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PROFILES IN TOXICOLOGY

The Legacy of Leon Golberg (1915–1987)

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Leon Golberg left a legacy of substantial contributions to the basic scientific underpinnings of toxicology, the application of that science to important societal issues, and most significantly, through the creation of institutions that have had a lasting impact on toxicology. He was truly a visionary who set high standards of performance for himself and those who had the privilege of working with him.

Golberg was born 22 August 1915 in Limassol, Cyprus, the son of a jeweler. He began his scientific career at the University of Witwatersrand, Johannesburg, South Africa. His earliest interests were in history and mathematics. However, when he was introduced to organic chemistry, it is reported that the experience was "like a blinding flash of light." His knowledge of chemistry and enthusiasm for its application to human health issues was one of the hallmarks of his career. From the University of Witwatersrand he received a Bachelor of Science (Honors) degree in Chemistry (1935), a Bachelor of Science degree in Mathematics (1936), and a Master of Science degree in Physical Chemistry (1937). Later he would receive a Doctor of Science degree in Biochemistry (1946) from that institution.

He received scholarships that enabled him to continue his graduate and professional studies in England. He received a Doctor of Philosophy degree in organic chemistry from the University of Oxford (1939) and a Master of Arts degree in Anatomy and Physiology from the University of Cambridge (1948). In 1951, he received a Medical Bachelor and Bachelor of Surgery degrees from University College Hospital Medical School in London. Later, in 1983, he was to receive an honorary doctor of science degree from the Philadelphia College of Pharmacy and Science in Philadelphia, Pennsylvania.

In 1944, Golberg married Bertha Klempman, also a physician, who was to be both his wife and colleague. The Golbergs had three children: Michael, Aron, and Laura.

Golberg's most significant early research that led to noteworthy publications was conducted while he was a graduate student and a member of a research team at Magdalen College at Oxford University. The team, under the leadership of Robert Robinson, examined the relationships between chemical structure and estrogenic activity of some stilbene and diphenylethane analogs. This research led to the synthesis of a number of hydroxylated derivatives called stilbesterols (Dodds *et al.,* 1938a,b,c, 1939). Of particular importance was the synthesis of diethyl stilbesterol, which eventually became widely used medicinally as a synthetic estrogen and as a growth stimulant for domestic animals. Robinson was knighted and received the Nobel Prize in Chemistry in 1947 for his work on the organic synthesis of alkaloids and other work including the synthesis of the stilbestrols. Reflecting on Golberg's participation in this pioneering research, his knowledge of modes of action of chemicals linked to their structure, and his interest in linking science and public issues, it is interesting to speculate as to how Golberg would have contributed to the "endocrine disruption" debates that began in the 1990s had he been alive.

Golberg returned to Johannesburg, South Africa in 1939, lecturing in Chemistry at the University of Witwatersrand and then serving as the head of the Biochemical Research Laboratory of the South African Institute for Medical Research. This portion of his career focused on studies of the chemical composition and nutritive value of common African foodstuffs. Reviewing his publications, one senses an increasing focus on medical issues and the linkage between chemicals and health. No doubt, this was a factor in his return to England and a continuation of his training in medicine.

In 1951, Golberg accepted a position as Senior Lecturer in Chemical Pathology in the Department of Pathology at the University of Manchester in England. And in 1955, he became the Medical Research Director of Benger Laboratories Ltd., Holmes Chapel, Cheshire, England. During the 1950s, Golberg's work centered in three areas: (1) the role of administered iron in health and in induced disease (Golberg, 1960; Golberg *et al.,* 1955), (2) galactosemia (Komrower *et al.,* 1956), and (3) lipid and cholesterol metabolism (Golberg and Morantz, 1957). In this phase of his career there was continued emphasis on developing an understanding of the pathogenesis of disease and, especially, the dynamic and time- and dose-dependent nature of processes by which agents influence the development of disease. The emphasis on understanding the mechanisms of toxicity of chemicals would continue throughout his career.

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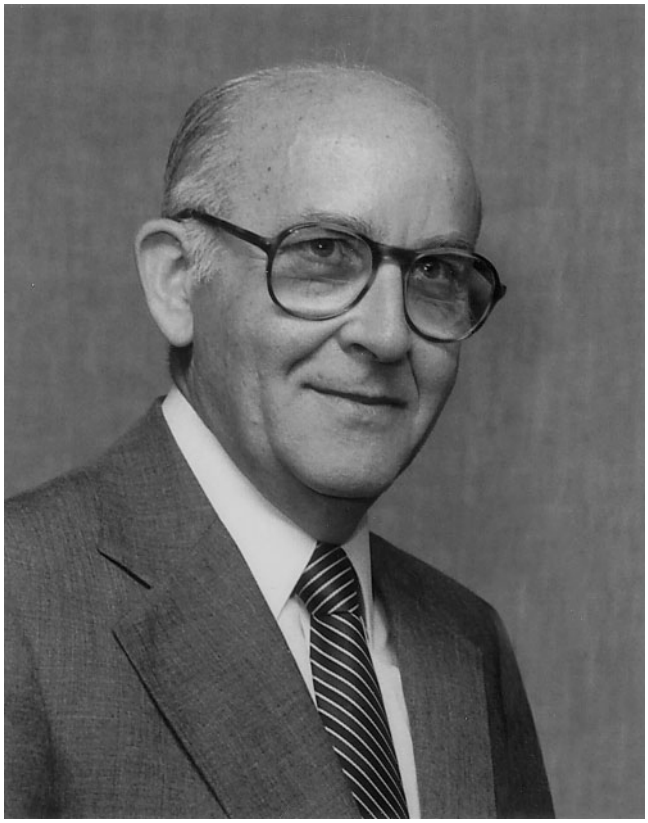

Leon Golberg

Examining Golberg's career and substantial achievements pre-1961, it is easy to project several paths he might have taken. It would have been easy to envision him as a professor at one of England's leading medical universities providing leadership for an academic-based research team, or alternatively, becoming a leader of a major international pharmaceutical firm's research and development efforts. Without question, in any of these roles he would have been an outstanding success. As it turned out, he did not pursue either of those courses.

Instead, in 1961 Golberg became the founding Director of the British Industrial Biological Research Association (BIBRA) in London. This new organization, a joint industry-government effort, was created to investigate mechanisms underlying toxic effects of chemicals, develop new or improved toxicity tests, and give advice and information on toxicological issues. BIBRA was intended to be an impartial forum for improved communication between industry, government, and academic personnel in addressing toxicological issues of major public significance, issues that were emerging with increasing frequency and contentiousness.

As expected, based on Golberg's role as head of BIBRA, the nature of his presentations and publications shifted. No longer was the focus on the details of conducting and interpreting scientific experiments. Now the focus was on how science could be used to address societal issues. He and his colleagues conducted noteworthy studies on the mechanisms of action of commercially important agents with a clear orientation to understanding the relevance of findings in rodents to predicting effects in humans (Gangolli *et al.,* 1967; Grasso and Golberg, 1966, 1968). The titles of two articles published in 1963 also reflected this new focus—"The Predictive Value of Animal Toxicity Studies Carried Out on New Drugs" (Golberg, 1963b) and "Guiding Principle and Problems of a Voluntary Scheme to Regulate the Use of Plastics in Food Packaging" (Golberg, 1963a).

Over the next six years, Golberg, as the head of BIBRA, laid the groundwork for an organization that has had international impact. He helped develop the operating principles that would ensure conduct of science of high quality as well as relevancy to public issues, and he assembled a team to carry out the science. An extraordinary group of scientists have been associated with BIBRA starting with the scientists Golberg recruited and continuing to the present time. Their impact is not related just to what they contributed at BIBRA, but also in their post-BIBRA activities. They learned and applied a way of "doing business."

In 1967, Golberg was recruited to the United States to become the Scientific Director of the Institute of Comparative and Human Toxicology at Albany Medical College in New York State. Golberg's scientific productivity and impact continued at a high level without interruption as he moved his base from the U.K. to the U.S. He continued to be involved in conducting and interpreting specific science and, as a senior spokesman, for applying high quality science to important human health issues. His research focused on a range of agents including ethylene glycol, sodium pyridinethione, carrageenan, monosodium glutamate, cyclamate, and saccharin. He also began conducting studies with nonhuman primates (Coulston *et al.,* 1975). The work on artificial sweeteners in monkeys was to have impact in several ways.

Golberg became one of the strongest proponents for not just testing artificial sweeteners and other agents for their toxicity, and then applying the data through a series of safety factors to humans. Rather, he advocated using all of the available scientific knowledge of agents in the several species to render a judgment as to the safety of the products (Golberg, 1975). In my opinion, Golberg's views had an important role, ultimately, in government decisions on the regulation of the artificial sweeteners.

Golberg continued to champion the importance of understanding the pathogenesis of chemical-induced diseases in order to make sound decisions on the safety of these chemicals to humans. This was emphasized in a chapter entitled "Modes of Action of Toxic Agents" (Golberg, 1970), which represents one of the earliest uses of the term "mode of action" as a concept in evaluating the safety of chemicals.

The impact of Golberg's work with nonhuman primates almost led to a shift for him and his family from New York to

New Mexico. This was about to occur in 1976 when Albany Medical College was selected to be the operating contractor for the U.S. Air Force Primate Center at Holloman Air Force Base, New Mexico. The Golbergs were literally packing their bags in anticipation of a move to New Mexico when another opportunity arose. That opportunity related to a new entity, the Chemical Industry Institute of Toxicology (CIIT), which was in the process of gestation. A group of major chemical companies in 1974 had decided it was in their best interest and that of society to create a new organization that would focus on developing information relevant to understanding the toxicity of chemicals. The idea of creating the new organization is traceable to Perry Gehring of the Dow Chemical Company, and many individuals were subsequently involved in bringing the concept to fruition.

The early history of CIIT is well documented (Mathias, 1985a,b,c). Specifically, the organization was to have a three-pronged mission: (1) conduct toxicity tests on a prioritized list of commodity chemicals, (2) conduct an in-house research program to develop new test methods and provide information to aid in interpreting the results of toxicity tests, and (3) promote the education of toxicologists. The organizers had made a number of tough decisions: the basic mission of the organization; the method of funding the research (dues payments from member companies); whether to operate as a contracting organization or have a stand-alone laboratory (they decided on the latter); operating guidelines (a focus on independence for the research team and full public disclosure of all findings without prior review by the sponsors); and where the institute would be located (Research Triangle Park, North Carolina, rather than in the "backyard" of one of the member companies). One key decision remained—the selection of a leader.

The search team was becoming quite frustrated with the task of finding the right person to lead this new and unique organization when one of the individuals by chance heard a presentation by Golberg on the use of animal data in evaluating human hazards. He reported back to the team that he had found the right individual—Golberg—"a man small of physical stature but an intellectual giant in understanding how to develop science that would have an impact on evaluating chemical hazards" (Monte Thordahl, personal communication, 1996). The rest is history—he was interviewed, hired, and Golberg moved to North Carolina where he would remain for the rest of his life.

Just as he did with BIBRA, Golberg set about organizing a new entity: hiring staff, developing a temporary laboratory in leased space, planning and constructing a new laboratory, selecting priority chemicals for study, and fine-tuning the approach to operating a unique laboratory. Golberg, as always, set high standards, standards that would ensure the credibility of research findings bound to come under scrutiny from the government, academic and, even the industrial community.

Indeed, two key early interactions I had with Golberg related to the issue of credibility. In one case, it involved studies that CIIT had contracted with the Industrial Bio-Test (IBT) organization in Decanter, Illinois, to conduct. When the credibility of work at IBT came into question, Golberg wanted an independent assessment as to whether, as he said, "we continue the studies to completion or pull the plug." As he requested, I carefully reviewed the in-life studies under way at IBT and reported the findings to Golberg and a decision was made to continue them.

The second situation involved studies with inhaled formaldehyde being conducted with mice and rats by the Battelle Memorial Institute in Columbus, Ohio. I received a call from Golberg in which he related that nasal tumors had been found in high incidence in rats at the highest exposure concentration (15 ppm) with a suggestion of an increase in mice. He related that because of the significance of the findings, CIIT was preparing to release the findings (as stipulated by CIIT Operating Guidelines) to the government, member companies, and the public at the same time. He asked if I would lead a team to evaluate the findings and determine "if they will stand the light of day including scrutiny by 'hired gunslingers,' perhaps even some hired by CIIT member companies." The team carried out the week-long review and reported that despite a few "warts and blemishes," not uncharacteristic of two-year studies, the research would indeed stand the light of day. Goldberg proceeded to publicly release the findings in the manner specified by CIIT's Operating Guidelines. The interpretation of the formaldehyde nasal tumor findings for human relevance have been a major drive of research at CIIT for two decades.

While leading CIIT and after his retirement, Golberg continued to speak and publish on important issues facing the field of toxicology. The topics were far-ranging and included the integration of basic sciences into the training of toxicologists (Golberg, 1976), the importance of viewing toxicology as a predictive science (Golberg, 1978), the importance of clinical toxicology (Golberg, 1980a), a code of conduct for scientists in reporting and reviewing information on chemicals (Golberg, 1982), the role of structure-activity relationships as a tool in toxicology (Golberg, 1983), and the charting of a course for using cell culture alternatives to animal testing (Golberg, 1986). These publications still provide valuable guidance for the field of toxicology.

The foundation that Golberg laid at CIIT has stood the test of time. CIIT has developed a well-deserved international reputation for the conduct of high quality research on the mechanisms of toxicity of chemicals and the application of that knowledge to assessing human health risks. As was the case with BIBRA, CIIT has also had substantial impact through its former employees who have filled responsible positions in industry, government, and academia. In addition, its substantial training program, especially at the post-doctoral level, has been a major source of toxicologists. Without question, the efforts of Golberg as reflected in the activities of both BIBRA and CIIT continue to have positive impact on the field of toxicology.

After retiring as President of CIIT, he served as Professor of Community and Occupational Medicine, Duke University Medical Center. He also played a key role as a consultant in the design of the comparative toxicity testing approach used by R. J. Reynolds in attempting to design and produce a "less harmful" cigarette.

Beyond his scientific and institutional legacy, Golberg had impact in three other major ways. One avenue of contribution was through his participation on numerous advisory committees. He served on eleven National Research Council Committees including chairmanship of two committees concerned with carcinogenicity testing of drugs. He also served on major advisory committees to the World Health Organization, the Department of Health and Human Services, and the Environmental Protection Agency. He was sought out for such activities because he could always be counted on to provide sound scientific advice irrespective of the circumstances under which the opinion was expressed.

Golberg was also a major contributor through his editorial role with 10 journals. This included service as the founding editor (1963–1987) of *Food and Cosmetic Toxicology* (now *Food and Chemical Toxicology*) and *CRC Critical Reviews in Toxicology* (1971–1987). I am proud that I was asked to succeed Golberg as the Editor of the latter journal.

Golberg also contributed substantially to 14 major professional organizations. He was a founding fellow of the Royal College of Pathologists, a fellow of the Royal Society of Chemistry, and a fellow of the Royal Society of Medicine. He gave freely of his talents to promote the Society of Toxicology including service as the Society's President in 1978–1979.

Golberg died on 3 May 1987 from a mesothelioma. After Leon's death, Bertha, his wife, continued to promote the science of toxicology. She was especially interested in working with young people and gave generously of her time and funds to support the Curriculum in Toxicology Program at the University of North Carolina at Chapel Hill. Bertha died on 29 November 1995.

Leon Golberg left the field of toxicology with a rich legacy. The breadth and depth of his training in chemistry, mathematics, physical chemistry, biochemistry, organic chemistry, anatomy, physiology, and medicine are rarely associated with a single individual. Indeed, today many research teams aspire to have this range of expertise represented in the membership of the team. Beyond this remarkable formal education, he had an uncanny ability to analyze an issue and envision an experimental path forward that would not simply result in the accumulation of data, but rather development of key information that would provide insight into the mode of action of the agent. And most significantly, he was always diligent in his interpretation of the scientific information as to its relevance in the assessment of human hazard or safety. He once indicated, "We must pursue meaningful answers to relevant questions, not simply generate negative data for regulatory authorities."

He was also mindful of the need to communicate not just with regulatory authorities but the broader public. Ever the optimist, Golberg believed that the best science and the best communication are compatible. This was emphasized in his remarks on the occasion of the dedication of CIIT's new laboratory in Research Triangle Park, North Carolina. He said, "I recall a large sign mounted on the wall of a microbiological laboratory in which I once worked. It read, 'Sterile enough is not sterile enough.' As practitioners of science in the public interest, all of us at CIIT feel that only our best is good enough" (Golberg, 1980b). This admonishment is equally fitting today for the entire field of toxicology.

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