Felix Theeuwes Memoir

(Felix and Marie-Therese Theeuwes Postdoctoral Fellowship at the University of Kansas; with thanks to A. Van Itterbeek, Richard Bearman, Takeru Higuchi and Alehandro Zaffaroni)

In 1965, Richard Bearman, then Professor of Chemistry at the University of Kansas, wrote to Professor A. Van Itterbeek at the Catholic University of Leuven in Belgium inquiring if any of his graduate students was interested in working as a post-doctoral student. Bearman's research was on the theoretical Percus-Yevick (PY) equation of state. He wished to compare this model against the real ideal fluids of liquid krypton and xenon. Heretofore, these liquids had not been studied extensively. At that time, I was completing my doctoral thesis on the thermodynamic properties of liquid normal hydrogen. When Professor Van Itterbeek approached me with this offer, I immediately loved the opportunity. Even though I could have stayed in Leuven as Assistant to Professor Van Itterbeek, the adventure to go to Kansas was too attractive to pass up.

In 1964, I was drafted in the Belgian military and served as officer in the reserve in the Belgian Air Force. I taught Thermodynamics of the Atmosphere and mathematics to recruits in the meteorological service while I was stationed in Evere close to Brussels. As part of my duty, I served one term as Officer of the Guard at the Royal Palace in Brussels where I was invited to lunch by the Adjudant of the King. He had served at Fort Leavenworth, Kansas, and told me all about the wonders of Kansas.

My wife, Marie-Therese, and I sold all our belongings for a one-way ticket to Kansas City. We arrived in May 1966 with our daughters Myriam (3 years) and Margaret (2 years), and son Marc (2 months). Richard (Dick) Bearman and his wife, Mirion, picked us up at the airport. They had found a house for us, next door to their home in the university town of Lawrence, Kansas.

Dick was very successful in attracting financial support from the National Science Foundation that allowed us to build the pressure, volume, temperature (PVT) equipment from scratch in the bottom floor of Mallott Hall, the chemistry building. The generosity and helpful attitude at the chemistry department at that time were overwhelming. I remember approaching Jack Rose, the Director of Laboratories, with a list of parts for equipment. My expectation was that I would have to submit the list, obtain approval, and wait three months for the arrival. I was amazed when Jack asked whether it would be all right if we picked up the equipment that afternoon. He drove us in his Volkswagen to the downtown hardware store to buy it. That same day, I retrieved supplies from the chemistry store room.

It took about a year and a half to build and calibrate the equipment to investigate krypton and xenon in a temperature range from 120 to 240 degrees Kelvin and pressures up to 300 atmospheric pressure. Our family acclimatized by cooling off in Lone Star Lake in the summer and ice skating on it in the winter. The neighbors and other Midwest folk were truly great company for a homesick Belgian family. As equipment construction neared completion, Dick, Mirion, and their children, Michael and Lynn, went to Australia on sabbatical leave. We stayed in their beautiful house on East 17th Street while completing our mission in the laboratory.

Equilibrium thermodynamics requires patience. As one cools and pressurizes the PVT equipment, it takes the better part of one hour to move from one data point to the next to collect the equilibrium data. Moving along isochores in this PVT space requires the equipment to be ready and safe under pressure at all times. Once the equipment was charged, it was on until all data were collected for that run. For safety purposes, I had constructed the equipment to read sensors for pressure, temperature, and vacuum insulation for the liquid nitrogen vessel cooling the pressurized test chamber. This monitoring was needed to prevent runaway pressure of the equipment with potential explosive consequences. These three sensors were monitored at all times. If they reached a set threshold, the alarm would buzz at home under our bed. Not often, but now and then, Marie-Therese and I would drive up in the middle of the night to the lab to fix a problem. It was a very productive time as we gathered data and published eight papers on the subject. The last of the series was: "F. Theeuwes and R.J. Bearman: The Equation of State of Dense Fluids. VIII. Comparison of the Internal Pressure from the PY Theory and the Lennard-Jones (6-12) Potential with Experiment." J. Chem. Phys. 53, 3114 (1970).

When the Bearmans returned from sabbatical leave in Australia to the University of Kansas, it was the height of the Vietnam War, with riots at Kent State and a bombed computer center at KU. The Bearmans decided to immigrate to Australia.

Our laboratory was shutting down and I was looking for a job! When we arrived in Lawrence four years earlier, industry was booming and Ph.D. graduates had multiple offers to join a variety of companies. Times had changed. I must have written more than fifty letters to various companies, but no offers were forthcoming. My hope was to be hired by Boeing in Seattle Washington where there was talk of flying a new class of airplanes with liquid hydrogen/oxygen fuel. But the industry was suffering, and the saying in Seattle was: "the last one to leave the city, please turn off the lights……"

And then a new professor came to town in Lawrence, Kansas. Professor Takeru (Tak) Higuchi joined KU as Regents Professor of Chemistry and Pharmacy and settled in his new laboratories in the West Campus. Tak at that time was famous not only as a scientist, but also as a promoter of the careers of many productive graduate students, as well as a premier consultant to the pharmaceutical industry. Around that time, Alejandro (Alex) Zaffaroni, founder of ALZA Corporation, approached Tak to join his company which was started in 1968 in Palo Alto, California. The result was that Alex built Tak a laboratory in Lawrence across the street from KU's West Campus. There, Tak joined ALZA as Vice President of Research and assembled a group of about twenty scientists. Tak's idea was that he needed scientists from different disciplines to interact in order to develop the new field of Controlled Drug Delivery. Dick Bearman arranged an interview for me with Tak and convinced Tak to hire me.

I told Tak that I knew nothing about drugs and kept refusing my only job offer, but Tak insisted that thermodynamics was all that mattered. So, I started as a consultant with ALZA in Lawrence in February 1970 while I was shutting down the equipment in Mallott Hall. In August, I joined the company full time as a research scientist. As a starting gift, Tak paid for a ticket back to Belgium with my family and handed me the book on Diffusion in Polymers by J. Crank and G.S.Park. He gave me the mission to visit as many of the investigators in the United Kingdom in that book. My wife and I did visit many of them during that visit. Professor Patrick Meares then in Aberdeen, Scotland, became a lifelong friend, consultant and mentor in the field of mass transport.

These were glorious days at ALZA in Lawrence. The saying at that time was that academia does fundamental work on irrelevant problems and industry does superficial work on relevant problems. Tak wanted both fundamental research and relevant problems. We had seemingly unlimited funds, great liberty in exploratory applied research, collaborations with graduate students and post-doctoral students in Tak's department. We worked long hours in the evenings and on weekends, spiked with great parties organized by Tak for colleagues and spouses.

ALZA's strategic plan then had four parts to it: RUMOSERT for delivery of tetracycline to the rumen of the cow for treatment of shipping fever, PROGESTASERT for delivery of progesterone for one year to the uterus for contraception, OCUSERT for delivery of pilocarpine to the eye to treat glaucoma, and prostaglandins (the fourth part of the strategic plan) as new chemical entities (NCE) for still undefined applications. In the end, none of these technologies became commercially important, but that is another story.

I joined the RUMOSERT team, which was focused on developing an osmotic pump for that application. The project became short-lived as John Urquhart demonstrated that tetracycline is degraded and ineffective when delivered via the rumen. It was just as well, since the science of drug delivery by osmosis was then ill-defined. The prototype osmotic pump was complicated with multiple parts, and outfitted with paper thin fragile membranes. This setback gave me the unique opportunity to explore fundamental system designs and the science of drug delivery by osmosis. Tak encouraged me to miniaturize the design of the osmotic pump. The first invention I made was to simplify the system as a mini osmotic pump with just three parts: drug reservoir, osmotic salt charge, and membrane that served as housing and was coated around the osmotic charge. We made the first prototypes in Lawrence based on a dip coating process. In Palo Alto at ALZA where I transferred in November 1971, we developed the science behind its operation: "F. Theeuwes and S.I. Yum: Principles of the Design and Operation of Generic Osmotic Pumps for the Delivery of Semisolid or Liquid Drug Formulations." Ann. Biomed. Eng. <u>4</u>, 343 (1977). This device was brought into commerce by ALZA Corporation in Palo Alto, California, as the ALZET osmotic pump now marketed by DURECT Corporation.

I made one further simplification in Lawrence and called it the Elementary Osmotic Pump (EOP), a name borrowed from the elementary particle physics laboratory where I worked, as a summer student, at CERN in Geneva in 1964. This system was designed with just two parts, the drug as osmotic charge and the coated membrane around the charge armed with a delivery orifice. The concept was written up in my notebook in Lawrence, but it was unclear at that time if we could ever find the right materials and equipment to make it work or where we would apply the technology. This record of invention became the background for the patent I coauthored with Tak, namely U.S. Patent No. 3,916,899. "Osmotic Dispensing Device with Maximum and Minimum Sizes for the Passageway." Issued Nov. 4, 1975. F. Theeuwes, T. Higuchi and assigned to ALZA Corporation. The first prototype of the EOP was made at ALZA Corporation in Palo Alto, where we developed the science and technology of operation of this osmotic pump, manufacturing process, and applications for oral controlled drug delivery. F.Theeuwes: The Elementary Osmotic Pump. J.Pharm Sci. 64,1987 (1975)

Even though I worked for only one year with Tak, we coauthored two papers and forged the beginnings of the commercial osmotic systems patents and business. One of these papers I still find quite elegant. It was based on Tak's well-conceived hypothesis, a Japanese graduate student's work, and my theoretical model: F. Theeuwes, K. Ashida, and T. Higuchi: The programmed diffusional release rate from a cosolvent system. J. Pharm. Sci. 65, 648 (1976).

I am forever thankful to Professor Richard Bearman, Professor Takeru Higuchi and the University of Kansas for creating this fertile environment where academia and industry bonded to give rise to the creation of new technologies, medicines, and also prosperity for a large number of families.