LYMAN CREIGHTON CRAIG

1906—1974

A Biographical Memoir by
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Lyman Craig was born on a farm near Carlisle, Iowa. He described his early experience as that of a typical farm boy, with attendance at a small country school and the nearest high school, at Hartford. During these years, farm work was always required, but not to the exclusion of an active participation in athletics. (Craig's skill in sports was to give him a long reign as the tennis champion of the Rockefeller Institute.)

His first three years of college were at Des Moines University. His roommate in his freshman year was his older brother, David, who had become attracted to chemistry through courses with a gifted teacher of that subject at the university. David went on to obtain a Ph.D. degree from the University of Iowa and to a highly successful career as an organic chemist with the B. F. Goodrich Company, in Akron, Ohio. Lyman's interest in chemistry was influenced by his brother's attraction to the subject; Lyman transferred in his senior year to Iowa State College, where in 1928 he earned his B.S. degree.

Both boys were encouraged in their educational plans by their father, who was a farmer by profession, active in community affairs, and a member of the Iowa State Legislature. Scholarship was a part of the family tradition; Lyman's paternal grandfather had been a college teacher of mathematics and languages before his career as a pastor in Iowa.
Lyman Craig entered the graduate school of Iowa State College with organic chemistry as his major subject and with entomology as his minor study. This combination of subjects grew in part from his practical appreciation of the role of insecticides in agriculture. Each major step in Craig's career was characterized by a logical progression from one interest, one fund of knowledge, to the next; he always built upon a firm intellectual foundation.

After earning his Ph.D. degree from Iowa State in 1931, he won a National Research Council Fellowship to extend his studies on insecticides at the Department of Chemistry at Johns Hopkins University. His postdoctoral advisor at Hopkins was E. Emmet Reid. During Craig's doctoral studies at Iowa State and his two years at Hopkins he published twelve papers, mostly in the *Journal of the American Chemical Society*, on the chemistry of nicotine alkaloids and their insecticidal action.

This record of accomplishment won him an appointment in 1933 as a research assistant in chemical pharmacology at the Rockefeller Institute for Medical Research in New York with Walter A. Jacobs, who had been looking for a young chemist to work on the alkaloids of ergot. Walter Jacobs, a native of New York, had earned his Ph.D. degree in Berlin in 1907 under Emil Fischer. The first paper by Jacobs and Craig (1934) was on the characterization of a product obtained upon alkaline hydrolysis of ergotinine; they named the compound lysergic acid, on the basis that it was obtained by the *lysis* of ergot. They also isolated proline and phenylalanine as hydrolysis products, and this was the beginning of Craig's experimental concern with amino acids.

Craig was a gifted experimentalist with skill in the design of equipment to facilitate microchemical experimentation. It was a privilege to watch him at the glassblowing bench as he fashioned apparatus to meet his special needs. In 1936 Craig pub-
lished a paper that described what was to be the first in a series of ingenious contributions to chemical instrumentation. In the alkaloid research he encountered a need to distill very small amounts of liquid in the days when microchemistry was in its infancy. He designed and built a microdistillation apparatus in which the flask had a capacity of 250 microliters and the distillate was collected from a small inverted cap that held about 200 microliters by capillarity.

Over a period of about ten years, skillful experimentation by Jacobs and Craig yielded sixty fundamental papers on the structural organic chemistry of alkaloids of the ergot, veratrine, andaconite groups.

In the early 1940s came the war years, and most of the work of the laboratories at the Rockefeller Institute was shifted to problems of immediate practical concern. Herbert Gasser, the Director of the Institute, was familiar with Craig's talents and facilitated the application of his efforts as a chemical pharmacologist to aspects of the wartime program on antimalarials. It was in the course of examining the question of whether atabrine, or a product of its metabolism, was the active parasiticide in man that Craig invented his technique of countercurrent distribution. The initial experiments grew, as he pointed out (see bibliography, 1943), from a suggestion made to him in a conversation with Milton T. Bush of the Vanderbilt University School of Medicine. The thought was that the distribution coefficient of an organic compound might be a useful additional physical constant, along with melting point and boiling point, for the identification of the compound, if the measurement could be made with precision on micrograms of material. Craig enlarged upon this idea by measuring a series of distribution coefficients as the percent of H₂O in an aqueous phase was varied. The resulting plots of distribution coefficient versus composition of the aqueous phase gave different, characteristic
curves for atabrine and several related compounds. The method was applicable to very small amounts of material, since atabrine could be determined fluorometrically.

These results then grew in Craig's inventive mind into a plan for equipment to use liquid-liquid extraction in a manner different from that of earlier approaches. Countercurrent extraction, with streams of immiscible liquids flowing continuously past one another, was a commonly used method in industry; A. J. P. Martin and R. L. M. Synge in England had recently introduced their technique of partition chromatography in which one of the liquid phases was immobilized in a gel, and their technique was beginning to open new worlds to the biochemist; Craig had a third idea (1944)—he decided to build a machine that was a series of twenty small separatory funnels with the capability, after each shaking and settling, of sliding the top phase from one funnel onto the lower phase of the next. The first apparatus was built by drilling holes in cylindrical blocks of stainless steel that had ground adjacent surfaces so that the transfers could be accomplished by rotating the upper section over the lower one. The procedure had the advantage over earlier techniques in that the distribution is theoretically a Gaussian curve that can be calculated precisely by the binomial expansion. His first test was with β-naphthoic acid in an ethylene dichloride–water–methanol solvent system, and he showed that very close to theoretical performance could be attained in practice with such a machine.

The first major application of this technique, made in cooperation with Vincent du Vigneaud of the Cornell University Medical College, was to the characterization of penicillins using an ether–aqueous buffer solvent system (1947). From the distribution pattern it was possible, by comparing the theoretical and the experimental curves, to estimate that the given preparation of the antibiotic contained approximately 90 percent benzyl penicillin. The amount of solute in each tube was
estimated by weight (after evaporation of an ether extract); Craig emphasized that weight was the most fundamental measurement when homogeneity was under test.

The next step in the instrumentation was the invention of an extraction train made from glass (Craig and Post, 1949) rather than metal and an increase in the number of tubes from 20 to 220 (1950) and finally to 1000 (Craig and King, 1958). The ingeniously designed glass cells permitted transfer of the upper phase to the next tube by decantation. During the course of this progress, Craig was promoted to Associate Member of the Rockefeller Institute in 1944 and to Member in 1949.

Each step in the development of the equipment for countercurrent distribution was accompanied by extensive applications of the technique to current problems in biochemistry. The potential of the method and Craig’s skill as a teacher in the laboratory attracted postdoctoral fellows with interests and experience in many fields of science. When the Rockefeller Institute became the Rockefeller University, graduate students became important contributors to the researches. The equipment made possible multiplate separations of high resolving power for mixtures of natural products that had presented difficult problems in fractionation. Among the substances examined in Craig’s laboratory were gramicidin (1948), bacitracin (1948), fatty acids (1951), insulin (1951), bile acids (1952), tyrocidine (1954), polymyxin (1954), serum albumin (1958), parathyroid hormone (1959), \(\alpha\)- and \(\beta\)-chains of hemoglobin (1962), ribonucleic acids (1964), ribonuclease (1965), Bence Jones proteins (1965), edeine (1966), ficin (1968), and nisin (1969).

One of the most tangible evidences for the quality of a scientist’s career is the record of those whom he has helped to train in their profession. The subsequent careers of young scientists who worked with Craig on the above projects give testimony to the productive atmosphere that he fostered over the years. Many applications of countercurrent distribution were
also made in academic and industrial laboratories around the world, frequently with generous counsel from Craig in the course of his international travels.

Craig always kept in mind the principle that methods are a means to an end and not an end in themselves; the pure antibiotic peptides prepared by countercurrent distribution were the starting products for several major programs in his laboratory on the determination of the sequences of amino acid residues in them. Extensive work on the sequences in the separated chains of human hemoglobin A was conducted by W. Konigsberg, R. J. Hill, and G. Guidotti (1962–1963). Countercurrent distribution was employed to advantage in the isolation of amino acids of unusual structure from peptides such as edeine (1968). A partial substitution method for the determination of the molecular weights of peptides, based upon dinitrophenylation, was developed by A. R. Battersby and Craig (1951) and was used by them on gramicidin and by E. J. Harfenist and Craig (1952) on insulin.

During the course of these studies, a little gem of a one-page paper was published by Craig, Gregory, and Hausmann (1950) under the title “Versatile Laboratory Concentration Device.” The elegantly simple rotary evaporator described therein is undoubtedly the most widely used of all of Craig’s inventions. The Claisen flask, with its fragile capillary, a standard item of laboratory equipment for nearly a century, has been replaced by the Craig rotary evaporator for the removal of solvents in most laboratory operations. Evaporation from the thin film in the rotating flask gives the process speed and also eliminates the problem of bumping of the solution.

Craig undertook to explore, as another major project, possible improvements in the use of dialysis for the separation of compounds on the basis of size. The experiments, begun with T. P. King (1955), resulted in a new chapter in the science of the use of semipermeable membranes (1964). A fundamental
investigation was undertaken of the parameters that govern the process of dialysis, a method which had not been extensively studied during the decades when other separation techniques had been subject to major improvement. A dialysis cell was designed (Craig and Stewart, 1965) in which the entering solution flows in a thin film over a cellophane membrane; the membrane is previously stretched or acetylated to vary the pore size. The variables in the process (Stewart and Craig, 1970) were defined, and the countercurrent possibilities were considered (Craig and Chen, 1969) relative to those of gel filtration.

Since diffusion through a membrane is dependent upon the conformation of the molecule, Craig also turned to optical rotatory dispersion (1968), nuclear magnetic resonance (1968), tritium–hydrogen exchange (1969), circular dichroism (1969), and fluorescent probes (1972) as sources of additional information on the shape of molecules in solution (Craig, Gibbons, and Printz, 1972). This broad approach to the subject of the conformation of polypeptides was conducted in cooperation with colleagues at the Rockefeller University versed in these special techniques and was the principal theme of Craig’s researches in the last decade of his very full life.

Craig’s contributions to biochemistry, as documented by the appended bibliography of nearly 300 papers, brought him wide recognition and many honors. He was elected to the National Academy of Sciences in 1950. He received the Albert Lasker Award for Basic Medical Research in 1963, the Fisher Award in Analytical Chemistry from the American Chemical Society in 1966, the Kolthoff Medal of the American Pharmaceutical Association in 1971, the Benedetti–Pichler Award in Microchemistry from the American Microchemical Society in 1972, an honorary D.Sc. from Northwestern University in 1973, and was elected to the Johns Hopkins Society of Scholars in 1974.

Craig was a highly productive scientist who always retained a modesty and a generosity that endeared him to all who knew
him. It was always a gracious occasion when young members of the laboratory or visiting scientists had an opportunity to join the Craigs and their three children, Anna, David, and Mary-Elizabeth, at their home. The life of a scientist is intimately interwoven with that of his family. When Lyman Craig met his future wife, Rachel Parker, she was an artist-in-residence at the Cold Spring Harbor Laboratory, where she drew the scientific illustrations for the articles by members of the staff. She was an artist who married a scientist, and the success of the Craig family was a tribute to the mutual interests that they shared. Her role in making it possible for her husband to devote such a major part of his life to research in behalf of long-range goals speaks for her deep understanding of the importance of his contributions to human welfare.
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KEY TO ABBREVIATIONS

Anal. Chem. = Analytical Chemistry
Annu. Rev. Biochem. = Annual Review of Biochemistry
Arch. Biochem. Biophys. = Archives of Biochemistry and Biophysics
Ciba Found. Symp. = Ciba Foundation Symposium
Cienc. Invest. = Ciencia e Investigacion
Iowa State Coll. J. Sci. = Iowa State College Journal of Science
Int. Congr. Biochem. = International Congress of Biochemistry
Int. Symp. Protein and Polypeptide Hormones = International Symposium on Protein and Polypeptide Hormones
J. Am. Chem. Soc. = Journal of the American Chemical Society
J. Econ. Entomol. = Journal of Economic Entomology
J. Biol. Chem. = Journal of Biological Chemistry

1930


1931

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1938

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1939


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1941


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