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Authors

Jan, Lily
Jan, Yuh

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Influences: Cold Spring Harbor summer courses and *Drosophila melanogaster* neurogenetics

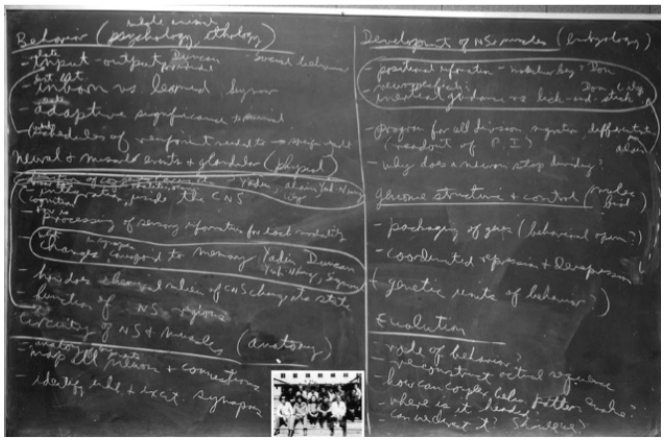
Lily Yeh Jan and Yuh Nung Jan

In the fall of 1968, we arrived at the California Institute of Technology (Caltech) to start graduate studies in theoretical high-energy physics, realizing a dream that we'd held since our undergraduate days in Taiwan. But after a couple of years studying physics, we were inspired by Max Delbrück to switch to biology. Thereafter began a journey that took us to Cold Spring Harbor Laboratory and Harvard Medical School before returning to California, where we started our little laboratory in the Department of Physiology at the University of California at San Francisco (UCSF) in 1979. These formative years spent as students and postdocs had a strong influence on our careers that continues to inspire our scientific direction and approach.

Our first few days at Caltech were disorienting. Besides the cultural shock, we faced our first experience of jet lag, having never traveled beyond a time zone previously. However, we soon settled, and while graduate students in Max Delbrück's laboratory, we benefitted from the nearly annual trip to Cold Spring Harbor Laboratory, where Max liked to spend the summer. We enjoyed the relaxed atmosphere and stimulating activities in and out of the laboratory at Cold Spring Harbor.

Having been inspired by the neurogenetics approach pioneered by Seymour Benzer while at Caltech, we were thrilled to join his laboratory in 1974, and took two Cold Spring Harbor summer courses to prepare for this venture into neuroscience. The lecture course, taught by Mike Dennis, Regis Kelly, Carla Shatz, and Eric Frank, plus guest lecturers that formed a Who's Who of neuroscience, was followed by a practical course of electrophysiology in which we learned to record from *Aplysia californica* neurons and frog neuromuscular junctions under the tutelage of Jac Sue Kehoe, Phillippe Ascher, and Enrico Stefani. Our summer course instructors patiently answered our naive questions, which ranged from basic physiological questions about neurons to the choice of scientific problems and experimental practices, and then generously provided us with mentorship and friendship that lasted for years.

At the end of the practical course, with three free days to apply our newly acquired skills to a preparation of our choice, we started to characterize the *Drosophila melanogaster* larval neuromuscular junction and realized it was well suited for electrophysiology. One year later, while in Seymour's laboratory, we accepted the generous offer of Mike Dennis to spend weeks at a time in his laboratory at UCSF. There, we practiced recordings



Research interests scribbled by Seymour Benzer on the lunchroom blackboard, circa 1975. Placed at the bottom of the blackboard is a group photo of the Benzer lab at that time. Lab members at one lunch session brought up scientific questions that interested them the most. Listed below is what we could decipher from the writing on the blackboard, starting from the upper left corner and ending at the lower right corner: "Behavior (whole animal psychology, ethology): social behavior; input–output for individual; inborn vs. learned; adaptive significance to survival; schedules of reinforcement needed to specialization (?). Neural and muscular events and glandular (physiology): integration inside the CNS; cognition; processing of sensory information for each modality; what changes in synapses correspond to memory; how does chemical milieu of CNS change its state; function of NS regions. Circuitry of NS and muscles (anatomy): map all neurons and connections; identify inhibitory and excitatory synapses. Development of NS and muscles (embryology): positional information – molecular key; neurospecificity: inertial guidance vs. lick-and-stick; program for cell division, migration, differentiation (readout of P.I.); why does a neuron stop dividing? Genome structure and control (molecular biology): packaging of genes (behavioral operon?); coordinated repression and derepression; genetic units of behavior? Evolution: role of behavior? reconstruct actual sequence; how can complex behavior patterns evolve? Where is it headed? Can we direct it? Should we?" Photo courtesy of Seymour Benzer.

Department of Physiology, University of California at San Francisco, San Francisco, CA.

Correspondence to Lily Yeh Jan: lily.jan@ucsf.edu.

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with Nomarski optics and a water immersion lens, which made it possible to see the nerve terminals in this preparation but provided a very short working distance for the placement of electrodes for recordings and calcium electrophoresis. Tutelage in these techniques proved to be instrumental as we continued our work on this preparation in Seymour Benzer's laboratory and successfully identified *Shaker* as a mutant with a likely defect in potassium channel function, a finding that later led to the cloning of the *Shaker* gene in *D. melanogaster*. During those visits to UCSF, we got to know John Heuser, who had a laboratory right next to Mike's. With the idea that reducing potassium channel function could enhance transmitter release, we helped with John and Tom Reese's efforts to visualize exocytosis at the frog neuromuscular junction by using quick freezing techniques combined with freeze fracture for electron microscopy. These fun interactions influenced our decision to join the UCSF faculty later on.

Some years later, after we started our laboratory at UCSF, we sought to repay the community for all the summer courses we'd benefitted so much from by restarting the Cold Spring Harbor summer course "Neurobiology of *Drosophila*" with Ralph Greenspan and Pat O'Farrell. We taught this course for four consecutive years, first with Ralph and Pat and later with Michael Bate. The logistics of running this summer course were challenging, particularly for the first year. At that time, Cold Spring Harbor Lab did not have a facility for making fly food. With our car loaded up with bottles and vials containing fly food made in our laboratory at UCSF, one of us had to drive across the country to supply the course. Nevertheless, teaching this course was a very rewarding experience. This Cold Spring Harbor summer course has been running annually for over three decades and is still going strong.

While in Seymour's laboratory, and with his blessing and encouragement, we and our laboratory mates exploited his genetic approach to explore the molecular and cellular mechanisms underlying neurobiological processes ranging from eye development to learning and memory. We held spirited discussions in the laboratory, during our road trips to meetings near and far, and in social gatherings such as the cooking classes alternately hosted by us (Chinese food) and our fellow postdoc Alain Ghysen from Belgium (French cuisine). These cooking classes involved serious note taking of recipes, followed by enjoyment of the product of the cooking demonstration with fellow laboratory members. As we have previously reminisced (1), Alain and his long-term collaborator, Christine Dambly-Chaudiere, maintained contact with us after we left Seymour's laboratory. In the early 1980s, Alain and Christine spent a few weeks every year in our new laboratory at UCSF to explore new research directions in neural development, which inspired our subsequent studies of neuronal cell fate specification, asymmetric cell division and, in recent years, dendrite morphogenesis.

With daily gatherings in Seymour's lunchroom, we carried on conversations about wide-ranging topics including, but not limited to, science and food. In one of those lunch gatherings, Seymour, Alain, Ilan Deak, Yadin Dudai, Bill Harris, Don Ready, Duncan Byers, and the two of us took turns to bring up big questions in neuroscience that fascinated us. Seymour made a record of this scribbled list on the blackboard with his Polaroid camera (see image). At the time, it was not obvious how to approach many of the questions on the list, though that did not deter us from dreaming—an unabashed optimism we had gotten used to given the focus of both Seymour Benzer and Max Delbrück on curiosity-driven research, especially in unchartered territories. Another tradition, that of geneticists to freely share reagents and mutant strains with their colleagues, is one we followed as our laboratory undertook the challenge of molecular identification of founding members of potassium channel families as well as elucidation of molecular pathways in neural development.

In 1977, after several happy and rewarding years at Caltech, we drove across the country with our newborn daughter to join Steve Kuffler's laboratory and the camaraderie of the Department of Neurobiology at Harvard Medical School (HMS). Like Caltech, the Department of Neurobiology at HMS had a great influence on our scientific careers, particularly during our postdoctoral training with Steve Kuffler, when we discovered that a luteinizing hormone-releasing hormone–like peptide is the transmitter for the late slow excitatory postsynaptic potential in the bullfrog sympathetic ganglion. But its influence began much earlier, during our first exposure to neuroscience at Cold Spring Harbor in 1974, when most of the instructors and guest lecturers were from the Department of Neurobiology at HMS.

By the time we started our second postdocs in Steve Kuffler's laboratory, Zach Hall had left the Department of Neurobiology at HMS to start the neuroscience graduate program at UCSF. Upon our return to the West Coast to start our laboratory at UCSF, we joined this nascent neuroscience program that attracted great colleagues including Louis Reichardt, Michael Stryker, Regis Kelly, Jim Hudspeth, Allison Doupe, and Jonathan Horton, all hailing from the same neurobiology department in Boston. In our fledgling laboratory, *Shaker* cloning and functional expression in *Xenopus laevis* oocytes was a result of the teamwork of Bruce Tempel, a graduate student of Chip Quinn (a fellow postdoc from Seymour's laboratory at Caltech), Tom Schwarz and Leslie Timpe from the Department of Neurobiology at HMS, and Diane Papazian from a neighboring HMS department. *Shaker* served as a starting point to identify other members of the voltage-gated potassium channel family in eukaryotes and prokaryotes, but this homology cloning approach was insufficient for identifying inwardly rectifying potassium channels. Instead, Yoshihiro Kubo succeeded by expression cloning the inward rectifier IRK1 in his two-year postdoc at UCSF. Yoshihiro did his graduate study at Tokyo University with Tomoyuki Takahashi, who was a postdoc with Ed Kravitz in the heyday of the Department of Neurobiology at Harvard Medical School.

We enjoyed variations of the same format for scientific discourse in these different institutions. Besides our lunch gatherings in Seymour's laboratory at Caltech, we had regular fly meetings in Southern California. In the close-knit Department of Neurobiology at HMS, we had evening meetings that featured the ongoing work of one laboratory and dinner for the entire department. At UCSF, our weekly faculty meeting at lunchtime is a beloved tradition that has lasted for over four decades and remains as popular as ever, typically with faculty (and sometimes the chancellor as well) taking up standing room at the back and floor space at the front while maintaining casual and

free-spirited discussions throughout. As our colleague Henry Bourne used to say, "The open and free exchange of ideas and expertise at UCSF make us infinitely smarter than we really are." As beneficiaries of these collegial interactions, we admire recent efforts devoted to innovations for global reach. Recognizing that scientific progress is fueled by an open exchange of ideas, our UCSF colleague Ron Vale founded iBiology a decade ago so that seminars and course materials that used to be accessible only to those who had the privilege to enroll in classes or work at scientific institutions could become accessible to a global audience without encountering barriers to learning (https://www.ibiology.org). We gladly contributed to the iBiology talks this year.

Whereas the power of genetics and the short lifespan of *D. melanogaster* and other model organisms make a strong case for the neurogenetics approach pioneered by Seymour Benzer, in which molecular pathways are unraveled in an unbiased manner based on mutant phenotypes, it is exciting to witness the expansion of genetic approaches to an ever-increasing number of organisms. The surprises we encounter in mutant studies have taken us time and again to unexpected physiological functions of our favorite molecules—a lucky happenstance. As Steve Kuffler said in his last paper, "After all, it is ongoing work which makes one go to the laboratory with a feeling of suspense and cautious expectation. Although success is rare, we continue in the spirit expressed by Robert Louis Stevens, that to travel hopefully is better than to arrive" (2).

Lesley C. Anson served as editor.

References

1. Jan, Y.-N., and L. Jan. 2014. *Soc. Neurosci.* 8:144–188.
2. Kuffler, S.W. 1980. *J. Exp. Biol.* 89:257–286.