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In Memorial, M. Daniel Lane, 1930-2014

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Dan Lane was a mentor, a teacher and most importantly a friend who cared about our careers, our families and us. Most of us simply knew him as Dan, but in 1930 in Chicago, he was born Malcolm Daniel Lane. He received his B.S. and M.S. degrees from Iowa State University and while there, met and married Patricia Sonquist, a marriage that lasted almost sixty years. Dan subsequently received his Ph.D. in 1956 from the University of Illinois and then joined the faculty of Virginia Tech University as an Associate Professor. It was his interest in nutrition and the role of vitamins that led Dan to spend the early part of his career examining the mechanism, function and regulation of biotin-containing enzymes. It was this early interest in vitamins that set the path for Dan Lane's entire career. From biotin-containing enzymes came lipogenesis, from lipogenesis came adipogenesis and from adipogenesis came central regulation of obesity. Tracing the career of Dan Lane, and those who were privileged to know and work with him, reveals an immense wealth of chemical, nutritional and molecular insight that was the trademark of our mentor and friend (Figure 1).

After joining the faculty at Virginia Tech University, Dan initiated studies addressing bovine hepatic propionate metabolism. His initial studies focused on propionyl-CoA carboxylase, a biotin-containing enzyme responsible for conversion of propionyl-CoA to methylmalonyl CoA. To address the mechanism of biotinylation of the enzyme, it was necessary to purify

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the apo-carboxylase and Dan chose to do that from calf liver. A story about this reveals a wonderful facet of Dan's personality—his marvelous sense of humor and ability to laugh at himself. In studies carried out by Dave Kosow, Dan's graduate student at the time, calves were maintained on a diet containing 30% raw egg whites to produce biotin-deficiency and maximize the amount of apo-carboxylase in the liver. One of the symptoms of biotin deficiency in the calf is hind-leg paralysis that was developed by the animals leading Dan to believe that the egg white diet was having a major metabolic impact. Unfortunately, raising calves on a concrete surface (basement of the Biochemistry building) also causes limb paralysis. Dan loved to tell the story of his misdiagnosis and the old farmer who laughed at him for keeping calves on concrete. He used this story as a teaching moment to show the importance of controls and always keeping an open mind towards alternate explanations for experimental results. Despite the setback with the calves, the work did come to fruition. Dan and colleagues went on to demonstrate that the transferase catalyzed a two-step reaction; the activation of the biotin moiety through the ATP-dependent formation of biotin 5-AMP, followed by the transfer of biotin to the ϵ -amino group of a lysine.

In 1964, after a fellowship with Nobel Laureate Feodor Lynen in Munich, Dan moved to the Biochemistry Department at New York University School of Medicine, having been recruited by another Nobel Laureate, Severo Ochoa. He initiated studies with acetyl CoA carboxylase isolated from chicken liver. He found that enzymatic conversion of acetyl CoA to malonyl CoA involved a carboxy-biotin intermediate and that the enzyme underwent a remarkable citrate-induced protomer to polymer transition. The EM image of polymerized chicken liver acetyl CoA carboxylase has been shown to countless students through publication in Lehninger's famous textbook "Biochemistry".

In 1970, Dan was recruited by Albert Lehninger to the Johns Hopkins University School of Medicine and in 1978 he was appointed Chairman of the Department of Physiological Chemistry (which then became Biological Chemistry). Howard Green had published on the differentiating 3T3-L1 cells and Dan's lab adopted this model as a vehicle for analysis of not only carboxylase, but also lipogenesis in general. As insulin serves as a primary regulator of the lipogenic process, he expanded his studies to the insulin receptor. Using density-labeling techniques (there were no antibodies available at the time) he published a series of studies on the expression and turnover of the receptor. In the following years he extended these studies to a variety of insulin-stimulated processes including 2-deoxy glucose uptake, lipogenesis and gene expression.

William Angus was the first of Dan's many students and postdocs to study the regulated expression of adipose genes during differentiation of 3T3-L1 cells and from the 1980's to the end of his career transcriptional control in fat cells was a major theme for the Lane lab. First with the analysis of the FABP4/aP2 gene and then with studies of stearoyl CoA desaturase and GLUT4, the Lane laboratory pursued a variety of molecular studies focused around the CCAAT/Enhancer-binding protein family of transcription factors and their role(s) in the adipogenic program. Based on binding and transactivation of a number of adipocyte promoters (e.g., SCD1, Glut4, FABP4, C/EBP α), his lab made the breakthrough finding that C/EBP α is necessary for adipogenesis and that ectopic expression of C/EBP α in 3T3-L1 preadipocytes stimulates preadipocyte differentiation. When leptin was cloned and identified

as an adipocyte hormone important for regulation of energy balance, the control of this important gene during adipogenesis and in adipose tissues became a focus of the lab. Critical observations included the finding that leptin is regulated by C/EBP α and by nutritional and hormonal factors, and that low expression in cultured adipocytes can be rescued by subcutaneous implantation into mice. Dan and his colleagues further discovered that C/EBP β , another member of the C/EBP family and a critical transcription factor for preadipocyte differentiation, is regulated by phosphorylation and glycosylation. It was shown that the coordination of such modifications is essential for C/EBP β to gain DNA-binding activity and to activate target genes. During this time Dan Lane was elected to the National Academy of Sciences USA and held important national society leadership positions, including President of the American Society for Biochemistry and Molecular Biology (formerly Biological Chemistry).

Always a lifelong interest, Dan Lane's passion with fishing was his trademark vacation activity. Always interested in the Chesapeake Bay and its beautiful waterways, and buoyed by his wife Pat's commitment to clean water and environment, Dan began a seemingly annual investment in newer, better and bigger fishing boats (particularly his favorite -- the Grady White). His home in Mt. Washington, MD was on a downward slope with a detached garage. Dan had to maneuver his trailered boat down the hill and into his garage without upsetting the structure or foundation. In the early days Dan could get his boat into his garage and close the door but in what seemed like an annual event at Lane lab parties, he needed more and more help finessing a bigger and bigger boat into the small space. More than once he knocked into the garage and weakened the foundation much to the delight of the on-looking crowd. Moreover, the boats became so large that the garage doors could not be closed leading to the mooring his boat on the Chesapeake. Having his boat on the water only fueled his passion and propelled him to spend more time going after his favorite target--the striped bass (Figure 2).

In 1998, Dan Lane stepped down as Departmental Chairman and was named a University Distinguished Service Professor. In the last decade of his career Dan began an era of investigation into how the nervous system sensed and responded to nutritional cues to control body weight. These studies started with the serendipitous discovery by Frank Kuhajda that an inhibitor of fatty acid synthase caused dramatic weight loss in mice. Surprisingly, and similar to leptin, the effects were mediated mainly through the central nervous system. Moreover, repeated administration of inhibitors of fatty acid synthase into the central nervous system could reverse obesity, even in morbidly obese *ob/ob* mice. These original observations using chemical inhibitors were later supported by genetic loss-of-function of the synthase in the hypothalamus. Several theories were put forth for the molecular mechanisms by which alterations in canonical fatty acid biochemical pathways could sense or elicit changes in animal behavior. Dan believed early on that malonyl-CoA was a likely and obvious metabolic node to coordinate these processes and the "malonyl CoA hypothesis" became a major theme for many laboratories. Through all these studies, Dan's enthusiasm for the pursuit of science was infectious and he constantly was asking students "what's new". It did not matter if he had spoken with someone earlier in the day—he always wanted to know the latest. This had powerful impact on students and postdocs

who ended up working even harder and becoming more productive, always thinking of what they had to report if Dan came around to chat.

In 2009 Dan Lane was named Professor Emeritus at The Johns Hopkins University and during his 30+ years of teaching, the “Lane Lectures” in metabolism became well known throughout the Hopkins community. He would get to class early in the morning and diagram metabolic pathways in great detail using colored chalk on multiple blackboards to the amazement (and sometimes horror) of first-year medical students. Such lectures were attended by not only beginning medical students but also by graduate students, postdocs and faculty who wanted a primer on intermediary metabolism and its control. Dan Lane was also a true leader who fought for his department, and for the right of his faculty to make their own choices, right down to the color of their lab doorframes. He was also a strong supporter of departmental social activities (including the much-coveted “Screw Up of the Year Award”), journal clubs, seminars, and evening research updates, complete with dinner and drinks. Before such events he would walk around the corridors and chase people out of their offices and labs, encouraging them to relax and interact with other members of the department. Dan was a fantastic mentor who set a great and inspiring example as a scientist and leader and who took exceptionally good care of his trainees from the minute they arrived till long after they left his lab. His role as lab-chief extended far beyond science to the well being of our families and his wife Pat was much beloved for her commitment to making Baltimore an exceptional place to live and work. The embracing care and respect that was felt for Dan and Pat Lane glued several generations of alumni together as a large extended family, a legacy that will last for years.

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Figure 1.
M. Daniel Lane.

Figure 2.
Dan Lane with his catch.