

Dora B. Goldstein – In Memoriam

Yedy Israel, John C. Crabbe, and R. Adron Harris

ONE OF OUR role models has departed, but not without leaving strong messages for our new generations. Dody was one of the most imaginative and charismatic scientists. She kindly accepted me in her laboratory to learn how to develop an alcohol withdrawal reaction in mice; which is today still used to generate an alcohol physical dependence. I was impressed by her charm and by her generous mind. Dody was first in placing mice in a closed chamber to breathe the ethanol vapor generated by a pump-controlled infusion of pure ethanol onto a porous air flowing surface. Initially it was necessary to carefully observe the animals to ensure that intoxication occurred without generating severe ataxia or animal death. Minor changes in the rate of ethanol metabolism—now we know—are able to greatly vary blood alcohol levels, given a constant infusion. Dody realized that the administration of the alcohol dehydrogenase inhibitor pyrazole stabilized blood alcohol alcohol swings and allowed better control of intoxication. After several days the mice were taken out of the chambers and, in a few hours, they developed a severe alcohol withdrawal reaction, which Dody showed could be clearly rated when animals were held a few seconds by their tails. I believe it was the first animal model to show a behavioral consequence of the alcohol withdrawal reaction.

Another important message left by Dody was on scientific rectitude. Dody and her associates had developed methods to determine the tumbling of molecules inserted into a lipid bilayer, such as the cell membrane. She was first in demonstrating that ethanol at anesthetic concentrations “fluidized” the lipid bilayers, shown as an increase in the tumbling of the molecular probes that she introduced in the membranes. The degree of fluidization was also shown for many other anesthetic drugs. The field, for about one decade, held that mechanism as the main mechanism of action of ethanol. However, I still remember Dody at an international meeting presenting data that countered her theory and stating that she had been wrong. She explained that increasing the temperature of the

bilayers by one or two degrees had a similar effect membrane fluidizing as an anesthetic. If so, said Dody, we would become anesthetized every time our body temperature would increase a few degrees. One can only admire a scientist that goes public to say that her previous ten years of research had been reinterpreted. But she was not altogether incorrect; further studies showed that some pockets—often hydrophobic—in some proteins can bind ethanol changing the characteristics of these molecules; which included GABA and NMDA receptors.

There was not a speck of ego in Dody’s actions; she genuinely admired creativity wherever she found it; as I remember her describing the work of other scientists or a new entrepreneurial activity—well ahead of their time—of one of their children. Avram, a lifelong partner admired her and both shared most gifted intellects, a combination rarely found in the world. Dody, you will always be with us.

Yedy Israel

My favorite story about Dody concerns her awaiting the arrival of a new postdoc. Mike (not his real name) had agreed to come to Palo Alto and only needed to finish up the last little polish on his thesis. Which appeared to take some time. Dody was rumored to have infinite reserves of patience with folks working in her laboratory, but she did not necessarily extend the umbrella of that patience without limits. Weeks turned into months, and one day the envelope from Stanford arrived. The letter was on the classic Stanford cardinal red letterhead, with both proper salutation and signature blocks, and it was even signed. The body of the letter, however, was as follows:

Dear Mike:

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Progress on the thesis accelerated forthwith.

Dody was a key to my nascent career. I obtained my first independent position in part because she and Henri Begleiter and others serving on a VA panel were willing to take a chance in 1978 on an off-the-wall proposal to study mouse genetics and map alcohol-related genes. The proposal was 5 pages long, incredibly and naively overambitious, and my entire portfolio of alcohol-related credentials was zero. But that grant, my first, allowed me to establish my VA laboratory and I still have the grant today. I am still using her dependence induction and withdrawal testing methods. I still go back to her classic set of papers from the 1970s and find new subtleties. These papers, and her monograph, are written with the crystal clarity that characterized her scientific talks. I only regret that I never was able to work directly with her. I will miss her dry sense of humor and remember fondly

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Received for publication October 31, 2011; accepted November 9, 2011.

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DOI: 10.1111/j.1530-0277.2011.01692.x

her boundless enthusiasm for everything scientific. As along as it was rigorous, that is. She had no patience for those whose egos exceeded their care in the laboratory, and she was not shy about expressing her scientific opinions, either. I am glad I had the opportunity to know her and learn from her.

John Crabbe

Dody influenced my career in many ways and I will always be thankful that she was so generous in supporting me when I was a beginning assistant professor. As was John Crabbe, I was selected for support by the VA for funding by Dody and others on the review panel. My research proposal was to define the role of membrane lipid physical properties, such as 'fluidity', in actions of alcohol on synthetic and biological membranes. As discussed by Yedy Israel, Dody was the pioneer, expert and leading light in the area where I had no training and provided a proposal which was naïve at best. Yet she encouraged and tutored me and wanted to share 'her' field of science with me and others. Dody possessed a wonderful mix of encouragement and rigor that promoted good science. It was the rigor that led Dody to reconsider whether the lipid disordering effects of alcohol were sufficient to account for any of the physiological or behavioral effects. She decided they were not and encouraged me to look more closely at proteins sites of alcohol action. My career benefited greatly from this advice! A few of Dody's key publications are given below and give a flavor of her career. Her first publication, from 1953, was on bacterial enzymology but she then spent time with her young children before returning to science and applying enzymology to the brain, with her first neurochemistry publication appearing in 1966. Dody then began her research on animal models of alcohol dependence

and membrane actions which was announced with seminal papers in Science. She never had, or wanted, a large research group, but accomplished a great deal with a few people and a lot of focus and rigor. During her time at Stanford, Dody did much to promote the fair treatment of women in science. The alcohol research community was fortunate to have her as a friend, colleague and mentor.

R. Adron Harris

SELECTED PUBLICATIONS

Chin JH, Goldstein DB. Drug tolerance in biomembranes: a spin label study of the effects of ethanol. *Science* 1977 May 6; 196:684-5.

Goldstein DB, Goldstein A. An adaptive bacterial cholinesterase from a *Pseudomonas* species. *J Gen Microbiol* 1953 Feb;8:8-17.

Goldstein DB. D-amino acid oxidase in brain: distribution in several species and inhibition by pentobarbitone. *J Neurochem* 1966 Oct;13:1011-6.

Goldstein DB. Injustice to women scientists. *Science* 1971 Sep 17; 173:1080.

Goldstein DB, Pal N. Alcohol dependence produced in mice by inhalation of ethanol: grading the withdrawal reaction. *Science* 1971 Apr 16; 172:288-90.

Goldstein DB, Chin JH, Lyon RC. Ethanol disordering of spin-labeled mouse brain membranes: correlation with genetically determined ethanol sensitivity of mice. *Proc Natl Acad Sci USA* 1982 Jul; 79:4231-3.

Goldstein DB. *Pharmacology of Alcohol*. Oxford University Press, New York, 1983.