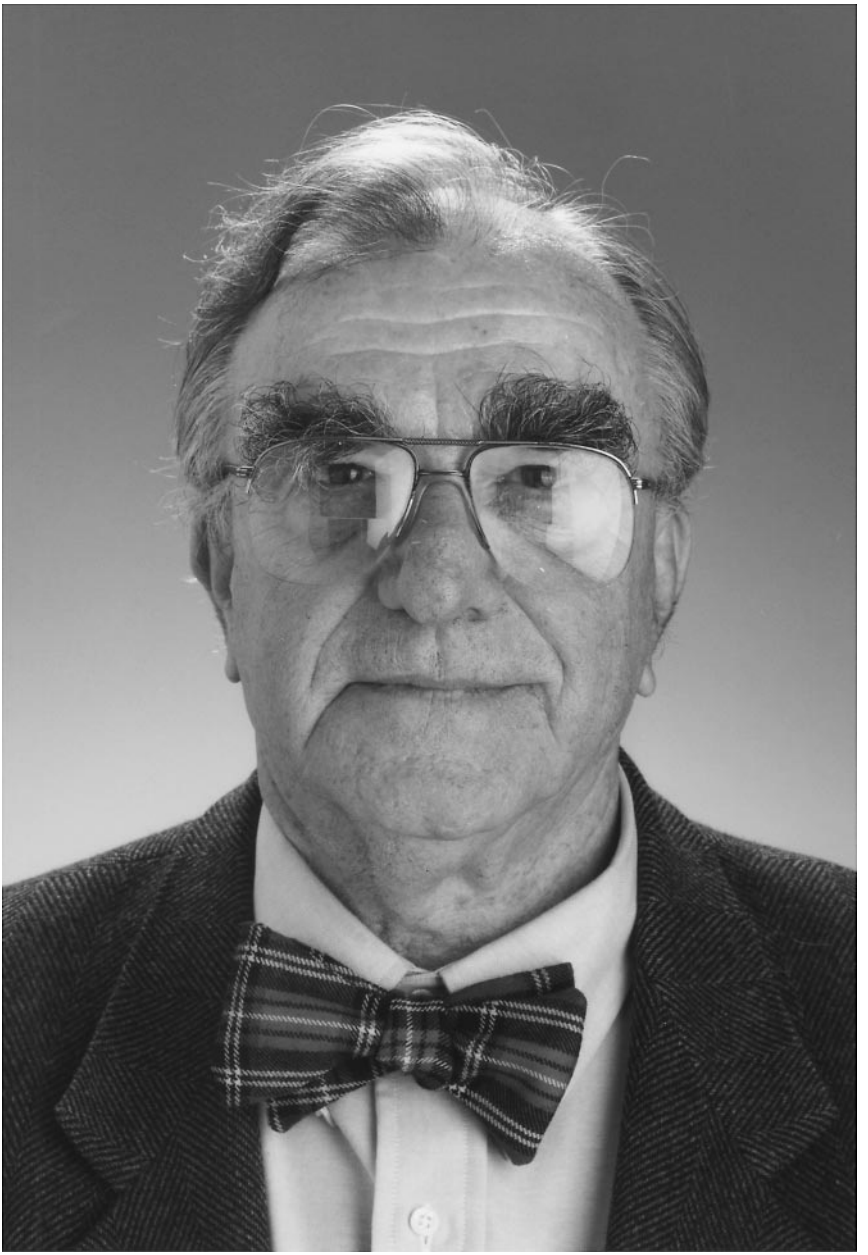

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TOXICOLOGY COMES OF AGE

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■ **Abstract** This paper contains recollections of some of the people and events that influenced the development of toxicology as an academic discipline. It also describes my experiences in pharmacology at the University of Chicago and the University of Kansas Medical Center and concludes with speculation concerning the future of toxicology.

Moderation in all things/Ne quid nimis.
—Terence in Andria

INTRODUCTION

Describing the origins of toxicology is somewhat controversial because there are those who argue that toxicology is one of the oldest of all sciences because its roots go back to when primitive man tested the safety of his food by giving it to his dog. Toxic substances have certainly been used for both offense and defense ever since our advent on this earth, but the earliest written records were probably the Ebers Papyrus and Hippocrates' description of hemlock as the state poison of the Greeks. Both the Romans and the Arabic physicians contributed to the science of toxicology, and our knowledge of poisoning and toxicology mushroomed during the Middle Ages and the Renaissance. There are others, however, who link the beginnings of toxicology, or at least modern toxicology, to Paracelsus, who established toxicology as a quantitative science, or to Orfila, who introduced qualitative science into toxicology. It is much easier to define toxicology's coming of age or the transition of toxicology into an academic discipline with journals, textbooks, departments, curricula, societies, annual meetings, certification, etc. This is because the origins of these developments are well documented and there are still some survivors with memories from the 1950s and 1960s, when many of these events took place.

Most of the key players in the development of toxicology as an academic discipline were pharmacologists, and two of these, Dr. Eugene Maxmillian Karl Geiling and Dr. Kenneth Patrick DuBois, were from the University of Chicago. Those of us who were graduate students in pharmacology at Chicago at that time,

shared in the excitement of these developments in toxicology. This was particularly true for those students who also worked behind the so-called "bamboo curtain" in the University of Chicago Toxicity Laboratory. The following pages contain my recollections of some of the people and events that have influenced the development of toxicology as an academic discipline. They also include a description of my experiences in the pharmacology departments at the University of Chicago and the University of Kansas Medical Center, and they conclude with some speculation about the future of our discipline.

CHICAGO AND THE TOX LAB

The University of Chicago Toxicity Laboratory, or the "Tox Lab" as it was commonly called, was created in 1941 to evaluate potential chemical warfare agents that were synthesized by chemists participating in the National Defense Research Council Office of Scientific Research and Development program. The University of Chicago was selected as the site for this laboratory in part because it had a very tall smokestack that was no longer in use and could be used to ventilate the laboratory (1). Dr. EMK Geiling served as the official investigator, and Dr. Franklin C McLean was appointed as the first director. In 1943 McLean resigned to accept a commission in the US Army Chemical Warfare Service, and Dr. Keith Cannan from New York University became the new director. Dr. William Bloom from the University of Chicago anatomy department was placed in charge of the programs to test agents with skin-blistering properties and to develop protective ointments. By this time the staff had increased to over 50 professionals. In addition to the program to evaluate potential chemical warfare agents there were programs under way to develop new nitrogen mustards and to evaluate these and other vesicants in recruits from the Great Lakes Naval Training Station. There were also programs to study the retention and distribution of various types of aerosols in rodents and primates and to study the toxicity of the nerve gases and related insecticides and other pesticides, such as alpha naphyl thiourea (ANTU), sodium fluoracetate [1080], and castrix.

In 1945 the Tox Lab became a part of the US Army Chemical Warfare Service, and Dr. William Doyle and Dr. John Hutchens served as interim directors until Dr. George Mangun was recruited for this position in 1946. Between 1947 and 1950 the Tox Lab operated under a contract with the Atomic Energy Commission to study the toxicity of radioactive metals and the medical effects of ionizing radiation. The name of the lab was changed in 1951 to the University of Chicago US Air Force Radiation Laboratory to reflect a new research program and source of funding, and Dr. Julius Coon became the director. Dr. Kenneth DuBois became the director in 1953 and he served until his death in 1973. The laboratory closed shortly thereafter. During the three decades of its existence, the Tox Lab was a research home for clinicians such as Drs. Erwin Levin, Leon Jacobsen, Charles Spurr, John Rust, Robert Block, and William Adams; anatomists William Bloom and William Doyle; pathologists Clarence Lushbaugh, John Storer,

Frank Fitch, Janet Rowley, and Draga Vesselinovitch; physiologists Dan Oldfield, Walter Stumpf, Herb Landahl, John Hutchens, and Franklin McLean; biochemists George Mangun, Keith Cannan, Robert Feinstein, and Jean Sice; and pharmacologists John Thompson, Dick Byerrum, Julius Coon, Ken DuBois, and John Doull. During this period the laboratory also employed graduate and postdoctoral students in all of these disciplines; over four hundred publications attest to the productivity of this group.

I came to the Tox Lab in the fall of 1946, after receiving a BS in chemistry from Montana State College in 1944 and then spending two years in the navy taking care of radar and other electronics on the battleship *New Jersey* in the South Pacific. Dr. BL Johnson, who was one of my professors at Montana State, had arranged an interview with Dr. George Mangun, a former Montana State graduate, who was then the director of the University of Chicago Toxicity Laboratory and a professor of biochemistry. Although I was admitted as a graduate student in biochemistry, Dr. Mangun suggested that I switch to pharmacology and work with Dr. DuBois, who became my graduate advisor, colleague, and good friend. My PhD thesis described the cardiotoxic and other effects of bufagin that we obtained from the parotid gland of the giant toad *Bufo Marinus* and labeled by feeding the toads ^{14}C-labeled algae. Most of my research during this period, however, involved the acute and chronic toxicity of the organophosphate (OP) insecticides.

During the war di-isopropyl fluorophosphate had been investigated as a potential chemical warfare gas. Although it was discarded as a war gas, it was shown to inhibit cholinesterase and was therefore evaluated for use in glaucoma and in myasthenia gravis. Thus, when the first organophosphate HETP (hexaethyl tetra phosphate) emerged from Dr. Gerhard Schrader's laboratory at Farbenfabriken, Germany in the early 1940s, DuBois and his associates recognized its cholinergic symptoms and showed that atropine would be an effective antidote. They also carried out similar early studies with tetraethyl pyrophosphate (TEPP), parathion (E-605), and later on with the nerve gases (tabun, sarin, and soman) when they became available. These studies stimulated a life-long interest for DuBois in the toxicity of the OP insecticides, and his students and associates shared his interest. Sheldon Murphy and DuBois, for example, elucidated the biochemical basis for potentiation of the effects of malathion and other OP insecticides, and Robert Neal and DuBois identified several enzymes that catalyzed the detoxification of some of the OP insecticides.

During my graduate period with Ken DuBois we characterized both the acute and chronic toxicity of several OP insecticides and a few cholinergic carbamates in rodents and beagles. Most of these agents were developed for agricultural use, and we worked closely with Drs. Dan MacDougall and Dallas Nelson from Chemagro (now Bayer, Inc.) in Kansas City in planning and carrying out the studies and eventually in defending them before the Food and Drug Administration (FDA). These meetings were usually held in the FDA commissioner's office, with Drs. Arnold Lehman, Garth Fitzhugh, Bert Vos, and Arthur Nelson representing the FDA, and DuBois, Doull, and McDougall representing Chemagro. In contrast to the complex and lengthy procedure currently required to obtain pesticide

tolerances, these meetings were short, informal, and focused on the science (toxicology and pathology) rather than on any of the legal or political considerations that often seem to be of primary importance today. It was in this office that the often-quoted admonition was displayed on the wall, "You too can learn toxicology in two easy lessons, each ten years long."

After receiving my pharmacology PhD in 1951 I enrolled in the University of Chicago Medical School but continued with the Tox Lab as a research associate working mainly on the toxicity of pesticides and radiation. When the US Air Force took over the Tox Lab in 1951, Vivian Plzak, Mildred Root, and I were requested to establish a screening program for radio protective agents. This program involved obtaining acute IP LD/50s on several thousand agents in mice. The resulting large data base of acute toxicity data in male mice has subsequently proven to be of more lasting value than the few radio-protectors we found. After finishing medical school in 1953 I became the assistant director of the Tox Lab in 1954 and began advancing through the academic ranks as an assistant professor of pharmacology. In looking back, these were indeed golden years. The university and the deans of biological sciences supported our program, grants were relatively easy to obtain, toxicology was becoming established as a discipline, and both our department and the staff and students at the Tox Lab were involved in the conversion process.

One of the most important accomplishments of the University of Chicago Toxicity Laboratory is the number of PhD and postdoctoral students who were trained during its 30 years. These include Drs. John Ballin, Robert Bagdon, Jules Brodeur, Gary Carlson, Kenneth Cochran, Bernard Conley, John Doull, Marion Ehrich, Bernard Heitbrink, Roy Herrman, Eugene Kimura, Florence Kinoshita, Hugo Moeller, Albert Moraczewski, Sheldon Murphy, Robert Neal, John Noble, Arthur Okinaka, Donald Petersen, Alfred Rider, Tetsuo Satoh, Mei Su, Maurice Sullivan, Robert Tardiff, Don Thursh, John Thompson, Edwin Uyeki, James Wilson, Dinah Wu, Kei Yam, and Gerald Zins, plus numerous other masters and nondegree students. Both student and staff members of the Tox Lab presented toxicology lectures to medical students and graduate students in other departments and postgraduate programs.

Dr. Geiling treated the staff and students in the Tox Lab and those in the pharmacology department like his family, and holiday dinners at his home were mandatory occasions. He took a personal interest in each student, technician, and faculty member, and his Christmas gift to each was always a book he chose carefully to relate to the specific interests of the recipient. Dr. Geiling never married, and although he tolerated marriage in his faculty and students, he regarded it generally as a detrimental or counterproductive influence. (Neither Ken DuBois nor I got married until after Dr. Geiling retired.) Dr. Geiling made all decisions regarding faculty promotions, and each year when he gave his recommendations for promotion to the dean, he included his own letter of resignation in the event that the dean failed to follow any of his recommendations. It was also traditional for Dr. Geiling to deliver serious good or bad news after a one-on-one breakfast at the University Club. Because one never knew whether the news was good or bad, it was

impossible to eat until it was too late. We discussed my going to medical school at one such breakfast, and when I indicated that I would like to think about it, he suggested that I do so quickly because I was already enrolled in gross anatomy starting the following week. When one compares this patriarchal approach to chairing a department to the more opportunistic approach exhibited today by most faculty, chairs, and even administrators, it is not surprising that institutional commitment is becoming a rare and vanishing trait in most universities. Dr. Geiling's approach was more in the nature of a benevolent advisor, and like most of his faculty I anticipated that Chicago would be my permanent academic home.

Dr. Geiling retired in 1957 and was replaced by Dr. Lloyd Roth. During the next decade, the environment at the University of Chicago and elsewhere in this country changed as applied research lost favor. The support of Dr. Leon Jacobsen, the Dean of Biological Sciences, shifted from studies that focused on whole animal responses to those that focused on DNA. By the end of 1967, Dr. Gail Dack was planning to move Chicago's Meat Institute to the University of Wisconsin at Madison, Dr. DuBois was considering closing the Tox Lab and returning to the McArdle Lab at Wisconsin, and I had accepted Dr. Edward Walaszek's invitation to become a professor of pharmacology and toxicology at the University of Kansas. Years later when I returned to the University of Chicago to accept a Distinguished Medical Alumnus Award, Dr. Jacobson told me that in retrospect he felt he probably made the wrong decision for Chicago regarding the merits of whole animal studies.

JOURNALS

Historically, the first step in the transition of toxicology into an academic discipline was the establishment of the *Journal of Toxicology and Applied Pharmacology* in 1959. The editors were Drs. Fred Coulston and Arnold J. Lehman, and Dr. Harry Hays was the managing editor. An editorial in the first issue stated that the journal was needed because "toxicology is emerging as a scientific discipline and that there is a need for centralization of toxicology data." The reluctance of the *The Journal of Pharmacology and Experimental Therapeutics* to publish toxicology studies on products or chemicals was not mentioned, although it was widely recognized and was certainly one of the reasons for creating the new toxicology journal. Dr. DuBois took over as the managing editor of the journal in 1960, and Dr. Coulston became the managing editor in 1964, with Drs. Horace Gerarde and Arnold Lehman as associate editors. Dr. Boyd Shafer became the editor in 1965, replaced by Dr. Earl Dearborn in 1967. Dr. Gabriel Plaa, who served as the associate editor for Dearborn became the editor in 1973. In 1980 Dr. Robert Neal became the editor and was succeeded by Dr. Wallace Hayes in 1981. Dr. Glenn Sipes became the editor in 1986, and Dr. Edward Bresnick, the current editor, took over in 1993.

Although the *Journal of Toxicology and Applied Pharmacology* became the official journal of the Society of Toxicology in 1963, it was not owned by the

society. After long deliberation, the society established a second journal, *Fundamental and Applied Toxicology*, in 1981, with Drs. William Carlton and Phil Watanabe as the editors. Dr. Bern Schwetz became the editor of this new journal in 1986, and from 1992 to 1998, the editor was Dr. Henry d'A Heck. The name of the journal was changed to *Toxicological Sciences* in 1998; Dr. Curtis Klaassen became the new editor and a new editorial board was appointed. They broadened the scope of the journal to include reviews, editorials, and coverage of contemporary issues in toxicology. More recently the journal has added a section titled Profiles in Toxicology, edited by Dr. Hans Peter Witchi, which is designed to call attention to historical events and contributors to toxicology. Today there are many journals devoted entirely or in part to toxicology, but the two journals described above were historically important factors in the transition of toxicology into an academic discipline. Furthermore, it is likely that they will continue to significantly influence the direction and development of toxicology as a science and as an academic discipline.

TEXTBOOKS

During the 1950s many departments of pharmacology began to introduce courses in toxicology into their graduate curriculum and toxicologic materials into the medical school courses. Because there was no textbook for this area of toxicology, DuBois and Geiling wrote and published the first textbook of toxicology in this country in 1959. During the late-1960s DuBois was working on a second edition of the book, but died before it was completed. A similar textbook was published by Ted Loomis in 1968; subsequent editions appeared in 1974 and 1978. The fourth edition of this book was published in 1996 as *Loomis's Essentials of Toxicology*, with Wally Hayes as a coeditor. In 1967 Lou Casarrett was searching for a toxicology textbook that would include not only the classes of toxic agents (metals, solvents, pesticides, etc) but also the organ system involved (kidney, liver, etc). Because neither the DuBois or Loomis texts provided this approach, Lou asked me to help him put such a textbook together. I agreed and we discussed this further during a dinner meeting after a National Institutes of Health Toxicology Study Section meeting in Bethesda. We recruited study section members who endorsed the plan to write chapters, and Lou then approached MacMillan to be our publisher. During a subsequent summer vacation in Hawaii with my family, Lou and I selected additional contributors and planned the organization of the book. Tragically, as the first chapters were being received, Lou developed brain cancer. With the perseverance of his wife Peggy, who read the chapters to Lou and handled the correspondence with the authors and with the enthusiastic and capable support of the contributors, friends, and colleagues, we finished and published *Toxicology, the Basic Science of Poisons* in 1975.

Drs. Curt Klaassen and Mary Amdur agreed to join me as editors for the second edition, and Mary Amdur suggested that we change the name of the book to *Casarrett and Doull's Toxicology* to provide a fitting memorial to Lou's dedication

to toxicologic education. The second edition was published in 1980, and third and fourth editions were published in 1986 and 1991, with the listing of the editors arranged to reflect which of us had the major responsibility for getting the book to press. Mary Amdur and I became emeritus editors for the fifth edition, which was published in 1996 with Curt Klaassen as the editor. Our textbook has been widely used in graduate courses of toxicology and is the basis for curricular design in such programs both in this country and abroad. It is widely used as a reference in other disciplines and is the choice of most students preparing for the certification exams in toxicology. Although Lou and I had high expectations for our book, neither of us could have anticipated that *Casaret and Doull* would become a major factor in the development of toxicology as an academic discipline and that it would persist as a virtual landmark in academic toxicology for over two decades and five editions.

SOCIETIES

The formation of the Society of Toxicology (SOT) was the third major event in the history of the transformation of toxicology into an academic discipline. It started in early 1961 with a discussion involving Drs. Fred Coulston, Victor Drill, William Deichman, Harry Hays, Harold Hodge, Arnold Lehman, and Boyd Schafer, with Drs. Ken DuBois and Paul Larson connected by phone. These nine individuals became the founders of the SOT. Although they were concerned about deleterious effects on the Society of Pharmacology, the group voted to form the SOT and elected Lehman as honorary president, Hodge as president, and DuBois as vice president. They planned for meetings to be held in conjunction with meetings of Federation of American Societies for Experimental Biology, American Industrial Hygiene Association, American Society for Pharmacology & Experimental Therapeutics (fall meeting), and the Gordon Conference to elicit support. All members who joined during the first year became charter members, and there were 183 of us by the time of the first annual meeting. The first annual meeting took place in Atlantic City in 1962, during which Drs. Torald Sollman, Wolfgang von Oettingen, and EMK Geiling became the first honorary members.

Dr. Geiling was a strong supporter of the new society and he provided advice based on his association with Dr. JJ Abel when Abel was attempting to separate pharmacology from physiology and biochemistry. Geiling first recommended that we focus on the unique aspects of the new discipline to sharply separate it from the old, and second to clearly identify the societal benefits the new discipline would provide. He noted that describing pharmacology as the science of drugs separated it from physiology and biochemistry, and that including therapeutics as part of the discipline identified the rationale for the societal support of pharmacology. He suggested defining toxicology as the science of poisons to separate it from pharmacology and advised including safety evaluation as the justification for support by the public. When we define toxicology simply as the adverse effects

of chemicals on living systems without including the use of that information to evaluate safety or predict risk we describe what we do but not why we do it. If our discipline focuses on this limited mission, we risk eroding public support for toxicology, the regulatory process, and science in general. In a previous prefatory chapter Dr. Avram Goldstein voiced similar concerns about the growing failure of pharmacology to focus on the unique attributes of the discipline rather than on the techniques of molecular biology (2), which suggests that toxicology and pharmacology face some common problems.

During its early history the SOT was closely associated with both pharmacology and industrial hygiene. Dr. William McCormack, the executive secretary for the American Industrial Hygiene Association, also served as the executive secretary for SOT until 1985 when we moved the office from Akron, Ohio to Washington, DC and hired Joan Cassidy as our new executive secretary. In 1986 we celebrated our silver anniversary in New Orleans with seven of the original nine founders in attendance (DuBois and Lehman had died). My first committee appointment with SOT was made on October 4, 1961 as a member of the technical committee, and this led to many other SOT committee appointments. My most prestigious, and also most enjoyable, task for SOT was serving as president from 1986 to 1987, and I later served as president of our Toxicology Education Foundation from 1998 to 1999.

In the nearly four decades of SOT's existence, it has exhibited remarkable progress, its annual meetings have become major scientific events, it has shaped and fostered the development of toxicology as a science, and it has been a key element in the transition of toxicology into an academic discipline.

CERTIFICATION

During the 1960s and 1970s there were a few episodes in which the FDA received erroneous or even fraudulent reports on toxicity studies, and the agency responded by issuing guidelines for "Good Laboratory Practice." Because of concern over the possibility that the agency might also define the qualifications for those who carried out such studies, the SOT council asked Dr. Fred Oehme to convene a group to explore certification for testing laboratories and toxicologists. In response to their recommendations and recognizing that such groups needed to be totally independent, the SOT council provided start-up funding, solicited nominees from SOT as well as other existing boards (forensic toxicology, veterinary toxicology and pathology, and occupational medicine), appointed a start-up board, and then cut the ties. The laboratory certification program was initially quite active, but demand for this gradually decreased and the program was essentially phased out by the end of the decade.

The toxicologist certification program was incorporated in 1979 as the American Board of Toxicology (ABT); the initial board members were Drs. Bert Dinman, John Doull, Bob Forney, Seymour Friess, Bert Koestner, Marv Kuschner,

Gene Paynter, Bill Rinehart, and Ray Suskind. Friess was elected president with Doull as vice president, Paynter as secretary, and Koestner as treasurer. The board decided that start-up board members would not be grandfathered into the organization and that board members would be required to wait for three years after completion of their term before applying for certification. Committees were appointed to evaluate the qualifications of the candidates and to prepare examinations that could be used by candidates for self-assessment and for certification. The eligibility committee required proof of both educational background and current involvement in the practice of toxicology, and their recommendations were reviewed by the full board. The exam committee relied heavily on a toxicology question data bank containing questions from Chicago and Kansas, and these were classified into three areas (general toxicology, special toxicology, and applied toxicology). Selected questions in each category were modified if necessary, additional questions were developed, and the sample and candidate exams were generated using a random numbering selection system. Finished exams were reviewed by the full board, and on August 4, 1980, the first certification examination was given simultaneously in Washington, DC; Indianapolis, Indiana; San Francisco; and London. There were 460 candidates taking the exam; 217 of these were certified in all 3 parts (general, special, and applied toxicology). Candidates who failed only one part of the exam were permitted to correct the deficiency when the exam was given the following year, but candidates failing two parts were required to retake all three parts of the examination. A total of 1751 candidates have become diplomates of ABT during the past two decades.

To provide for an orderly replacement of the start-up board by diplomates, it was agreed that three new members would be elected each year. In 1981, Drs. James Beall, John Moore, and Fred Oehme were elected, and Dr. Charles Reinhardt replaced Kuschner, who resigned. Doull became the president in 1982, with Charley Reinhardt as vice president and Beall as secretary and Drs. Mike McKenna, Paul Newberne, Robert Scala, and TJ Terhaar were elected to replace Dinman, Forney, Friess, and Paynter. In 1983, Charley Reinhardt became the president, Scala became the vice president, and Moore became the secretary. Sue Moore was appointed as administrative assistant to handle the increasing correspondence and administrative duties of ABT, and Drs. Jim Bus, Robert Drew, Bernard Goldstein, and Mark Hite were elected to replace the four remaining members of the start-up board (Doull, Koestner, Suskind, and Bill Rinehart). The following year the board, under the direction of the new president, Dr. Robert Scala, appointed Sue Moore to be the Executive Director of ABT, and she has continued to serve in this position to the present.

The Academy of Toxicological Sciences was established at about the same time as ABT. Its purpose is to honor and certify toxicologists who have achieved peer recognition for their expertise and sound scientific judgment. The criteria for certification in the Academy of Toxicological Sciences include formal training, proven ability, and experience; selection is by peer review involving the entire board of directors, and certified experts are awarded the title of Fellow. There are

currently more than 176 fellows, although 24 of these are now emeriti. Dr. Donald Gardner is the current president with Drs. John Thomas and David Brusick as vice president and secretary. In 1997, 1998, and 1999 the Academy awarded two student travel awards to the American College of Toxicology meeting and in 1999, a $1000 travel grant to the British Toxicology Society. The Academy will also sponsor lectures at the European Toxicology Society meeting in 2000 and at the 9th International Congress of Toxicology in 2001.

Although there have been several attempts over the years to consolidate the ABT and the Academy of Toxicological Sciences, these efforts were not able to resolve the issue of the examination requirement. However, the proposed formation of a new International Assembly for the Recognition of Toxicologists, which would be open to all organizations that recognize toxicologic expertise, may ultimately diffuse or resolve the issue.

THE KANSAS YEARS

My family (wife Vera, daughter Ellen and twin sons John and James) and I arrived in Kansas in the spring of 1967. Leaving Chicago, which was still suffering the aftermath of a record snowfall, and arriving with the flowers blooming seemed like a good omen. We were surprised and delighted to find that the Kansas City landscape was not flat but gently rolling. I was also surprised to learn that Kansas has a strong historical association with toxicology. In 1884 a chemistry professor, Dr. Edgar Henry Summerfield Bailey, was teaching toxicology to medical students in Kansas while JJ Abel was still a graduate student in physiology at Johns Hopkins (3). Although Bailey's course was called pharmacology, the catalog described the course as "including a discussion of the source, properties, methods of detection, post mortem appearances, fatal doses and methods of treatment for inorganic and organic poisons." Bailey was also ahead of his time as an environmental activist. He analyzed many samples of food, water, and various remedies of that time to detect adulteration. Thus, if we follow the example of naming Abel as the father of pharmacology because of his early contributions to pharmacology, we might consider a similar argument for EHS Bailey as the father of academic toxicology and Lawrence, Kansas as its birthplace.

Shortly after my arrival in Kansas, Dr. Daniel Azarnoff and I applied to NIH for a Center in Clinical Pharmacology and Toxicology. When the grant was awarded in 1968, we recruited Dr. Aryeh Hurwitz, who had gone to NIH after getting his MD at Washington University in St. Louis, and Dr. Curtis Klaassen, who had just finished his PhD with Dr. Gabriel Plaa at the University of Iowa. Because we were short of space, we negotiated a provision whereby the center grant could pay rent to the Endowment Association, who then agreed to erect a building to house our new center. During the next decade we focused on developing a pharm/tox research program and on training graduate and medical students and residents. During the second five-year renewal of the center, Dr. Azarnoff left to become

the research director of GD Searle and no further renewals were submitted. The clinical pharmacology program has continued, however, as an active research and training division in the Department of Medicine, with Dr. Aryeh Hurwitz as the clinical director.

The toxicology program at Kansas gained momentum in 1979 when Dr. Curtis Klaassen obtained a National Institute of Environmental Health Sciences toxicology training grant (which has now been active for over 20 years). In 1981 Dr. Karl Rozman, who graduated from Leopold Franzen's University in Innsbruck, Austria, was recruited in part because of Klaassen's sabbatical with Dr. Helmut Greim at the GSF Institut für Toxikologie in Munich, Germany. In 1982 Klaassen received the Burroughs Wellcome Toxicology Scholar Award, and as a result salary funds became available to hire Dr. Andrew Parkinson, who had trained with Drs. Stephen Safe and Allen Conney. During this period Dr. Edwin Uyeki who trained at Chicago with DuBois, Dr. Tom Pazdernik who trained at Kansas with Dr. Ed Smissman in medicinal chemistry, and Dr. Stata Norton who had previously managed toxicology programs for the Burroughs Wellcome company changed the focus of their research from pharmacology to toxicology. Our department received permission to grant a doctorate in toxicology rather than in pharmacology, and the department changed its name from Pharmacology to Pharmacology, Toxicology, and Therapeutics. This was actually a transcription of a previous name adopted by the department in 1909 but abandoned in 1926.

Largely as a result of these advances, the State of Kansas provided funds in 1986 for an Environmental and Occupational Health Center, and I became the director with Dr. Klaassen as the associate director. Funds were provided for equipment and salaries. We used the equipment money to establish a common instrument room, and we hired Drs. Gregory Reed and David Beer with the salary funds. Reed had worked with Dr. Larry Marnett at Wayne State University and with Dr. Tom Ealing at NIEHS, and Beer worked with Dr. AM Malkinson at the University of Colorado and had postdoctoral training in the laboratory of Dr. Henry Pitot at Wisconsin.

In 1989 I developed kidney cancer and resigned as the center director. Dr. Curt Klaassen served as interim director until 1991 when Dr. H William Barkman was recruited from the pulmonary medicine division at the Tulane University Medical School. During his tenure Dr. Barkman has strengthened the links between the center and the clinical departments, between the School of Veterinary Medicine and other departments at Kansas State University and similar programs in Iowa. He has also organized several joint regional conferences on Agro Medicine. Dr. Thomas Pierce has been recruited to provide industrial hygiene expertise for the center and to set up a laboratory to measure environmental levels of metals and other xenobiotics.

Dr. Salvatore Enna became the chairman of the department in 1992, and although he has recruited toxicologists as faculty, these additions have not replaced the loss of David Beer, the retirement of Ed Uyeki, and the emeritus status of Stata Norton and John Doull. Thus, toxicology will probably retain a strong

presence in this department in the coming years, but it does not seem poised to regain the prominence it exhibited during the past two decades.

Another program developed during my early years at Kansas was the computerized teaching system known as Computer Assisted Teaching System (CATS). Together with Drs. Stata Norton, Stan Nelson, and Ed Walaszek, we developed an interactive computer-based program for our medical school pharmacology course. We also developed an extensive question bank in pharmacology and toxicology so that we could generate examinations almost on demand to respond to student requests, and we developed an exam scoring system and grade book program to manage the entire system. Because other medical schools were interested in sharing in the development and use of this system, we created a consortium of CATS users in 1974 and began holding annual meetings to encourage growth of the program. During the early 1980s, over 60 medical and dental schools plus some graduate schools used all or part of the 166 interactive teaching programs that were available in CATS. Through the cooperation of our partners in CATS, there were over 26,000 questions in the exam database, although only half of these were included in the preferred file. With the development of similar commercial programs in pharmacology and other areas during the early 1980s, interest in our programs declined, although the grading program is still used by the ABT and pharmacology courses at the University of Kansas Medical Center. During the past few years, interest in these teaching and grading programs has been rekindled by Dr. Lazlo Kerecsen, a former staff member who is teaching pharmacology at the Glendale Campus of the Midwestern University in Phoenix. Dr. Kerecsen, in cooperation with Dr. Tom Pazdernik, has updated the existing course material, added new programs and converted all of the computer programs into a more powerful and contemporary language.

While I was at Chicago we developed a database that could be used in the emergency room to diagnose and treat poisoning. Like most systems of that time, it consisted of a card file, wall charts on snakes and plants, and a few books on clinical toxicology. When I was asked to establish a poison control center at the University of Kansas Medical Center, I duplicated this system. However, when Dr. Barry Rumack introduced a computer-based system for generating poison control information at Denver General Hospital, we were anxious to implement the system in our medical center. To facilitate this, I joined the newly created Academy of Clinical Toxicology and served on its board during the period when building the computer database was an Academy-related activity and continued on as a consultant when the database was taken over by Micromedex. During this period we also instituted a series of quarterly lectures in toxicology for each new group of incoming interns and residents in our emergency room and we provided them with consultant support as needed. We also identified regional experts who could be consulted for poisoning by plants, snakes, spiders, and other local problems. An ancillary task was to oversee the University of Kansas Medical Center Safety Office and ensure compliance with the requirements of the Joint Commission regarding electrical, chemical, and radiation safety. With the

help of Ruth Schukman-Dakotas, who now serves as the director of the Medical Center Safety Office, we increased the staff in industrial hygiene and radiation safety and expanded the services provided to the hospital and basic science areas.

My first association with the Environmental Protection Agency (EPA) came in 1976 as a member of the Federal Insecticide Fungicide and Rodenticide Act Science Advisory Panel. Unlike the Science Advisory Board, which reported to the administrator, our panel was linked to Congress, and the EPA administrator was required to respond formally to recommendations of our panel. With members such as Drs. Edward Smukler, Robert Metcalf, Robert Neal, and Christopher Wilkinson, this panel was a strong advocate for basing decisions on good science rather than on policy or politics. My subsequent service on the Environmental Health Committee of the Science Advisory Board, the Dioxin Reassessment Review Committee, and other EPA committees has been rewarding, but the growing resurgence of policy rather than good science as the basis for many decisions in recent years is disappointing.

The three professional groups I have most enjoyed working with are the Expert Panel of the Flavor Extract Manufacturing Association (FEMA), the National Academy of Sciences/National Research Council's Committee on Toxicology (COT), and the Threshold Limit Value (TLV) committee of the American Conference of Governmental Industrial Hygienists. The reason for this is that these three groups and the Food and Drug Administration are among the leading proponents of the first and most venerable principle of toxicology, which is that "the dose makes the poison."

The FEMA expert panel was established following passage of the 1958 Food Additives Amendment in which the concepts of preclearance and safety in use were introduced. This led to the concept of GRAS, which stands for generally recognized as safe by experts qualified by scientific training and experience to evaluate a substance's safety under specified conditions of use. Beginning in 1960, this approach was used by FDA and by a FEMA-sponsored expert panel appointed by Dr. Bernard Oser to classify the safety of food additives. Dr. Oser served as the nonvoting chair of this panel, which included Drs. David Fassett, Horace Gerard, Maurice Seevers, Howard Spenser, Jakob Stekol, and Lauren Woods. Over the next few years, Drs. Frank Blood, Frank Strong, Anthony Ambrose, and R Tecwyn Williams were appointed as new or replacement members. I joined the panel in 1977 along with Paul Newberne and Carrol Weil. The current members of the FEMA expert panel are Drs. Victor Feron, Jay Goodman, Larry Marnett, Ian Munro, Phillip Portghese, Robert Smith, William Waddell, and Bernard Wagner. During the four decades of the panel's existence, several thousand flavors have been evaluated, over 2000 have been GRASed, and a few have been deGRASed. The criteria used by the panel include (*a*) exposure to the flavor in specific foods, the total amount in the diet and the total poundage; (*b*) natural occurrence in food; (*c*) chemical identity; (*d*) metabolic and pharmacokinetic characteristics; and (*e*) animal toxicity (4). In recent years, the panel has become increasingly involved in global certification issues, in developing protocols for assessing the safety of

natural flavors and other mixtures, and in the utilization and role of cutting-edge toxicologic techniques and procedures in safety evaluation.

The COT is one of the oldest of the National Academy of Science/National Research Council committees. It has provided military and civilian agencies with scientific information and expert advice on issues involving toxicology and the health effects of hazardous substances since 1947. To celebrate the "First 50 Years," the COT recently held a colloquium in which previous members described contributions of the COT and offered predictions for the future (5). Many of the issues considered by the COT over the years have been extremely controversial. Thus, the ability of the many COT committees to deal with these issues in a balanced yet authoritative way while maintaining credibility with the scientific community and various other stakeholders provides a validation of the COT model. The COT, like other National Research Council committees, has learned that the only effective way to manage bias is not to eliminate it but to balance it, because real experts are rarely unbiased. A major responsibility of the COT during its long history has been to provide emergency response advice and guidance to the Armed Forces. The COT director and staff usually provided this service, although COT members were occasionally involved. The executive directors of the COT have included Drs. Harry Hays, Ralph Wands, Gordon Newell, Gary Kielson, Francis Marzulli, and Richard Thomas; the current director is Dr. Kulbir Bakshi. Previous chairs of the COT were Drs. HH Shrenk, Lawrence Fairhall, Harold Hodge, Norton Nelson, Arnold Lehman, William Sutton, Herb Stockinger, Bertram Dinman, Joseph Borzelleca, Roger McClellan, John Doull, Rogene Henderson; the current chair is Dr. Bailus Walker.

In addition to the COT committees, I have also served on the Food Protection Committee, the Committee on Mixtures, the Safe Drinking Water Committee, the Committee on Hazardous Air Pollutants, which produced the book *Science and Judgment* and others, and am currently serving on the Subcommittee on Acute Exposure Guideline Levels. These experiences have convinced me that there is no substitute for using scientists to resolve science issues and that the academy committees are the closest approach we have to a supreme court for science in this country.

The origin of the TLVs as occupational exposure limits is often attributed to Professor Warren Cook, although Dr. William Fredrick served as the chair of the first American Conference of Governmental Industrial Hygienists TLV committee, which published an exposure limit list in 1942 (6). In 1945, Cook published a list of maximum allowable concentrations for 132 substances, and the TLV committee used this list plus other sources to develop the first official TLV list in 1946. The concept of excursion limits with short-term exposure limits and ceiling values was introduced in 1961 along with the SKIN and cancer designations, and the first volume of TLV documentations appeared in 1962 when Dr. Herbert Stokinger was the chair. TLVs for physical agents were introduced in 1969, and the biological limit values appeared in 1974. Particle size selective threshold limit values were introduced in 1982, although the distinction between "respirable" and "total" dusts was

discussed in the earlier lists. I was appointed as chair of the American Conference of Governmental Industrial Hygienists Chemical Substances TLV Committee in 1990 and with the help and support of Dr. William Wagner as mentor, colleague, and friend, I served through 1998. During that period we focused on improving the documentation for the existing TLVs and developing closer ties with Dr. Helmut Greim and the German *maximale Arbeitsplatz Konzentration* (MAK) commission and with other groups involved in setting occupational exposure levels. To increase the epidemiologic strength of the TLV committee, we added Drs. Philip Guzelian, William Waddell, and Ian Greaves to the committee and we recruited Drs. Bob Scala, Karl Rozman, and Roger Smith to strengthen the toxicology input. In addition to stimulating the interest of the committee in kinetics and Structure Activity Relationships, Dr. Rozman served as liaison to the German MAK commission. The major hurdle to the harmonization of TLVs with MAKs or other occupational exposure limits in Europe is the result of differences in our approach to genotoxic agents and carcinogens. With the dedicated but patient efforts of Dr. Helmut Greim and the members of the MAK commission and the TLV committee, we have made significant progress in resolving these issues. We have also moved closer to the idea of sharing resources in the preparation of common documentation for occupational exposure limits. Because all such documentation is based on the same toxicology and epidemiology databases, different exposure-setting groups or countries could use the same basic documentation and customize the rationale for their individual occupational exposure levels as needed.

THE FUTURE

Before speculating on the future of toxicology, I would like to briefly consider its current condition. Toxicology, like medicine, is both a science and an art. The science of toxicology consists of the observational or data gathering phase, and the art of toxicology is the predictive or application phase. In most cases, the science and the art of toxicology are linked because we use the facts provided by the science of toxicology as the basis for the prediction or hypothesis regarding the potential adverse effect of exposure to an agent in a situation where we have limited information. For example, the argument that chloroform is a carcinogen is a fact because it has been shown to cause cancer in rodents, but the prediction that it will also cause cancer in humans is a hypothesis. We now have several hundred agents that are known to cause cancer in rodents, and although some of these would probably do so in humans, there are actually only a few dozen known human carcinogens. By distinguishing between the science and the art of toxicology, we recognize that the validity of our prediction or hypothesis depends not only on the quality of the science in the toxicology data base but also on the relevance of that information to the species or situation for which we are predicting. When we fail to clearly distinguish between the science and the art of toxicology, we tend to confuse our facts with our hypotheses and argue that they have equal validity,

which they clearly do not. Separating the science from the art of toxicology can often be helpful in determining whether flaws in our risk assessments are the result of problems in the data gathering process or occur because of how we analyze or interpret the data from the toxicology and epidemiology data bases.

During recent years we have witnessed a virtual explosion in the science of toxicology. This has resulted primarily from the contributions of molecular biology and transgenic technology (we now have over 1000 types of knockout mice) to understanding toxicologic mechanisms of action. There have also been major advances in neuro- and immuno-toxicology, in the use of alternative species as predictors, and in other areas related to hazard identification. Advances in the art of toxicology have been less dramatic and have focused primarily on new approaches for exposure assessment and on dose response. Thus, for the two major problems in risk assessment (species-to-species and high to low dose extrapolations) it is likely that we will make more progress in resolving the species-to-species extrapolation issues because these can and are being resolved by advances in the science of toxicology.

Although toxicologists attribute the axiom "the dose makes the poison" to Paracelsus, this concept is much older. Publius Terentius Afer (also called Terence) (c. 190–159) suggested "moderation in all things" in *Andria* (*The Lady of Andros*) (7:96), and there is a similar biblical admonition in Proverbs 25:27. Based on this principle, toxicologists conclude that there are no safe chemicals because all chemicals will be toxic under some conditions of exposure. Conversely, we also conclude that there is no chemical that cannot be used safely by simply reducing the exposure. Distinguishing between a safe and a toxic dose for any chemical or agent is determined by our ability to establish a threshold for its adverse effects. This is more complex for agents that have low-dose beneficial effects, such as drugs, or are essential nutrients because the dose responses for the beneficial and adverse effects may overlap.

This phenomenon of low-dose stimulation by toxic agents is called hormesis by Calabrese, who has linked it to the Arndt-Schultz law (8). Most drugs and other chemicals exhibit more than one type of effect and thus, low-dose effects may appear to be antagonistic to high-dose effects. However, even when the low- and high-dose effects involve the same response, it is likely that these effects have different mechanisms of action. If we use Sagan's definition of hormesis as a paradoxical or unanticipated effect of a toxic agent at low doses (9), then hormesis would be the rule rather than the exception not only in pharmacology but also in toxicology and most other biological sciences. However, the most important contribution of this concept derives from the regulatory implications of hormesis. Because the U-shaped dose-response curves that are characteristic for hormetic agents all have thresholds, the linear multistage or no-threshold approach should not be used for regulating hormetic agents. Furthermore, banning or any approach that relies on a zero tolerance is not appropriate for agents with beneficial effects at low doses. Tolerances for such agents should be established by setting exposure levels that preserve the beneficial effects and protect against the adverse

effects (10). In his dedication to *Toxicology and Risk Assessment*, George Koelle argues that we should abandon the concept of zero tolerance for any regulatory purpose because it lacks a scientific basis (11). The existence of hormesis as a toxicologic or biologic phenomenon also raises serious questions about the validity of using the maximum-tolerated-dose approach in testing for carcinogenesis and about any similar attempt to use a high-dose effect to predict a different low-dose effect.

Faced with the need to develop regulations for exposure to carcinogens in the early 1970s and lacking evidence for carcinogenic thresholds, the EPA developed the linear multistage, or no-threshold, approach for regulating carcinogens. This approach extrapolated the results of high-dose studies in animals to zero, and the slope of this line was used to estimate the potential human health risk at very low exposures. This extrapolation had two errors; First, it assumed that time is not a variable of exposure at low doses and second, it used zero rather than one molecule as the intercept for the extrapolation. Biological effects result from the interaction of chemical and host molecules and do not occur with less than whole molecules. Thus, one molecule is an absolute threshold dose for every chemical, including both genotoxic and nongenotoxic carcinogens. It is also more informative when expressing such data graphically to define thresholds in terms of the number of molecules of the agent rather than as dose per body weight or with surface area metrics (12).

The Presidential/Congressional Commission on Risk Assessment and Risk Management was concerned by the discrepancies in the way our society currently regulates carcinogens and noncarcinogens, and recommended changes to improve the regulatory process (13). These and other changes are being included in the development of new risk-assessment protocols (14–16), and the new EPA cancer risk guidelines now include a threshold or reference dose option for all carcinogens (17). These changes provide support for previous recommendations that it is time to abandon the linearized multistage approach and use the reference dose or threshold approach for all toxic effects (18–20). This would simplify risk assessment and improve the balance of regulation but would not eliminate all of the high to low dose extrapolation problems.

Rozman has suggested a new paradigm for risk assessment that would address these problems and would also enhance our concepts of toxicology (12, 21–23). This paradigm is based on the recognition that both dose and time are independent variables in exposure. Dose or concentration is a simple variable (number of molecules), whereas time is a complex variable with both kinetic and dynamic time scales in addition to frequency/duration. We can use both variables to define the minimal exposure conditions (worst case) of dose and time that will produce a specific adverse effect with continuous exposure. Plotting the logs of these time and dose values will produce a line with a slope of -1 (Figure 1), which can be described by Haber's Law ($ct = K^H$). The ends of this line are determined by the dose and time thresholds for the specific adverse effects. The time threshold occurs when further increases in dose do not result in any further shortening of the time to

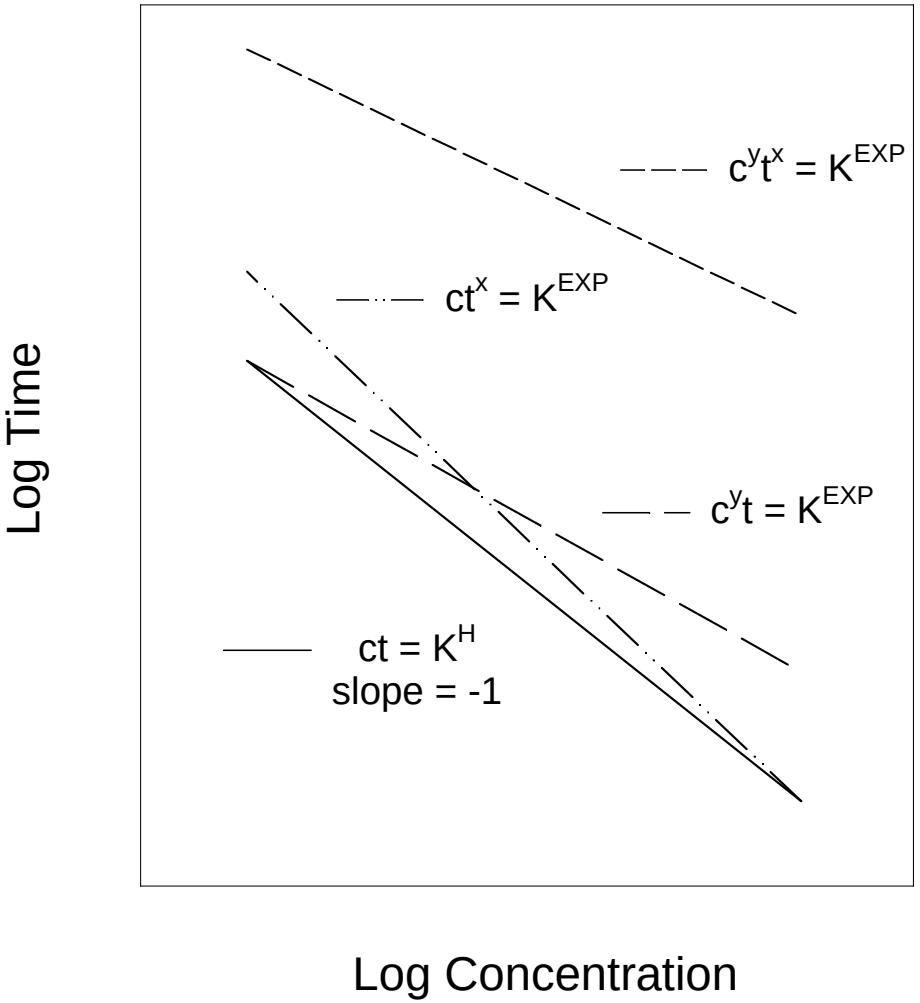

Figure 1 Concentration time relationships using Haber's Law (24)

response, and the dose threshold occurs when increases in time no longer reduce the dose needed for an effect. Practical limits for the dose and time thresholds are provided by the life span (limits dose threshold) and by the amount of material that can be administered to the host (limits time threshold). Because any combination of dose and time that produces values below this Haber's line would not produce the specified adverse effect, this line defines safety. Fractionation of either the dose or time will produce lines with different slopes and *K* values ($ct^x = K$, $ct^y = K$), as will fractionation of both dose and time values ($c^x t^y = K^{EXP}$). To establish a margin of exposure for any real-world situation, we can simply compare the

K values for the real world or experimental situation and the Haber's or worse case situation (margin of exposure $= K^{EXP}/K^{H}$).

The advantages of this approach over the methods currently used in risk assessment are that it is based on actual data rather than on defaults, assumptions, models, or other hypothetical guidelines and that it allows us to base our decisions on safety rather than risk. Furthermore, this paradigm, like the principle of dose response, is independent of any mechanistic considerations. Although this approach provides a new paradigm for risk assessment, the concept inherent in Haber's Law has been used for many years by the National Academy of Science/National Research Council Committee on Toxicology and by groups both in this country and abroad to evaluate and predict hazards. The line in Figure 1 represents a single effect in a single species, but similar lines could be obtained for other effects (either adverse or beneficial) and other species. The first step in using this approach to evaluate toxicity is to determine which of the candidate's toxic effects is most critical, and the second is to determine whether the critical toxic effect is mediated primarily by the toxicokinetics or the toxicodynamics of the agent. Toxicity will only be produced by continuous or fractionated exposure when intake exceeds elimination (via distribution, metabolism, or excretion) or when injury exceeds recovery (via recovery, repair, or adaptation). For chemicals with a very long half life, such as mirex or dioxins, kinetics is likely to be the mediating or rate-limiting step, whereas dynamics is likely to be rate limiting in chemicals that produce persistent damage, such as nitrosomines (24). This concept has implications for both the science and the art of toxicology and could be important for other disciplines in which time is an independent variable.

It seems clear that the future of the science of toxicology is promising and will be exciting. However, the future of the art of toxicology may depend on the recognition by toxicologists that it is fundamental part of our discipline and is worthy of greater attention. In the final remarks of his prefatory chapter, Bob Neal (25) admonished toxicologists to "take a more active role in refuting public announcements of chemical risk by other scientists and by the print and electronic media that are not based on a scientific objective evaluation of the available data." In a previous similar commentary, Bob and I suggested that toxicologists also need to be more responsible in presenting the results of their own studies and evaluations (26). We tend to focus on the trees of our individual findings or opinions rather than on the forest of public health. Writing in a similar vein, Scala suggested that scientists must become democratically accountable to the broader needs of society in order to sustain societal support (27). The common thread of these messages suggests that the mandate of toxicology is not to use "what if" predictions to produce media headlines or to stimulate funding to investigate phantom risks, but it is rather to improve public health. To do this we must tell both sides of the story. There is a statue of Albert Einstein in the front yard of the National Academy of Sciences, and carved into its base are some of his quotes and observations. One of these that I think is particularly appropriate for toxicologists, risk assessors, and all scientists is "The right to search for truth

implies also a duty; one must not conceal any part of what one has recognized to be true."

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LITERATURE CITED

1. Hutchens JO. 1948. The Tox Lab. *Sci. Mon.* LXVI:107–12
2. Goldstein A. 1997. A rewarding research pathway. *Annu. Rev. Pharmacol. Toxicol.* 37:1–28
3. Nelson SR, Walaszek EJ. 1976. A history of pharmacology at Kansas University. *J. Kansas Med. Soc.* LXXVII:339–43
4. Woods LA, Doull J. 1991. GRAS evaluation of flavoring substances by the expert panel of FEMA. *Regul. Toxicol. Pharmacol.* 14:48–58
5. Natl. Acad. Sci./Natl. Res. Counc./Comm. Toxicol. 1999. Four decades of scientific service: a celebratory colloqium. *Inhal. Toxicol.* 11:455–636
6. Cook WA. 1985. History of ACGIH TLV's. In *Ann. Am. Conf. Gov. Ind. Hyg*., 12:3–9. Cincinnati, OH: ACGIH. 389 pp.
7. Bartlett J. 1981. *Familiar Quotations 15th and 125th Anniversary Edition*, ed. EM Beck. Boston/Toronto: Little Brown
8. Calabrese EJ, Baldwin LA. 1999. Chemical hormesis: its historical foundation as a biological hypothesis. *Toxicol. Pathol.* 27:195–216
9. Sagan L. 1993. A brief history and critique of the low dose effects paradigm. *Belle Newsl.* 2(2):1–7
10. Rozman KK, Doull J. 1999. Hormesis, regulation, toxicity and risk assessment. *Belle Newsl.* 8(1):2–6
11. Koelle GB. 2000. Dedication: the zero tolerance concept. In *Toxicology and Risk Assessment*, ed H. Salem, EJ Olajos, pp. vi–ix. Philadelphia: Taylor & Francis
12. Rozman KK, Kerecsen L, Viluksela MK, Osterle D, Deml E, et al. 1996. A toxicologist's view of cancer risk assessment. *Drug Metab. Rev.* 28:29–52
13. Risk Commission. 1997. *Risk Asseement and Risk Management in Regulatory Decision Making in U.S.* Comm. Risk Assess. Risk Manage. Final Rep., Vol. 2. Washington, DC: GPO #055-000-00568-1
14. Crump K. 1996. The linearized multistage model and the future of quantitative risk assessment. *Hum. Exp. Toxicol.* 15:787–98
15. Gaylor DW, Kodell RL, Chen JJ, Krewski D. 1998. A unified approach to risk assessment for cancer and noncancer endpoints based on benchmark doses and uncertainty/safety factors. *Regul. Toxicol. Pharmacol.* 29:151–57
16. Gaylor DW, Kodell RL, Chen JJ, Krewski D. 1989. A unified approach to risk characterization. *Inhal. Toxicol.* 11:575–78
17. Environ. Prot. Agency. 1996. Proposed guidelines for carcinogenic risk assessment. *Fed. Regist.* 61(79):17960–8011
18. Lu FC, Sielkin RL. Assessment of safety/risk of chemicals: inception and evolution of the ADI and dose response modeling procedures. *Toxicol. Lett.* 59:5–40
19. Doull J. 1994. Back to basics. *Int. J. Toxicol.* 16:185–91
20. Purchase IFH, Auton TR. 1995. Thresholds in chemical carcinogenesis. *Regul. Toxicol. Pharmacol.* 22:199–205
21. Rozman KK. 1999. Delayed acute toxicity of 1,2,3,4,6,7,8-heptachloro dibenzo-p-dioxin (HpCDD) after oral administration obeys Haber's rule of inhalation toxicity. *Toxicol. Sci.* 49:102–9
22. Rozman KK, Doull J. 2000. Dose and time as variables of toxicity. *Toxicology* 144:169–78
23. Rozman KK. 2000. The role of time in toxicity or Haber's ct product. *Toxicology* 149:35–42

24. Doull J, Rozman KK. 2000. Using Haber's law to define the margin of exposure. *Toxicology* 149:1–2
25. Neal RA. 1996. A career in toxicology. *Annu. Rev. Pharmacol. Toxicol.* 36:35–46
26. Neal RA, Doull J. 1995. Commentary: the discipline of toxicology. *Fund. Appl. Toxicol.* 24:151–53
27. Scala RA. 1998. Reflections. *Int. J. Toxicol.* 18:1–6