Melvin E. Andersen Receives ATS 2016 Mildred S. Christian Career Achievement Award

Dr. Melvin E. Andersen received the Mildred S. Christian Career Achievement Award from the Academy of Toxicological Sciences at the ATS Annual Reception on March 16, 2016. The annual ATS reception is held during the Annual Meeting of the Society of Toxicology.

ATS established the Mildred S. Christian Career Achievement Award to honor the memory of Dr. Christian. Millie was one of the founders of ATS, one of its early presidents, and secretary-treasurer for many years. She devoted a significant amount of passion and hard work to establish ATS as a scientifically recognized organization. The Award is conferred to an ATS Fellow in good standing who has clearly demonstrated a lasting impact on toxicological sciences and extraordinary scientific achievement through publications, professional activities, and/or leadership that have enhanced the practice of toxicology.

Dr. Melvin (Mel) Andersen received the 2016 Mildred S. Christian Award at the ATS business meeting at the Society of Toxicology Meeting in New Orleans. The following text covers the key points made in Mel's short talk at the meeting.

"First, let me express my thanks to you, Dr. Holsapple, and the Academy on honoring me with the 2016 Mildred Christian Award. This award, in its sixth year, has gone to a distinguished group of career toxicologists. I feel extremely honored to be included with these individuals as a recipient of this award. In the next 8 -10 minutes, I'd like to tell you all about the indirect route that led me to toxicology and reflect on lessons learned in my 45-career.

Some of you may know that my late-career achievements also include playing harmonica in a blues band (The Belladonna Blues Band – www.belladonnabluesband.com). The lead singer, bass guitar player, lyricist is Harvey Clewell with Jerry Campbell on rhythm guitar. We produced one CD in our time together: Belladonna Blues Band – The Toxic Years.

My title of my talk this evening has a similar ring to it:

Mel Andersen: Accidental Toxicologist – The Early Years (1971-1990).

My training in college was in chemistry at Brown University (1967) followed by a PhD in biochemistry and molecular biology from Cornell University (1971) studying oxygen binding and protein association processes with hemoglobin from lampreys (primitive jawless fish). Looking back, it's fair to say that I am a chemist by training, by inclination, and likely by birth. In addition, I met my wife in high school chemistry in Cranston Rhode Island. Clearly, there was a lot of chemistry in chemistry for me.

In 1970, I was accepted to do post-doctoral fellowship at Woods Hole Oceanographic Institute on Cape Cod (only 50 or so miles from my home in Cranston, RI) and study the binding of oxygen and other small molecules to hemoglobin from large-bodied sharks and bony fishes – that is elasmobranchs and teleosts. The selective service system and the military draft had other ideas. At the end of 1970, a letter came informing me that I would be drafted at the beginning of the calendar year in 1971. To side-step the draft I visited the first recruiter on the main street in Ithaca NY. He represented the US Navy and told me the Navy needed a biochemist in Bethesda, MD. It was a bit of false-advertising. What the Navy really wanted was an individual to run a clinical chemistry laboratory at the US Navy Toxicology Unit (NTU) – an organization established in 1962 to examine the safety of naval operational environments, with particular attention on adverse effects that might arise from contaminants or operational chemicals found in submarine atmospheres. The workhorse experimental systems at NTU were 2 cubic meter Rochester exposure chambers in which we simultaneously exposed rats, guinea pigs, squirrel monkeys and beagle

dogs to gases and aerosols for 23.5 hours per day – every day for 90 days. The exposures were meant to mimic a seaman's 90-day tour on a nuclear submarine. Our Officer-in-Charge, CAPT Jacob Siegel had been involved in creating and running the toxicology programs at NTU. He was a charter member of SOT. In addition to inhalation studies, I also had responsibilities for conducting ocular, skin and acute toxicity tests with various materials. The posting gave me a crash course in occupational toxicology and industrial hygiene.

One of my first projects was examining the toxicity of an airborne contaminant that was found at low levels in some submarine atmospheres – 1,1-dichloroethylene (1,1-DCE). This compound is converted in the body to a highly toxic metabolite – likely chloroacetylchloride – and causes severe, fatal liver toxicity. The mortality curves with 1,1-DCE were perplexing – both for oral dosing and for short-term (4 hour) inhalation studies. With oral dosing, 72-hour mortality reached a plateau and sometimes even came down at higher doses. With inhalation, the morning after single exposures, the rats were either moribund with blood transaminases over 10,000 units or perfectly fine. My standard deviations were enormous. How was I to make any sense of these mortality curves? My fledgling toxicology reading had already introduced me to probit analysis (which didn't exactly make sense to a card-carrying biochemist accustomed to either linear or semi-log plots) and the expectation that increasing dose should increase response (read mortality with 1,1-DCE) smoothly from 0% responding to 100% responding as dose or concentration increased. Not with 1,1-DCE! It appeared that I was headed for early failure as a practicing toxicologist.

On the other hand, the chemist/biochemist in me became interested in answering a different set of questions. How much 1,1-DCE is metabolized for different dosing/exposure situations? What is the relationship between metabolized dose and lethality? How might a dose response curve change from one species to another, i.e., from the rats to people on board submarines? And, how did the increasing amount of metabolized dose lead to hepatocyte death, liver failure and, ultimately, death of the rats? To a large extent these questions about the chemical and biological basis of incidence-dose relationships have remained the focus of my entire 45-year career while working in eight different organizations, the US Navy (active duty), US Air Force (civil service), Chemical Industry Institute of Toxicology, National Health Effects Laboratory -USEPA, ICF Kaiser, Colorado State University, The Hamner Institutes for Health Sciences and now ScitoVation, LLC. In the larger perspective, my research interests began with pharmacokinetics and throughout the 1990's morphed increasingly to pharmacodynamics and then, cell based incidence-dose modeling in the last 10 years.

To really make progress with my dose-response related questions, I needed to work with individuals with skills in laboratory work and others with skills in computational sciences. In the Navy, I found a gifted, organized young colleague -Mike Gargas. He ran the laboratory and developed key tools using closed chamber, gas uptake inhalation for assessing metabolism of inhaled vapors and gases. He had the good sense to tell me to keep my distance from the lab and not jeopardize the studies. My growing interest, in any case, was in modeling these gas uptake curves, but I had not developed any strong skill set in PK modeling, nor did I have any specific idea of the approach that we should use. Serendipity came along in the form of a request from Dr. Leon Goldberg, the editor of Critical Reviews in Toxicology, for me to expand on our 1,1-DCE research and contribute an article on "Saturable Metabolism in Relationship to Toxicity". While writing this article, I discovered the work going on in physiologically-based pharmacokinetic (PBPK) modeling of cancer chemotherapeutics, led by Drs. Ken Bischoff and Bob Dedrick. Writing this review and discovering PBPK modeling changed the entire course of my career.

In 1978, I left active duty in NTU (which had moved to Wright Patterson AFB in Dayton OH in 1977) to take a civil service position with the US Air Force at the Toxic Hazards Division, Armstrong Aerospace Medical Research Laboratory, also located at Wright Patterson AFB. The Toxicology Branch Chief, Dr. Ken Back (also a Charter member of SOT) and a Branch-PI, Marilyn George, had been impressed with the advances in PK modeling coming from Dr. Perry Gehring and his colleagues at Dow Chemical in Midland, MI and wanted to bring the approach into the Air Force program. They hired me to develop a program to evaluate the pharmacokinetics of compounds used in Air Force operations. I quickly recruited

Mike Gargas to our group. In 1982, the Division Director, Col Mike MacNaughton, recruited a colleague he had worked with at Tyndall Air Force Base, Maj Harvey Clewell, to join our PK team. Harvey (who is now an ATS fellow) arrived in 1983 and provided critical expertise in computational science and computer programming to put our PBPK modeling programs into high gear. His formal training was in chemistry and was a natural fit to the programs.

In a parallel effort, I had initiated collaboration with John Ramsey from Dow Chemical. He had completed extensive studies on the time course and tissue distribution of styrene after inhalation exposures across various concentrations and durations of exposure. We met for the first time at the SOT meeting in New Orleans in 1979. So it is fair to say that the beginning of PBPK modeling in toxicology and risk assessment took place in a room at the Westin Hotel here in New Orleans, 27 years ago. In 1984, John Ramsey and I finally completed our key paper- A Physiologically Based Description of the Inhalation Pharmacokinetics of Styrene in Rats and Humans. This paper highlighted the manner in which PBPK models supported extrapolations of tissue dosimetry across dose, dose route and species.

Then in 1987, a broader team from both Wright Patterson (Harvey, Mike and I) and Dow (Dick Reitz and Fred Smith) published a paper, "Physiologically Based Pharmacokinetics and the Risk Assessment Process for Methylene Chloride", showing the use of a PBPK model to calculate measures of internal dose and conduct a tissue dose based risk assessment. The interest and controversy engendered by this paper within the broader risk assessment community prompted the National Academy of Sciences (NAS) to call a workshop to discuss whether PBPK models were ready for use in risk assessment. In the meeting report (Pharmacokinetics in Risk Assessment: Drinking Water and Health Volume 8) the NAS gave these PBPK methods the seal of approval and the field began a period of rapid growth that continues to this day. Harvey would become increasingly interested in showing how these tools could contribute to resolving challenges in risk assessment. I remained more wedded to developing an understanding of the biological, physiological and biochemical processes that lead to non-linear behaviors for various chemicals in the body and eventually moving to pharmacodynamics and computational systems biology pathway (CSBP) modeling. In 1989, I left Dayton to take a position at the Chemical Industry Institute of Toxicology (CIIT). One positive that came from my leaving Dayton was that over the next 10 years, most of the original Dayton team went on to distinguished careers of their own in a variety of independent positions in areas of toxicology and risk assessment.

So, that's a synopsis of PBPK activities in my early, formative years. Rather than moving on to look at aspects of biologically based dose response and cell based modeling that came after the blossoming of PBPK modeling as a dose-response tool in toxicology/risk assessment, I would like to close the talk emphasizing five lessons from this period of my career – lessons that became key to all my subsequent activities.

1. **Find an important problem!** There is great value in having a clear problem on which to work. In my case, the problem was, and has remained, very broad. What data are required to understand the shape of dose response curves and what types of models work best to create testable hypotheses. You need both: high quality data and good quantitative tools! I have kept my eyes on this problem with single-minded, almost monomaniacal attention. In addition, the consistent focus on this overarching problem has caused me to continually reevaluate the types of experiments and the types of modeling approaches that were necessary. Clearly, the tools for pharmacodynamic modeling in the 1990's were very different from those available in 2016 due to the fabulous advances in understanding cell response pathways and cellular signaling motifs.

2. **Surround yourself with individuals brighter than yourself!** Making progress in any large endeavor requires surrounding yourself with people with diverse skills, all interested in making progress on these problems. I've consistently had the good fortune of working with colleagues much more skilled than I am. In the laboratory there was Mike Gargas in Dayton and various

staff in the latter parts of my career, including Rusty Thomas and Rebecca Clewell at Hamner (now ScitoVation). With respect to computational applications, there was Harvey who has worked with me in various capacities since 1983, then Rory Conolly bringing BBDR approaches using Moolgavkar-Venzon-Knudson models, Qiang Zhang and Sudin Bhattacharya teaching me CSBP modeling, and most recently Patrick McMullen providing modern bioinformatic applications.

3. **Make hay while the sun shines or carpe diem!** Our efforts with styrene and methylene chloride brought attention to the use of PBPK tools for risk assessment extrapolations. But, we weren't about to rest on our laurels! The team in Dayton included Harvey and Mike, plus Jim McDougal, Jeff Fisher, Jeff Gearhart, and Gary Jepson, all hungry to attack problems to understand tissue dosimetry in various situations. They team used PBPK tools to examine dermal uptake (Jim McDougal), cholinesterase inhibition by organophosphates (Gary Jepson and Jeff Gearhart), life stage modeling in pregnancy and lactation (Jeff Fisher), inhibitory interactions in the intact rat by co-exposures of 1,1-DCE and trichloroethylene (Kris Severyn and Mike Gargas), glutathione depletion (our team plus Richard D'Souza from Procter & Gamble), and again with the larger team, suicide enzyme inhibition from cis- and trans-1,2-dichloroethylenes and multi-product inhibition of metabolism with compounds such as hexane, benzene, and more recently atrazine. In addition, by extending the gas uptake tools to some 40 chemicals, Mike Gargas began a body of work developing structure activity relationships for metabolic parameters and tissue partitioning for a wide variety of volatile compounds. Mike, Jeff and Gary completed PhDs based on their work during the 1980's at Wright Patterson.

   By late in the 1980's, the Dayton team had also begun collaborative work on non-volatiles, including nicotine (with David Plowchalk and Don deBithezy at RJReynolds) and tetrachlorodibenzo-p-dioxin (with Hon-Wing Leung and Dennis Paustenbach at Syntex) and started work on pharmacodynamics (with organophosphates, styrene, TCDD, chloroform and nicotine). Over a span of just about 5 years, the WP-AFB group had tackled in at least some preliminary form most of the key issues that would arise in using PBPK tools for evaluating tissue dosimetry as a risk assessment tool. Importantly, Harvey Clewell began his career-long efforts to show how to apply these tools for sensitivity and variability analysis and for the broader applications of PBPK models in risk assessment. It was an invigorating atmosphere – referred to by several of the Dayton team as 'Camelot'.

4. **Educate the next generation of users through papers, seminars and short-courses!** You need to begin to train others if you plan the work to have a lasting influence. Harvey, Dick Reitz and I did our first PBPK training session at an Ohio-Valley Chapter of the SOT in 1986. We followed that with sessions at the annual toxicology conference held in Dayton. Ray Yang attended some of these meetings and developed an interest in PBPK modeling. He then brought a PBPK focus to his program in mixture toxicology at Colorado State University when he became Chair, Department of Environmental and Radiological Health Sciences in 1990. In 1992 Ray began biannual, two-week long courses in PBPK modeling. By 1994, Ray, Harvey and I were the lead instructors in the course. In more recent times at Hamner, a broader team developed a series of 1-week courses including PBPK Modeling in Risk assessment, Interpreting Biomonitoring Studies with PBPK Modeling, PBPK Modeling and In vitro-In vivo Extrapolation, and Computational Systems Biology Pathway Modeling. Miyoung Yoon has become a key contributor in

developing these courses in recent years. Ray, though retired, teaches a course in PBPK modeling for beginners in Ft Collins most summers.

Through these various courses, we have trained 300 to 400 students and, to the extent possible, made all training materials - lectures and models - available through the Hamner web-site. (We are now working to make these materials accessible from the ScitoVation, LLC web-site in the near future.) In addition to Ray Yang's program at CSU, two former colleagues, Jeff Fisher a graduate student from my Dayton days and Kannan Krishnan, a post-doctoral student from my time at CIIT (1989-1992), went on to faculty positions where they developed programs at the University of Georgia and University of Montreal, respectively, training a new generation of students in PBPK and, especially at Georgia, in both PBPK and PBPD modeling. Kannan now says that I am the great grandfather of PBPK modeling in toxicology, since he is training his third generation of students and post-doctoral fellow. I am not sure he intended this as a compliment.

5. **Share the credit for success as broadly as possible!** Lastly, and arguably most important, I learned that it is simply astonishing what a team can accomplish when no one individual has to get the credit. My early career work, starting in the US Navy and as a civilian with the US Air Force, relied on energetic, dedicated teams, full of talented individuals with diverse interests who quickly became a group of close friends contributing broadly to most of the research initiatives in the lab. This evening, I am grateful to receive an individual award from the ATS. However, I owe the successes throughout my career to teams at various institutions/organizations who wanted to work together to solve problems. I was extremely fortunate that so many wonderful colleagues came my way over these 45 years. They enriched my life with their intelligence, hard-work and, what have now become, enduring friendships.

So, what did I contribute to the mix? Let's see. There was the consistent focus on the longer term problem, for sure. And some questionable personal characteristics - I was consistently impatient with the small things - getting experiments completed, writing papers, setting up courses- generally patient pursuing the larger goals of working to understand incidence – dose relationships, persistent in maintaining focus on this larger goal, and now-and-then decidedly pigheaded. It's probably essential to have persistence, patience and pigheadedness to work on a single topic over such a long career.

Nonetheless, most-of-all you need great colleagues, good fortune and a supportive wife and family. In all these areas, I have been extremely fortunate and feel a deep sense of gratitude.

Oh yes, that girl I met in high-school chemistry, Christine Jaeger, is here to share this wonderful evening with me. Thank you for our long partnership, Chris".