A Tribute to Dr. Alfred G. Gilman (1941-2015)

Submitted by T. Kendall Harden, PhD

Biomedical science, and pharmacology in particular, lost an iconic leader with the passing of Alfred Goodman Gilman on December 23, 2015. Al's influence spanned from the field-pervading assay for cyclic AMP that bore his name, to his groundbreaking Nobel Prize-recognized research on basic mechanisms of cell signaling, to two decades as editor of the premier textbook of pharmacology, to the development and direction of one of the world's best departments of pharmacology, to his deanship of a major medical school, and to his leadership of a major new effort supporting cancer research. He also provided enormously wide-ranging counsel for many university, government, and industrial agencies and endeavors over many decades.

Alfred Goodman Gilman was born on July 1, 1941 in New Haven, Connecticut. He often pointed out his good fortune of birth and the positive influence his parents had on his career. An oft-quoted joke about Al was that he was "named for a textbook (of pharmacology)"–and in effect he was since his second name was in honor of Louis Goodman who coauthored the first editions of *"The Pharmacological Basis of Therapeutics"* with Al's father, Alfred Z. Gilman. Al clearly was immersed in biomedical research from birth. His father was a professor in the Department of Pharmacology at Yale University and in 1956 became the first chair of pharmacology at Albert Einstein College of Medicine. Al colorfully described his early years in a number of publications including "Silver Spoons and Other Recollections" in the *Annual Review of Pharmacology and Toxicology* **52**:1-19, 2011. One of those silver spoons much later served him an enormous amount of work after he assumed (for 25 years) the editorship of the now gargantuan textbook of pharmacology that his father and Lou Goodman had begun in 1941.

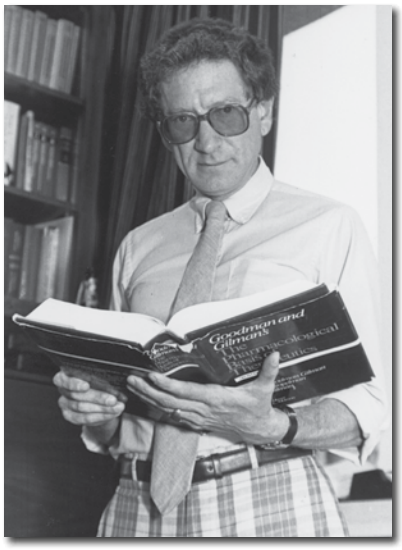
Dr. Gilman graduated with a major in biochemistry from Yale University in 1962 and was convinced by a future Nobel Awardee, Earl Sutherland, to join the new MD/PhD training program at Case Western Reserve in Cleveland, Ohio. Although Sutherland left for a position at Vanderbilt University, Al trained with Sutherland's former postdoctoral fellow and co-discoverer of cyclic AMP, Ted Rall, carrying out early work on this "second messenger" in thyroid gland function. He moved to the NIH in 1969 as a postdoctoral fellow with Marshall Nirenberg, recipient of the 1968 Nobel Prize in Physiology or Medicine, to study neuronal development. During this time Al developed the protein binding assay for cyclic AMP, which became known as the "Gilman assay," and that afforded investigators worldwide a means to quantify cyclic AMP in small samples. This assay enormously expanded the number of laboratories engaged in

cell signaling research, and the paper has been cited over 5000 times.

Dr. Gilman's first academic appointment was as an assistant professor in the Department of Pharmacology at the University of Virginia (UVA) in 1971. Pharmacology at UVA, led at the time by Joseph Larner, was a hot-bed of early research on signal transduction, and much of Gilman's ground-breaking work leading to the Nobel Prize was accomplished there. The overriding question was how do hormones like adrenaline pass signals across membranes to regulate activity inside cells? Martin Rodbell (who in 1994 would share the Nobel Prize in Physiology or Medicine with Gilman) at NIH had shown the requirement of GTP for hormone-stimulated production of cyclic AMP in well-washed plasma membrane preparations. Research of Rodbell and others including Gilman also strongly suggested that the adenylyl cyclase and the hormone receptor likely resided on separable proteins. Gilman's work discovered that a third protein (a GTP-binding protein) existed in the middle, and he described what that protein really was. Much of the research identifying the adenylyl cyclase-activating G protein was driven by Elliot Ross, a postdoctoral fellow in the Gilman lab. In a series of simple but elegant experiments, Ross illustrated that the conversion of ATP to cyclic AMP and the capacity to bind GTP occurred independently on two separable proteins.

John Northup

and Paul Sternweis, also postdocs in the Gilman lab, were the first to purify this GTP-binding protein Gs and then purified its co-conspirator in the regulation of adenylyl cyclase, Gi, which mediated receptor-promoted inhibition of the enzyme.



Dr. Gilman became chair of the Department of Pharmacology in 1981 at the University of Texas Southwestern (UTSW) Medical School in Dallas, TX. Although many of the key research advances that led to the Nobel Award had been accomplished by then, much of what is known about mechanism in the cyclic AMP generating pathway, and for certain, the breadth and depth of our current knowledge of heterotrimeric G protein signaling in general was to be learned in the decades that followed in Dallas. The competition was no doubt fierce, and many outstanding scientists worldwide contributed to our collective knowledge of heterotrimeric G protein signaling. However, the Gilman lab continued to make front-of-the-field advances until after the turn of the millennium. The work had a remarkable signature. Gilman papers almost always appeared with an enviable depth and breadth of information – and a quality that often seemed difficult to produce in one's own work. One of us remembers devoting a week to read and try to understand the four papers published back-to-back-to-back-to back that unveiled the reality of the Gi heterotrimer, its biochemical properties, its activation cycle, and a model of its mechanism of inhibition of adenylyl cyclase – a tour de force of depth rarely enjoyed in today's rapidly changing/progressing scientific pursuits. The Gilman lab made many seminal advances in the 1980s and 1990s. In fruitful collaborations with the laboratory of Melvin Simon at Cal Tech,

they introduced molecular cloning into the production of G protein subunits and adenylyl cyclase and produced a broad range of these signaling proteins in sufficient quantities to understand the complexities of their regulation in exquisite biochemical detail. In a long-term collaboration with the structural biologist Stephen Sprang, they were the co-firsts (with the Sigler lab at Yale) to obtain structures of the heterotrimeric G proteins in their various activation states and provided the first structures of a G protein bound to its effector (adenylyl cyclase) and to a regulator of G protein signaling (RGS) protein. Thus, the processes of activation and deactivation of G proteins, and therefore of their downstream effectors, were described in intricate detail at the atomic level.

Al Gilman's potent intellect was complemented by a sharp wit, a wonderful sense of humor, and an unsurpassable integrity. He selflessly mentored hundreds from all walks of biomedical science. His research goals, ambition, and technologies were at the front of the field for three decades, and his scientific influence continues to expand through the scores of scientists who trained in his laboratory over the years. Most who passed through his lab will argue that there could not have been a more stimulating and productive research environment than the one he directed. The weekly research meetings, Friday at 8:15 AM, of the Gilman lab were legendary – they often lasted all morning, had a laser focus on what is the important question and how can it truly be answered, and frankly, were not for the faint of heart. Gilman-lead excellence in training also was routinely proffered in the bimonthly "B and B"s (definition of acronym not to be revealed) where an individual faculty member from the UTSW Department of Pharmacology presented a "chalk talk" (no slides please!) on her/his current and future research directions. These provided wonderful research training opportunity for students and postdocs, as well as faculty both young and old. Then there was the Christmas party. Al negotiated with the dean on his recruitment to be allowed to have a departmental party at the Faculty Club. Live music, a wonderful buffet, an open bar, and of course the "Ignobel Award Ceremony" were on the agenda. The Ignobel was awarded to the departmental honorees who committed the most ignoble act(s) of the year. And why the party? It was the annual Pharmacology Family Christmas Party, and it was a fun time for Al's science family.

The Department of Pharmacology at UT Southwestern became one of the premier departments worldwide during Gilman's 25-year tenure as chair. Remarkably, he became dean of UT Southwestern Medical School in 2004, and served as executive vice president for academic affairs and provost in 2006 until his academic retirement in 2009. He then became the initial Chief Scientific Officer of the Cancer Prevention and Research Institute of Texas serving until 2012.

In addition to the 1994 Nobel Prize in Physiology or Medicine, Al Gilman received many honors and awards. He was a member of the National Academy of Science (1985) and received the Albert Lasker Basic Medical Research Award in 1989. He also was recipient of ASPET's John Jacob Abel Award (1975), the Goodman and Gilman Award (1990), and the Torald Sollman Award (1997). He was a founding scientist of Regeneron Pharmaceuticals, and for over two decades was a member of the Board of Directors of Regeneron and of Eli Lilly and Company.

The Gilman Family

Al Gilman is survived by his wife, Kathryn, two daughters, a son, and five grandchildren. As a proud scientific father, he also is survived by all his scientific family and progeny and their progenies.

Dr. Gilman was a member of ASPET since 1973.