NATIONAL ACADEMY OF SCIENCES

LYNDON FREDERICK SMALL

1897—1957

A Biographical Memoir by

ERICH MOSETTIG

Biographical Memoir

Lyndon B. Johnson

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August 16, 1897–June 15, 1957

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LYNDON FREDERICK SMALL was born in Allston, Massachusetts, on August 16, 1897, the second child (and the second son) of Frederick Eugene Small and Amanda Edmond (Corey) Small. His grandfather, Ebenezer Small, Jr., was a physician, and Small's mother also had strong inclinations toward a medical profession. On various occasions, Lyndon Small has indicated to us his own early desire to become a surgeon.

In 1905 Small's father moved with his wife and three children (Harold Corey, Lyndon Frederick, and Dorothy) to Needham, Massachusetts.

From his earliest boyhood, through his years of high school and college, and his adult life, Small was devoted to swimming, skiing, hunting and fishing, camping, and mountain climbing. From the little one could extract from a man not much inclined to social talk, particularly when his own history was concerned, one picture came out quite clearly: His years as a child and a boy were happy ones. A genuine respect and friendship bound him to his father, his brother Harold, and even more to his sister, Dorothy. From his father, a machinist and inventor by profession and a strong personality and individualist by nature, Small acquired not only many personality traits, but also a love for the lathe and the machine shop. The lathe he inherited from his father followed him for many years, even to Charlottesville and to Bethesda. Wherever the Smalls lived, in their city residence or at their beach home in North Carolina, the

machine shop was an important part of the home and, particularly in his later years, the mainstay of his recreation. There is no doubt that intimately connected with Small's love to produce with his hands were not only his unusual skill in glass-blowing, equal to that of a professional, and his perfect mastery of and love for Pregl's microanalysis, but above all his astounding skill as an experimentalist—astounding because of the simplicity of technical means with which he conducted the most complex procedures. A few test tubes and glass rods, a Bunsen burner, and a simple lens were the most important items of his technical arsenal.

The first person who had an influence in shaping Lyndon Small's future was Frank P. Bunker (Dartmouth '02), science teacher of the Needham High School, who recognized Small's penchant and talent for physical sciences and nourished and furthered them to the utmost. Under the stimulus of this man, young Small began to realize that there was a lot to be gained by continuing his formal education. "This is a debt I can never repay, except in the scientific results." He enrolled in Dartmouth (1916) on a budget that would be ridiculous today, but he managed to make out. Because of financial pressure perhaps, but more likely because of love of knowledge for its own perfection, in his first semester he stood first in his class of some 400, an achievement which made him eligible for the unusual freshman fellowship in the second semester (this fellowship supported him throughout the Dartmouth years). This academic recognition, moreover, had a corollary in the form of complete discretion granted such students over attendance at classes, an advantage which was promptly used for time in the mountains and woods. This paradise of education and exploration of the White Mountains was rudely interrupted in October of 1917, the beginning of the sophomore year, by a polite invitation to join the U. S. Armed Forces in the First World War. Small joined, with little or no reluctance, the U. S. Coast Artillery at Fort Standish, Boston Harbor, where he was "taught to give enemas to constipated mules, to sleep on corn husks (pretty good) and to fend off tarts on Atlantic Avenue." He also had to

learn that it was obviously poor tactics to receive a diagram of a machine gun in the morning and know more about it by noon than the sergeant did. After six months of conflicting rumors that his outfit was to be sent abroad, having never fired a rifle or any of the many impressive guns that decorated the fort, those who had positions waiting for them were released. Though "College Student" was not classified as a position, he managed to get out. The release from the Army allowed him now to return to college work—as far as it could be conducted in the mountains. He became Phi Beta Kappa in 1919 and received his first degree from Dartmouth, that of B.S., in 1920.

After graduation Small took a summer job at Camp Serrana, in Pike, New Hampshire, as "hiking and camping counselor." On the train up to his summer's destination he happened to meet a young girl by the name of Marianne C. Brown, also going to the camp as "the secretary to the camp director." The following summer the hiking counselor and the director's secretary were engaged to be married. From 1920 to 1922, Small was a Henry Elijah Parker Fellow from Dartmouth College at Harvard University where he received his M.A. degree (under the late Professor Kohler) in 1922.

In June, 1922, Lyndon and Marianne were married. The honeymoon was spent in true Small fashion, the groom and bride roaming the White Mountains for three months, each loaded with 40- to 50-pound packs, including tents, axes, fishing and cooking equipment, food, and blankets.

To keep the home fires burning, Small took the position of instructor in inorganic chemistry at the Massachusetts Institute of Technology for the academic year 1922–23, and the following summer both Smalls functioned as swimming instructors at Camp Aloha in Fairlee, Vermont. The following three years (1923–26) Small spent at Harvard (as assistant, instructor, and Du Pont Fellow) working under James B. Conant for his Ph.D. degree, which he received in the summer of 1926. Professor Conant, to whom Small was strongly attached, influenced Small's career considerably. The sum-

mers of this period of arduous work and professional development were spent in summer camps, both young parents (their first child, Donald Clayton, was born in April, 1924) teaching young girls in Camp Alleghany, West Virginia, swimming and diving. The baby came along free as the camp's mascot. Upon the recommendation of Professor Conant, Small was awarded the Sheldon Travelling Fellowship (for one year) and the Small household moved to Munich in September, 1926. The funds for a second Munich year were provided by a National Research Council Fellowship.

These two years in Munich were decisive ones for Small's future. There was, first of all, a close relationship between the great master Heinrich Wieland and the young, eager disciple who was bent to absorb the maximum from the wisdom, knowledge, and experimental skill of his new teacher. Small adapted himself very fast to his new surroundings and became in no time even more Bavarian than the Bavarian students, donning *Lederhosen* and *Lodenrock,* heavy stockings, and all that goes with them for his daily street-wear, whereupon Wieland called him affectionately his "Amerika Seppl." Small's frank and refreshing ease of manners, his sincere respect for greatness and achievement free from stiff and bureaucratic formality, quickly won Wieland's heart, and at once gained him the friendship of his new European colleagues. Heinrich Wieland and Lyndon Small died less than two months apart. Responding to a letter of condolence by Mrs. Small, Mrs. Wieland wrote: ". . . und danke Ihnen sehr, auch im Namen meiner Kinder. Sie haben ja meinen lieben Mann auch so gut gekannt, und wissen freilich was wir verloren haben . . . Auch ich traure mit Ihnen, liebe Frau Small um Ihren lieben Mann, den wir alle hier so gerne hatten; er ist ja viel zu früh von hinnen gegangen. . . ."

The Smalls were taken graciously and with open arms into the Wieland household and spent many happy hours there, becoming particularly attached to the Wielands' children, Eva (now Mrs. Feodor Lynen) and Theodor (now Professor of Chemistry at the University of Frankfurt). Lyndon was given laboratory space in the

"Kalbstall" which he shared with Maximilian Ehrenstein (now at the University of Pennsylvania Medical School), Wilhelm Wenner (now with Hoffmann-La Roche at Nutley, New Jersey) and Fräulein Dane (still at Munich). The laboratory brought him into close contact with Clemens Schöpf, and a lifelong friendship developed between them. Of three research projects that Professor Wieland suggested to him, Small chose the alkaloid problem, "The Ozonization of Thebaine." Within two years he acquainted himself thoroughly with the complex chemistry of the morphine alkaloids which became his life's work, as can be seen by a mere glance at the list of his publications. With very few exceptions, his publications from 1928 to 1956 deal with structural features and reactions of morphine, codeine, and thebaine.

The Smalls made good use of the time allotted to them in Europe. There were numerous visits to academic and industrial laboratories, a microanalytical course in Pregl's laboratory, and an extensive visit to the Glaswerke of Jena. For recreation there were many hiking trips, long *Faltbootfahrten* on the Rhine, the Inn, and the Danube, the climbing of Mount Etna and, to crown everything, the ascent to the top of the Matterhorn, no small alpinistic achievement at that time. The Smalls left Munich with heavy hearts in 1928.

Professor Conant had asked Small to come back to Harvard as his private assistant, an offer which Dr. Small gladly accepted. It developed, however, that the Department of Chemistry of the University of Virginia was looking for a research associate, and offered this position, upon Conant's recommendation, to Small. He accepted and, after his return from Europe, moved directly to Charlottesville, continuing immediately his research with morphine alkaloids. At the same time Small built up a microanalytical laboratory and gave courses in microanalysis for graduate students.

In 1929 the Division of Medical Sciences of the National Research Council established a committee under the chairmanship of William Charles White, with the purpose of finding and studying means to reduce or correct the evils of drug addiction. The theoretical con-

ception, based in part on the replaceability of cocaine by the safer novocaine, was the separation of the addiction liability of morphine from its other salutary properties by chemical modification. Such a program necessitated the organization of chemical, pharmacological, and clinical studies. It was a fortunate coincidence that a man uniquely competent to direct the chemical studies was available, and Dr. Small, again through the recommendation of Dr. Conant was appointed Director in Charge of Chemical Research, continuing at the same time in his position of research associate at the University of Virginia. The University was most generous in providing space for the "Drug Addiction Laboratory."

The new assignment gave Small the opportunity to build up a research group of considerable size, consisting of Ph.D.s and graduate students, and it was during these ten years that Small performed a long series of masterly and painstaking researches on morphine and allied compounds. In addition he wrote, assisted by Professor R. E. Lutz of the University of Virginia, *The Chemistry of the Opium Alkaloids,* which for the first time marshalled together the whole chemistry of the alkaloids contained in opium. Although today somewhat out-of-date and, unfortunately, out of print, this book is still the most comprehensive and informative monograph on the subject and is found on the desk of everyone working with morphine alkaloids.

Dr. Small approached the problem of finding non-habituating drugs in two ways. First, it could be expected that by proper modification of the functional groups of the morphine molecule compounds might be found in which undesirable effects were diminished and analgesic effect perhaps enhanced. The second approach was to introduce functional groups of morphine into simpler ring systems and stepwise build up synthetics resembling in one or more ways the morphine molecule. Small concerned himself primarily with the first approach. Although it seemed that morphine chemistry had been fairly well exhausted and that not much could be discovered or added to the earlier extensive researches, particularly by

German and British scientists, Dr. Small unearthed with ingenuity and tenacity a wealth of new reactions and new transformation and degradation products. There was discovered and structurally elucidated a long series of desoxycodeines and desoxymorphines, their respective codeinones and morphinones, and their alkylation and reduction products. Notable among these efforts was the synthesis of metopon, which represented the first known nuclear-alkylated morphine derivative. This substance proved to be an excellent analgesic and showed promise of being superior to morphine in that its use was attended by a less rapid development of tolerance and dependence. Further, it could be administered orally and produced fewer side effects than morphine. Because of these attributes its general use in the control of chronic pain was advocated.

Particularly intriguing to Small was the chemistry of thebaine, its complex reduction products and, finally, the most difficult of all, the chemistry of the phenyl dihydrothebaines. Here, Dr. Small and his collaborators produced the most unexpected and fruitful results. Again and again throughout all these studies Small's unusual experimental skill, the simplicity of methods applied, and his immense amount of patience became evident. The hundreds of morphine derivatives so produced and pharmacologically studied by Dr. Nathan B. Eddy, at the University of Michigan, established well-defined correlations between structure and activity. This was done by analyzing all the effects produced by individual changes on the molecule, such as muzzling of the phenolic hydroxyl, covering, substituting and eliminating the alcoholic hydroxyl group, changing steric factors, substituting the nucleus, and altering the nature of the nitrogen function. Many of the new morphine derivatives were tested in man for addiction liability and some (metopon, desomorphine, monoacetylmorphine) were proved to be superior by further clinical testing.

With the rather rapid and continuous appearance of some fifty papers by Dr. Small and his associates, Small's reputation as an alkaloid chemist and specialist in morphine chemistry grew accord-

ingly and he was elected to a number of important offices. He was Chairman of the Division of Organic Chemistry of the American Chemical Society in 1936; Consultant to the U. S. Public Health Service from 1929 to 1939; U. S. Technical Representative to the League of Nations in Geneva in 1931, and a member of the Opium Assay Commission in London in 1937.

In 1939 he received (jointly with Dr. Nathan B. Eddy) the first Annual Scientific Award of the American Pharmaceutical Manufacturers Association. In 1938 Dr. Small became editor-in-chief of the then two-year-old *Journal of Organic Chemistry*. In this office, where he was so ably assisted by his wife, he earned the lasting gratitude of American organic chemists. His thoroughness, keen and clear judgment, tact and impartiality, his unsparing effort and personal editing of every paper, brought this publication to the standard of a first-rate professional journal. As a token of appreciation his friends and colleagues dedicated the papers in the November, 1957, issue to his sixtieth birthday anniversary, which he was not to see.

Everyone associated with Small during the Charlottesville years (1928–39) will remember this period with joy and pride. It did not take the Smalls long to become an integral part of the University of Virginia community. The beautiful natural setting of Thomas Jefferson's university, the gracious hospitality and culture of Southern society added a happy tone to the serious and hard work carried on in the "Drug Addiction Laboratory," where almost regularly the lights burned deep into the night. To continue work after dinner until all hours was an accepted rule. The life in the laboratory was that of a large family. Mrs. Small (called the "Frau Vorstand" in reminiscence of the Munich days) was officially the laboratory's secretary, but essentially its executive officer. Since she had acquired by that time an astounding knowledge of chemistry, her assistance in putting the numerous papers into publishable shape was invaluable. As the writer well remembers, all of us depended on her to an almost unpardonable degree, handing to her not more than rough drafts and having returned to us the final reorganized, corrected, edited,

and neatly typed papers. Greatly adding to the spirit and atmosphere of Small's laboratory was the genuine and intense interest shown by the Chairman of the Drug Addiction Committee, Dr. White, in the progress of the research at Charlottesville and of the pharmacological unit at the University of Michigan. The intimate friendship with Dr. White greatly shaped Small's thinking and acting. The passing away of this outstanding man in 1947 was a keenly felt shock to Small and to all of us who had the honor to work under Dr. White's leadership.

The Smalls, their family having been enlarged by daughter Ruth (now Mrs. Edward D. Farren of Kensington, Md.), acquired a large and comfortable house with a good-sized yard which induced Small to add to his hobbies a new one—that of gardening. This was pursued with as much thoroughness and skill as his other hobbies, and the multitude, beauty, and variety of his flowers attracted wide attention. Their home was open to anyone in the laboratory and to all their friends at any time. Once a year there was a big "laboratory party" to be remembered by everyone who attended. The same hospitality extended to their beach home in North Carolina, where many of us spent happy days of fishing and swimming which are still remembered.

When in 1938 the outbreak of the Second World War was a near certainty, Dr. R. E. Dyer, then Director of the National Institute of Health, inquired whether Dr. Small and some of his key men would be willing to shift, at least temporarily, their interest from morphine substitutes to quinine substitutes. The decision for Dr. Small probably was not an easy one. But eventually he and a small group of his associates, among them the writer, moved to Washington, D. C., and were attached as a unit to Professor Claude S. Hudson, Director of the Division of Chemistry of the National Institute of Health. In this new field Small and his associates moved ahead energetically and successfully, and became part of the wide-flung antimalarial program of the Office of Scientific Research and Development. Hundreds of compounds were synthesized, among them a dozen or more

derived from polynuclear hydrocarbons, effective enough to replace quinine and atabrine. Many were studied intensively, pharmacologically and clinically.

In 1941 Small was elected to the National Academy of Sciences, and he received in 1949 the Hillebrand Prize of the Washington Section of the American Chemical Society for outstanding research on alkaloid chemistry.

After the war Dr. Small was eager to return to basic research. Although his resignation from the editorship of the *Journal of Organic Chemistry* in 1951 made more time available for his own work at the bench, so dear to him, new duties restricted considerably his research activities. He was elected Member of the reorganized Committee on Drug Addiction and Narcotics, National Research Council, in 1947; Consultant to the Technical Command, Army Chemical Center, Maryland, in 1950; Chairman of the Post Office Advisory Committee in 1951; and Member of the United Nations Opium Committee in 1954. In 1951 he succeeded Professor Hudson as Chief of the Laboratory of Chemistry, National Institute of Arthritis and Metabolic Diseases.

Upon the outbreak of the Korean war in 1950, Dr. Small was authorized to reassemble what remained of the old "Drug Addiction Laboratory" personnel, whose immediate objective was to develop adequate, total-synthetic morphine and codeine replacements, because of the obvious threat to our opium source. From the efforts of this group emerged several clinically efficacious synthetic analgesics of greater potency and less side-action liability than are inherent in morphine and codeine, which could serve as capable substitutes for these two naturally occurring drugs should the need arise. At the same time significant progress was made along theoretical lines. Dr. Small's most recent and personal research efforts were directed toward the elucidation of the structure of certain unusual thebaine derivatives, and the results will be published posthumously.

Dr. Small's excellent command of the English language made him an outstanding lecturer, and it was a great pleasure, unfortunately a

too rare one, to listen to his clear and precise presentations. Although Small appeared retiring in his professional daily life and even somewhat aloof, he was a close and true friend to all his associates. He was a man with a courageous and kind heart.

On June 9, 1957, he was awarded *in absentia* the honorary degree of Doctor of Science by Dartmouth College, where he had begun his career as a chemist forty-one years before. He died in the early morning hours of June 15.

KEY TO ABBREVIATIONS

Ann. = Justus Liebigs Annalen
Ann. N. Y. Acad. Sci. = Annals of the New York Academy of Sciences
Ann. Rev Biochem. = Annual Review of Biochemistry
J. Am. Chem. Soc. = Journal of the American Chemical Society
J. Org. Chem. = Journal of Organic Chemistry
J. Pharmacol. Exp. Therap. = Journal of Pharmacology & Experimental Therapeutics
P. H. R. Supp. = Public Health Reports Supplement

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