen mustards, both of which it was feared would be used against American troops. Even before he left Yale early in 1942 a contract had been signed between Yale University and the Office of Scientific Research and Development to investigate these chemical warfare agents. The study of the nitrogen mustards was assigned to Alfred Gilman and Louis S. Goodman. Early in the course of their study of the nitrogen mustards, it became apparent that the agents were cytotoxic following absorption; in particular they destroyed lymphatic tissue. After the nitrogen mustard treatments were shown to cause regression of experimental lymphoma in mice (and not many days after!) Gustaf E. Lindskog, an assistant professor of surgery, was persuaded to supervise a clinical trial on a patient in the terminal

stages of lymphosarcoma which was resistant to X-ray therapy. The response of this first patient was as dramatic as that of the first mouse. Within forty-eight hours after initiation of therapy, softening of the tumor masses was detected. By the fourth day cervical masses were no longer palpable and a few days later the axillary masses had completely receded; however, as one might have anticipated from the mouse studies, the tumor slowly regenerated. A subsequent course of therapy resulted in only partial improvement and a third course had relatively little effect. That the treatment was only a partial success is irrelevant. The point is that tumor growth had been clearly shown to be susceptible to chemotherapy, and treatment was no longer limited just to radiation or to radical surgery. From this insightful beginning medical oncology grew and now is one of the recognized medical subspecialties.

Much of Gilman's immense contribution to the field of therapeutics is not immediately apparent, for it came outside academia in a lifetime of acting as consultant to several pharmaceutical companies (for example, Burroughs Wellcome and Smith Kline French) who sought his advice. Gilman did not see academia and industry as being completely independent entities or rivals. Rather, as far as therapeutics was concerned, they were quite complementary, each depending critically on the other. Academia was the basis for training each new generation of pharmacologists, but the final development of new agents was the province of industry—with, of course, the counselling of academia. One example comes from the field of diuretics in which Gilman had a lifelong, passionate interest. Following therapy with many diuretics there is often an increased secretion of potassium by the kidneys. In otherwise healthy patients, the consequent hypokalemia may be of little clinical consequence; however, it may cause cardiac arrhythmias and high-risk pa-

tients who have symptomatic coronary disease or congestive heart failure need to be protected. These considerations led to Gilman's participation with one pharmaceutical company (SKF) to develop a potassium-sparing diuretic. The first drug to be tested was a failure; the second taken orally worked excellently in all experimental animals tested, but, unfortunately, not in the human! The third drug (triamterene) was a success and it has become part of the present-day pharmaceutical armamentarium. Gilman continually cited this experience as an example of the value of the interdependence of industry and academia. The latter may provide sage counsel, but only the industrial company can gather multidisciplinary teams of appropriate magnitude that lead to ultimate success and afford the many expensive failures (of which the public usually remains unaware) on the road to success.

Among Gilman's scientific achievements were several important contributions to our understanding of kidney function. Exploring the effects of administering large amounts of urea to experimental animals, Gilman and his junior colleagues, Mudge and Foulks, were surprised at the excretion of large amounts of potassium that the diuresis induced. They were able to show that the rate of excretion was too great to be attributed to glomerular filtration alone and that potassium must, therefore, be actively transferred from blood to urine by the renal tubules. This was particularly surprising because the amount of potassium usually excreted in the urine is only some 5% or 10% of the amount in the glomerular filtrate so that filtration and reabsorption would alone easily explain potassium excretion under all but the most unusual circumstances. Nevertheless, Gilman suggested what seemed at the time an outrageous idea, namely, that all or most of the filtered potassium was reabsorbed and that what eventually appeared in the urine was

added by secretion by the tubules. Subsequent work by others has shown that this insightful conjecture was indeed correct.

Another major finding was Gilman's demonstration with Brazeau that an increase in the CO_2 tension of the blood increased the capacity of the renal tubules to reabsorb bicarbonate. Such an increase in CO_2 tension occurs in many forms of pulmonary disease leading to the condition known as respiratory acidosis. It was well known that respiratory acidosis is associated with a compensatory increase in the concentration of bicarbonate in the blood, a compensation that raises the pH toward a more normal value. The finding of the effect of respiratory acidosis on renal bicarbonate reabsorption was a nice explanation for the phenomenon.

Alfred Gilman was truly a national and international figure. He was elected to the National Academy of Sciences in 1964. In 1967 he became chairman of the National Academy of Sciences's Drug Efficacy Review Committee and the work of the numerous expert panels that he oversaw was a landmark in modern therapeutics. No longer could claims of efficacy be made without the support of objective evidence. For example, at an international meeting in Geneva an irate clinician challenged Gilman for classifying the physician's treasured bioflavonoid as ineffective. Speaking as an experienced physician, the clinician assured Gilman that he knew that this drug was valuable in the treatment of asthma. Gilman listened attentively and then calmly noted that the bioflavonoid, which was given by mouth, was not absorbed at all from the gastrointestinal tract!

Gilman left Columbia University in 1956 to become professor and chairman of the Department of Pharmacology at the newly founded Albert Einstein College of Medicine. The young faculty that he attracted to the department was

soon recognized for its excellence in research, however teaching continued to be of major importance. Gilman went to most lectures, as did all the faculty. It was not uncommon for the lecturer on finishing his didactic hour to be politely asked to come with Gilman to his office where it would be suggested, in the kindest possible way, that the lecturer had perhaps been inaccurate at some point or, much more likely, had laid insufficient emphasis upon a key point. Gilman's appointment as chairman coincided with the initiation of the medical scientist training program, the combined M.D./Ph.D. program. Einstein was the recipient of one of the first three grants from the National Institute of General Medical Sciences of the National Institutes of Health. Gilman was the creator as well as heart and soul of this program, which has since been running for three decades and which is considered one of the most successful in the nation. In 1964 he assumed the additional responsibility of becoming the first associate dean for graduate studies at Albert Einstein.

Gilman's dedication and devotion to pharmacology and science were passed on to all those fortunate to have been touched by him. He wanted students to know and understand how drugs acted in the whole animal, rather than just in isolated tissues in experiments or in the test tube. He was more than just a teacher or head of a department; he was a gentle, caring human being with whom one could share one's problems, whether career-related or of a personal nature. He would sit one down and give advice in a personal, fatherly manner. That he was nearly always available as mentor was considerably helped by the fact that unlike many scientists of his intellectual seniority, he spent most of his time on the home ground of his department rather than traveling worldwide to this or that "important" symposium. He served as an excellent role model for his students, postdoctoral fellows, and junior faculty. His keen

intelligence, sharp wit, consummate ability to make complex problems simple, and his unexcelled teaching ability were greatly admired.

On retiring from Einstein, Gilman returned to Yale as a lecturer in his old Department of Pharmacology, where three of his "young men" from Einstein were now full professors. There, untroubled by any administrative responsibilities, he did what he always like doing best—talking to graduate and medical students about their problems and discussing the research problems of the faculty. His door was always open and his encyclopedic knowledge freely available. He volunteered his services to his alma mater joyously, out of his love for pharmacology and students, and entered into the regular teaching of the pharmacology course at Yale. He taught with vigor, enthusiasm, and great effectiveness into his seventy-sixth year. Indeed, on the very day he died he was to have given the concluding lecture in the pharmacology course, an overview of the status of pharmacology and therapeutics that was eagerly awaited by students and faculty alike.

Alfred Gilman had a love for life, and he did not neglect his family. He had great fun with music and would play the saxophone or violin or almost anything else, particularly at neighborhood parties. He could essentially pick up any instrument and play any tune without music. This interest and talent developed in early boyhood, undoubtedly stemming from the fact that his father, Joseph Gilman, owned the Gilman Music Store in Bridgeport. Music continued to be important throughout his family life. This love of music was shared by his wife Mabel (nee Schmidt) whom he married in 1934. Mabel, the daughter of a professional trombonist, was herself a talented pianist.

Gilman was extremely keen on fishing, which helped to nurture the collegial relationship he had with his son Alfred

Goodman Gilman (Nobel prizewinner in medicine in 1994), fishing together from a rowboat in Long Island Sound. Later, when the Gilmans acquired a place on Cape Cod, summer fishing and clamming was Gilman's joy, particularly when he could have his children along. Joanna, his daughter, tells how she learned from observation of her father how not to be lonely with oneself, for Gilman could sit quietly and not be idle because he was thinking and working things through. Even the book had a family basis. The dedication of Mabel, his wife, to the preparation of the second and subsequent editions of the textbook of pharmacology was awe-inspiring to those who appreciated the formidability of the task with its endless combing of the basic science and clinical literature, abstracting, typing, editing, and indexing as the editions of the classic began to take shape and grow. In this day of word processors, computers, Medline, and research staff it must be remembered that the *Pharmacological Basis of Therapeutics* was prepared by Alfred and Mabel on the East Coast by themselves together with Lou Goodman in faraway Utah.

HONORS AND DISTINCTIONS

DEGREES

B.S., Yale University, 1928
Ph.D. (biochemistry), Yale University, 1931

HONORARY DEGREE

D.Sc., Dartmouth College, 1979

UNIVERSITY APPOINTMENTS

Research fellow, biochemistry, Yale School of Medicine, 1931-32
Research fellow, pharmacology, Yale School of Medicine, 1932-35
Assistant professor of pharmacology and toxicology, Yale School of Medicine, 1935-43
Captain and major, Sn-C., A. U. S., chief, Pharmacology Section, Medical Division, S. W. S., 1943-46
Associate professor of pharmacology, College of Physicians and Surgeons, Columbia University, 1946-48
Professor of pharmacology, College of Physicians and Surgeons, Columbia University, 1948-56
Professor and chairman, Department of Pharmacology, Albert Einstein College of Medicine, 1956-73
Associate dean for graduate studies, Albert Einstein College of Medicine, 1964-69
Lecturer in pharmacology, Yale University School of Medicine, 1973-84

MEMBERSHIPS

Sigma Xi
American Physiological Society
Society for Experimental Biology and Medicine
Harvey Society
American Society for Pharmacology and Experimental Therapeutics
New York Academy of Sciences
New York Academy of Medicine
Honorary fellow, American Academy of Allergy
Fellow, American Association for the Advancement of Science

Honorary member, Alpha Omega Alpha
National Academy of Sciences
Fellow, American Academy of Arts and Sciences

PROFESSIONAL AND PUBLIC SERVICE

U.S. Public Health Service:
Member of the Pharmacology and Experimental Therapeutics Study Section, 1946-49 and 1950-55; chairman, 1956-60
Member, Pharmacology Training Committee, 1960-63
Member, Heart Special Projects Committee, 1963-65
Advisory Council on Research, New York Heart Association, 1958-64
Scientific and Educational Council, Allergy Foundation of America
Editorial Board of *American Journal of Physiology* and *Journal of Applied Physiology*, 1950-56; consulting editor, 1956-57
Editorial Board of *Pharmacological Reviews*, 1948-55
Advisory Council, Cystic Fibrosis Research Foundation, 1960-65
Advisory Council, New York City Health Research Council, 1960-65
President, American Society for Pharmacology and Experimental Therapeutics, 1960-61
National Academy of Sciences/National Research Council:
Member, Division of Medical Sciences, 1962-71
Executive Committee, Medical Division, 1962-64
Member, Drug Research Board, 1963-72
Chairman of Organization Committee, Drug Efficacy Review, 1966-67
Chairman of Executive Committee, Drug Efficacy Review Committee, 1967-69
Chairman, Drug Research Board, 1971-72

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1933

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1934

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