Toxicology at the University of Rochester: From the Manhattan Project to the Environmental Basis of Human Diseases

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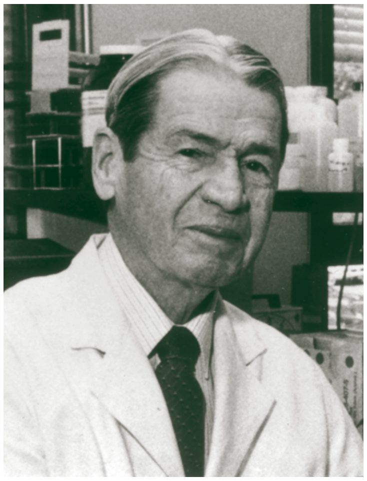
The University of Rochester has a long history as an internationally recognized center for research and training in toxicology. The genesis of toxicology at Rochester can be traced back to World War II when the Manhattan Project sponsored critical studies on health problems associated with atomic energy and weapons production. Over the years, the research has evolved with advances in science and technology, but has preserved its interdisciplinary nature, with a strong emphasis on the basic principles that now define the field of toxicology. Until 1961, toxicology had remained a somewhat orphan discipline, grafted on well-established fields such as pharmacology or biochemistry, but it possessed no clear identity on its own. Like nuclear physics, World War II had called on it to create new science. It responded with technologies such as inhalation toxicology, prompted, like physics, by the demands of the Manhattan Project.



Harold C. Hodge, first President of the Society of Toxicology

A band of scientists, some of whom had served the Manhattan Project, came together to form the Society of Toxicology (SOT). Harold Hodge of the University of Rochester became its founding President and presided over the first Annual Meeting of SOT in 1962. Not one of the founders possessed a degree in toxicology, but they agreed that the "…Society should encourage universities to set up departments of toxicology…". It was in essence a call to arms that was answered by the University of Rochester, whose history uniquely equipped it for this leadership role. Rochester was the first institution to establish specific formalized pre-doctoral and postdoctoral training programs in toxicology, in 1965. Since their inception, these programs have provided state-of-the-art training in the environmental health sciences, and have placed its graduates in significant leadership positions in academia, government, industry and other occupations related to environmental health and public policy. Over 160 students have earned a Ph.D. in toxicology and over 110 postdoctoral fellows were trained from 1965–2009.

Genesis of Toxicology at Rochester

In 1943, the Atomic Energy Commission chose the University of Rochester as the site to examine the potential adverse human health effects of atomic energy production (the Manhattan Project). Rochester was selected for this project in part because of its strong interdisciplinary and interdepartmental approaches to solving human health problems. In these early translational toxicology studies, teams of clinicians and basic scientists from different disciplines worked closely together to determine the health effects of uranium, fluorides, mercury and other agents used in the process of nuclear weapons production. These endeavors focused on identifying routes of human exposure, defining mechanisms by which these elements would impair function, assessing vulnerability at different life stages, and developing approaches that could ameliorate toxicant burdens in target tissues. During the years of World War II, the Manhattan Project focused largely on the toxicology of the different forms of uranium, but also examined the toxicology of polonium, radium, plutonium, radon, fluorine, and fluorides. It also contributed to the development of basic instruments for the detection and analysis of exposure to these agents, and there was a large genetic study in the mouse on the effects of X-rays, which served as a pilot study for a large mouse experiment performed post-war at the Oak Ridge National Laboratory in Tennessee.

When the Manhattan Project was established in Rochester, Harold Hodge (Morrow *et al*. 2000), who had joined the University's Biochemistry Department in 1931, was selected to lead the newly created Division of Pharmacology and Toxicology. The primary goal of this Division was to evaluate the toxicology of inhaled materials being utilized and developed in the atomic energy program. The initial focus of Hodge's Division was on the inhalation toxicology of uranium and beryllium. This early work was spearheaded by Herbert Stokinger, a pioneer in the field of inhalation toxicology. The term "Rochester Chamber" was coined at that time and remains well known today, and Rochester quickly gained a reputation internationally for its inhalation toxicology program and its work with metals.

Under the leadership of J. Newell Stannard, Rochester also made major contributions to research on the health effects of radiation and to the education of students in both basic and applied radiation protection. In 1950 Newell Stannard developed the world's first Ph.D. program in radiation biology, whose graduates made significant contributions to radiation protection and related professions in industry, education, research, medicine, and government.

What emerged from this wartime project was an international resource in the toxicology of metals and inorganic elements that remains one of the strengths of the research programs at Rochester. This tradition of interdisciplinary and translational research continues to this day, Rochester being among the first institutions selected by NIH to lead the emerging field of clinical and translational research, with the establishment of the Rochester Clinical and Translational Science Institute (CTSI) in 2006. The award to Rochester recognized its strengths in interdisciplinary programs, ability to train successful academic researchers, and in producing innovative technology and methods that can efficiently treat patients.

Expansion of Toxicology Research in the Fifties and Sixties

Since the early studies on uranium in the forties, Rochester has pioneered the joint application of aerosol physics and pulmonary biology to control and quantify inhalation exposure of both animals and humans. At the end of World War II, the Department of Radiation Biology was formed, and this allowed the wartime research to continue on an academic footing. The studies of fluoride toxicity, originating from uranium hexa-fluoride used in the Manhattan Project, blossomed into a major research theme that was directed by Harold Hodge, Frank Smith and Don Taves. Their work contributed to the scientific basis for establishing the fluoridation of drinking water in the USA and abroad (Hodge and Smith, 1968).

During this time period research in toxicological questions also broadened from inhalation toxicology and metals used in the atomic bomb, to other metals of environmental relevance and in particular mercury, as well as to areas of radiation biology, cancer, and the more subtle neurotoxic effects of environmental agents. The leaders of the Department of Radiation Biology, William Neuman and Aser Rothstein, were visionaries in this emerging new discipline of toxicology, and expanded the Rochester program by recruiting talented scientists in related basic science areas. The initial steps toward behavioral toxicology research were taken by Harold Hodge. Traveling on a plane home from a trip to Oak Ridge National Laboratory, where he had consulted on the toxicity of mercury, he recalled that Lewis Carroll was of course describing a behavioral change when he created the Mad Hatter. He soon was planning a research program on poisoning by mercury vapor. Guided by P.B. Dews and W.H. Morse of Harvard, Hodge initiated a study that "was the very first to examine how chronic mercury poisoning affected any aspect of an intact animal's biological functioning, as well as apparently the first to use schedule-controlled behavior to study a toxic substance" (Laties and Wood, 1986, page 77). The success of this research (Armstrong *et al*., 1963), led directly to the recruitment of Bernard Weiss and Victor Laties in 1965 from Johns Hopkins University to expand this novel program in behavioral toxicology.

Over the past four decades, Weiss and Laties have been instrumental in establishing neurotoxicology as a respected scientific discipline (Weiss and Laties 1969). These neurobehavioral studies at Rochester remain at the forefront of toxicology and are currently guided by Deborah A. Cory-Slechta as part of the Neurodevelopmental Disorder & Neurodegenerative Disease Program of our Environmental Health Sciences Center (EHSC).

Tom Clarkson (center, left) and his trainees

Likewise, studies on the toxicology of mercury, started in the fifties, lead to the recruitment in 1965 of Thomas W. Clarkson, an expert on mercury toxicology. Mercury research at Rochester was in response to occupational exposure to mercury vapor as a result of the enormous quantities of liquid mercury needed for the production of lithium deuteride used as fuel for the hydrogen bomb (literally millions of pounds of liquid mercury). Tom Clarkson and his subsequent trainees quickly established an internationally recognized program in mercury disposition, biochemistry, and human health effects. An especially important contribution to the mercury program came from Tor Norseth, one of the first Ph.D. students in the newly established Rochester toxicology Ph.D. program. Norseth, an M.D. from the University of Oslo with a career interest in occupational health, made groundbreaking studies on the metabolism of methylmercury in his Ph.D. thesis that helped to place Rochester as a National center in mercury toxicology by 1970. The visiting scientist program of the Rochester EHSC also contributed to Rochester's strengths in mercury toxicology. Laszlo Magos, a visiting scientist from the Toxicology Unit of the Medical Research Council in the U.K., established a new analytical method for mercury that has been used worldwide even to the present time. When national concern broke over the discovery of methylmercury in fish in the Great Lakes at about this time, Rochester was in a unique national position to respond. The National Science Foundation, through its new program entitled "Research Applied to National Needs," awarded Rochester a large program project grant to support the mercury studies. The new staff and students assembled by this program also placed Rochester in a position to assist the health authorities in Iraq in dealing with the major outbreak of methyl-mercury poisoning related to tainted grain that erupted in that country in 1971–72.

As the dose-response relationship is the cornerstone of the science of toxicology, it is of interest that the studies in Iraq established for the first time two dose-response relationships in human subjects, first for exposure of adults (Bakir *et al.* 1973) and next for prenatal human exposure to ethylmercury (Cox *et al.* 1989). These relationships have been used ever since by expert national committees charged with setting health guidelines for methylmercury exposure. Subsequent studies on fish eating populations, such as the current child development study in the Seychelles Islands, were designed to see if the Iraq dose response relations based on subjects eating contaminated grain predicted the outcome of exposure to methylmercury in fish (Myers *et al.*, 2000). One of the major recent findings of the Seychelles child development study is that components of the diet such as the omega-3 fatty acids in fish tissues can modify the toxic action of methylmercury (Davidson *et al.* 2008).

The late sixties saw the birth of the Rochester Conference series. These annual conferences, with the proceedings published in book form, served as an enrichment to both research and training. The first conference, held in 1969 and organized by Morton Miller and George Berg, had the singularly appropriate title of "Chemical Fallout" indicating the transition from atomic energy related projects to more broadly based chemical pollution (Miller and Berg, 1969).

The Seventies And Eighties: Mercury Toxicology, Drug Bioactivation and Elimination, and Receptor-Mediated Toxicology

The NIEHS-funded Environmental Health Science Center (EHSC) grant at Rochester was first awarded to Tom Clarkson in 1975, and its emphasis on methylmercury was based largely on the groundbreaking studies in exposed human populations. At that time, there were 22 members of the EHSC, representing eight Medical Center basic science and clinical departments. At present there are 47 EHSC members representing 13 different departments.

The Rochester programs have been greatly enhanced by close interactions with clinical departments, in particular with the Departments of Medicine and Pediatrics. In the late seventies, under the leadership of Paul E. Morrow, a specialized clinical inhalation facility was developed in the NIH-supported Clinical Research Center. The human inhalation facilities developed there have been widely adopted by other programs. Research performed in Rochester's facility made critical advances in understanding lung function, size-dependent aerosol and particle deposition and retention, and the cell biology and mechanisms of the lung's response to injury. Results of the combination of state-of-the-art experimental animal research and strong human inhalation facilities in a clinical setting has led to a recognition that inhaled particles, and in particular ultrafine and engineered nanoparticles, can affect not only the lung but also the cardiovascular and nervous systems. This scientific leadership and tradition of excellence in lung biology and toxicology continues in the Pulmonary and Cardiovascular Disease Program of our Environmental Health Sciences Center, as well as in the EPA-supported Particulate Matter Center directed by Günter Oberdörster, and the Lung Biology and Disease Program directed by Richard P. Phipps.

In the eighties, the EHSC gave further focus to cellular and molecular mechanisms of toxicity and recruited several new faculty, including Tom Gasiewicz, Angelo Notides, and Ned Ballatori, to bring in new research approaches. The origin of this research program was the elegant structure-activity relationships of the dioxins described by Alan Poland's research at the University of Rochester in the seventies (for a review, see Poland and Kende, 1976). There was an emphasis on receptor-mediated mechanisms, cell signaling pathways and altered expression of genes as targets of environmental toxicants, and transport processes. In 1982, M.W. Anders was recruited to the University of Rochester as chair of then Department of Pharmacology, which eventually merged with the Department of Physiology to become the current Department of Pharmacology and Physiology. Anders is an expert on chemical bioactivation and the role of cellular cytoprotective mechanisms in modulating toxicity. He recruited additional scientists with overlapping interests, and spawned the creation of a Mitochondrial Research Interest Group, whose focus is on mitochondrial pharmacology and toxicology.

The Nineties to the Present: Osteotoxicology, Environmental Agents as Risk Factors for Disease, Latent Effects of Early Environmental Exposures, and Stem Cells as Sensitive Targets

The collective strengths in environmental health sciences research at Rochester resulted in the formation of the Department of Environmental Medicine in 1992 with Tom Clarkson as its first Chair. The creation of the Department of Environmental Medicine enhanced and further focused the strengths in environmental health sciences research in Rochester and the institution's commitment to these programs. The scope of the toxicology programs was then broadened by the award of a grant from NASA supporting a Center in Space Toxicology. The Department of Environmental Medicine continues to be the administrative home of both the NIEHS-funded Environmental Health Sciences Center and the toxicology training program, an arrangement that has proven to be of great mutual benefit. It has been mainly through this administrative structure that environmental health research has become widely integrated across the University of Rochester.

In the early nineties, the EHSC made several Pilot Project awards to individuals within the Department of Orthopedics who, in collaboration with several EHSC members, were examining the long-term consequences of bone as a storage site for several metals, particularly lead (Pb). Subsequent research led to the discoveries that not only does Pb concentration in bone serve as a risk factor for the development of osteoporosis, but that humans with elevated Pb levels may suffer from different types of other bone diseases. These studies along with others eventually led to the formation of a musculoskeletal disease program within the EHSC, headed by Edward Puzas.

In addition to the EHSC, this department also administers the Particulate Matter Center, one of six such Centers supported by the U.S. Environmental Protection Agency (U.S. EPA), directed by Günter Oberdörster. Faculty within the Particulate Matter Center carries out cutting-edge research on the relationship between air pollution and lung and cardiovascular diseases. These studies aim to identify health hazards of sourcespecific physicochemical components of fine particulate matter (e.g., ultrafine particles and organics) in epidemiological, controlled clinical, animal, and *in vitro* studies. A main focus is on sources and on pathophysiological mechanisms by which ambient ultrafine/fine particulate matter trigger adverse cardiovascular health effects, with specific emphasis on events leading to endothelial dysfunction. Such studies are important for risk assessment and will serve to strengthen risk management decisions with respect to regulatory actions. The Department of Environmental Medicine also houses the Division of Occupational Medicine, headed by Mark Utell, whose clinical specialists play an active role in graduate education.

Rochester has also established a Multidisciplinary University Research Initiative (MURI), a Department of Defense program that supports research teams from the University of Rochester, University of Minnesota and Washington University at St. Louis, and that combines biomedical and engineering sciences to uncover potential adverse effects and identify underlying mechanisms of nanoparticles/cell interactions.

The theme of environmental agents as risk factors for disease continues across investigations being carried out at Rochester. Some faculty are examining the role of environmental exposures as cofactors in neurodegenerative diseases such as Alzheimer's and Parkinson's. EHSC scientists are also examining the concept that the developing nervous system may be especially sensitive to some chemicals, and that neurological effects may not be manifest until years after exposure. Latent effects of early environmental exposures have also become the focus of other investigations. Shanna Swan was recruited to Rochester in 2005. Swan along with Bernie Weiss and Paige Lawrence are exploring the consequences of prenatal exposure to phthalates and bisphenol A on the developing nervous, immune, and reproductive systems. In conjunction with these studies, other EHSC investigators such as Tom Gasiewicz and Lisa Opanashuk have focused attention as stem cells as being sensitive targets of environmental agents. Kim Tieu is studying molecular mechanisms of neurodegeneration in Parkinson's disease and Huntington's disease, with primary emphases on glial-neuronal interaction and mitochondrial dysfunction. Studies in the pulmonary and cardiovascular program bring together a multidisciplinary group of basic and clinical scientists whose research focuses on the impact of several types of environmental exposures on cardiopulmonary health. These exposures include ambient and occupational particulates, oxidant gases, ionizing radiation, and engineered nanoparticles. Several faculty members are investigating the pathogenesis of pulmonary inflammation and fibrosis (including Jacob Finkelstein, Richard Phipps, Gloria Pryhuber, Irfan Rahman and Patricia Sime). Other faculty, including Günter Oberdörster, Mark Utell, Mark Frampton, and Alison Elder, are examining the potential of inhaled potential ambient particulate matter to induce effects/diseases in secondary target organs. Yet additional faculty is investigating the increased vulnerability of the adult respiratory tract towards inhaled pollutants due to early life exposures (Finkelstein, Paige Lawrence, Michael O'Reilly, and David Topham).

In the past five years, environmental health sciences research at Rochester has continued to undergo significant growth and evolution. In particular, pathways for clinical/translational research have been enhanced. At present, 30 percent of the EHSC faculty is physicians. This breadth of training and expertise is a key strength of Rochester, allowing the formation of collaborative groups to address pressing issues in environmental health at levels that span basic to translational efforts. A continuing strength of the Department of Environmental Medicine and of our EHSC are the many community outreach and education programs, directed by Dina Markowitz and Katrina Kormacher, whose goals are to address the environmental health issues and concerns identified in the community through a Community Advisory Board and partnerships with community groups, and to provide information and education related to environmental health issues to concerned citizens, educators, children, and health professionals.

Development of Toxicology Training Programs

In 1965, Harold Hodge along with William F. Neuman, and Aser Rothstein, co-chairs of the Department of Radiation Biology, formally established the environmental toxicology training program, and obtained permission to award the Ph.D. in Toxicology from the New York State Board of Regents. It was the first such program in the U.S. Tom Clarkson became the program's first director, as well as director of the NIGMS training grant that initially supported this training program, in 1966. The first toxicology Ph.D. students and postdoctoral fellows were supported on an NIGMS training grant, which was replaced by an NIEHS grant in 1978, and this NIEHS grant is still active. John C. Smith, who succeeded Tom Clarkson as training director in 1975, was program director for this grant until he left Rochester in late 1978. Victor Laties served as program director from 1978–91, and was succeeded by Tom Gasiewicz. In 1999, Tom became department chair and EHSC Director, and stepped down as training program director, to be succeeded by Ned Ballatori, the current Director.

The first two Rochester toxicology Ph.D. degrees were awarded in 1970 to John E. Ballou and Tor Norseth. Since that time 163 students have earned the Ph.D. in toxicology, and over 110 postdoctoral fellows received advanced training in toxicology. In early 2010, we had 30 toxicology Ph.D. students and 16 postdoctoral fellows in residence.

The current Rochester environmental toxicology training faculty comes from 13 different basic science and clinical departments, and its members are highly interactive, as evidenced by the large number of joint grants and publications. The training faculty's strong focus on the environmental health sciences is evidenced by their publications, grant support, trainee research projects, and participation in relevant societies, centers, and advisory boards.

Current faculty research programs span the entire spectrum of toxicology, from molecular mechanisms to cellular processes to whole animals and human populations. Areas of emphasis now include: Neurotoxicology, pulmonary toxicology, osteo-toxicology, molecular modifiers of toxicity, immunotoxicology, and reproductive and developmental toxicology. A distinguishing feature of the training program is its remarkable collegiality, evidenced by the extensive research collaborations among its faculty members and trainees. These interactions are fostered by the Medical Center's history and tradition, its administrative organization, its geographic layout, and by the formation of research centers and programs of excellence. The entire Medical School, School of Nursing, and Hospital complex is under one roof, a result of the founding Dean's belief that scientists should be within "bare-headed" distance of their colleagues. This close physical proximity makes it easy for faculty and students to interact, share reagents, and utilize common facility cores, thereby greatly expanding research and training opportunities. There are currently 382 medical students, 48 M.D./Ph.D. students, 394 Ph.D. students, 159 postdoctoral fellows, over 200 clinical fellows, and 437 nursing students in residence at this school, all under one roof. Moreover, normal departmental boundaries, both physical and scientific, are rather loosely defined, and faculty members are strongly encouraged to collaborate with other basic science and clinical faculty. The Ph.D. programs and our research centers and programs are all highly interdisciplinary, thereby generating many opportunities for collaboration. The overall graduate program is considered an important mechanism that facilitates these interdisciplinary interactions. An additional strength of the toxicology training program is the extensive base of research support, particularly that provided by the NIEHS. The high level of funding offer trainees a unique opportunity to learn modern research approaches while addressing significant issues in toxicology. The program is also enhanced and distinguished by the presence of an NIEHS-sponsored EHSC within the Department of Environmental Medicine. As noted above, the Rochester EHSC was established in 1975, and has had a major influence on the Toxicology Training Program by serving as a focus for much of the research carried out by its trainees. At the same time, the continued excellence of the research programs within the EHSC is highly dependent upon a strong graduate training program. As indicated above, 29 of the 37 training program faculty are members of the EHSC, and most of the graduate students are in laboratories of EHSC faculty. The synergy between the Toxicology Training Program and the EHSC is facilitated by the many enrichment and outreach activities that are sponsored by these programs, and by the presence of a full-time program coordinator for the training program and a full-time director of the EHSC's community outreach programs, who help to orchestrate all of the various trainee- and outreach-related events. For example, graduate students and postdoctoral fellows can take advantage of opportunities to volunteer with local community-based organizations on outreach and education projects dealing with issues in environmental health such as childhood lead poisoning.

In addition to the environmental toxicology program, from 1992 to the present Rochester has also administered a program in environmental health biostatistics, which is directed by David Oakes. The environmental biostatistics training program is a collaborative effort between the Department of Biostatistics and Computational Biology, the Department of Community and Preventive Medicine, and the EHSC. This program, which was recently renewed through 2014, supports two predoctoral and two postdoctoral students in each year. The program provides training in biostatistical methodology and its application to environmental health sciences, with the ultimate goal of increasing the number of qualified biostatisticians involved in environmental health research. Since 1999 Rochester has also administered a clinical pulmonary training grant, directed by Mark Frampton and Richard Phipps. This training program aims to develop skilled investigators with research-oriented careers directed at solving basic and clinical problems in lung disease, and spans a variety of disciplines, including toxicology.

The Future of Toxicology at Rochester

The long-term goals of environmental health sciences research and training at the university remain focused on carrying out basic and clinical research in environmental health to develop effective preventive, intervention, and therapeutic measures that affect public health and public health policies. Utilizing our established strengths, we will continue to define the relationships between environmental exposures and the development and outcomes of pulmonary and cardiovascular disease, neurodevelopmental and neurodegenerative diseases, and musculoskeletal diseases. Some of these approaches will use existing models and develop/improve more realistic models that are relevant to human exposures and disease. This will include moving beyond the impact of exposure to single toxicants to consider multi-pollutant exposures, modifiers, and other risk factors that determine cumulative risks to humans. Some of the new and emerging areas of focus will include the role of epigenetics in the fetal basis of adult disease, stem cells as targets of environmental agents, dietary interventions in environmentally-related diseases, and the toxicology and biokinetics of engineered nanoparticles.

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Figure 3. Tom Clarkson with some of his former students and postdoctoral fellows at the University of Rochester's 2006 SOT reception. From left: Ned Ballatori, James T. MacGregor, Tom Clarkson, Tore Syverson, Paul J. Kostyniak, and Michael Aschner.