James A. Birchler

How did you spend your career?

I grew up on a farm near a small town, Sparta, Illinois. In addition to farming, my father was a high school physics and chemistry teacher, and my mother taught first grade. I was in my father's class for both physics and chemistry. At home, he was usually all business with farm duties, but in the classroom he was very dynamic, throwing solid sodium into water to see the sparks fly, shattering hot dogs dipped in liquid nitrogen, giving students an Einstein hairdo with a Van de Graaff generator, et cetera. He was also the vice principal and disciplinarian, so my friends were limited to the well behaved!

But there was fun on the farm with fishing, frogging, and foraging for mushrooms, berries, nuts, persimmons, and honey. Mother filled the house with cacti, African violets, and identification guides for birds, flowers, and trees, as well as the notes of Chopin and Schubert, her favorites to play on the piano. I applied to one college, Eastern Illinois University (EIU), on the high recommendation of a student a year ahead of me at Sparta High School. I was not sure which branch of science I would major in, but a second course in biology as a senior in high school settled me on biology. EIU did not have a major in biology, so I chose botany with a minor in zoology, but over four academic years as well as three summers I also took many courses in chemistry, physics, anthropology, and philosophy.

I did not set foot on the campus until I enrolled. EIU had a policy to limit class size to 35. Thus, I knew all my professors personally, and they knew me. Their personal acquaintance set me on my career path because they encouraged me to enter graduate school. I can remember the exact moment—I was walking down the hallway in the Botany Department—when one of them, Charles Arzeni, passed me and declared, "You're going to graduate school, and I am writing you a letter." Doc Arzeni encouraged many students on their career paths; he had great enthusiasm in the classroom and in life. He loved to travel and would sponsor student trips to Central and South America at every break and during the summer. My first airplane flight was on one of these ventures, a field trip to the Amazon rainforest in Leticia, Colombia. I also attended summer school two different years in Monterrey, Mexico, for courses led by Arzeni. He set me on my initial career path and sparked an interest in travel and different cultures that continues to this day.

Years later at the University of Missouri, I learned that I had taught two of Arzeni's grandsons in genetics classes in different years. When I found this out from Arzeni's widow, I announced to my class that "[John Doe]'s grandfather was a biology professor, and I had him in college." Later I learned that the class interpreted this statement to mean that I had *taught* his grandfather, rather than vice versa! Students keep you humble when you realize they think you are over 100 years old.

After I settled on graduate school, another parameter was involved. The Vietnam War was ongoing during my college years, and upon official graduation I was reclassified for the draft. There was a lottery system in place, and my number ensured that I would be called. I got so far as to take the physical exam. But shortly before I was to receive a notice, President Nixon suspended the draft, never to return. Despite his shortcomings and my cheering at the time of his resignation, I do have a twisted affection for him.

Knowing what was coming with regard to the draft, I had applied to Indiana University (IU), across the border from EIU, with the intention of securing a graduate student position when I returned. Shortly after applying, I received a pleasant letter from Marcus Rhoades confirming my acceptance to the Plant Science Department. I had decided to focus on genetics in graduate school with a minor in biochemistry. At IU, I took many courses in various

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aspects of genetics and biochemistry. My training at EIU had been very classical, albeit extensive across biology, so I entered graduate school without any idea whom to work with in the department. I was given an office in a closed-off portion of Rhoades's laboratory that was used by several graduate students. Because I was not in a lab at first, I spent considerable time there. Another student who was finishing his graduate work, Mike Freeling, also spent much time in this office writing his thesis, and we ventured into discussions about scientific topics and philosophy.

At the end of my first year, having settled the draft issue, I inquired if I could join Drew Schwartz's laboratory, where Mike was finishing. Schwartz set me on a project to perform an ethyl methanesulfonate mutagenesis of a tandem duplication of the alcohol dehydrogenase-1 gene in maize, to test an idea of his that the two genes composed an operon. He had formulated a competition model of gene regulation, and the observations on the duplication did not fit unless one postulated that the two copies were transcribed together. My eventual studies of gene and chromosomal dosage suggested that this was not the case, which did not sit well with Schwartz. Although he held to his own ideas strongly, Schwartz was a rigorous scientific critic of others' work, which was good preparation for us graduate students. His critiques could sometime seem quite strong, but he defended his students to anyone with the same vigor as he defended his ideas.

It was during this work that I discovered the inverse dosage effect: changing the number of chromosomes can modulate the expression of genes elsewhere in the genome with a negative correlation with the dosage. It was also found that a dosage series of the long arm on chromosome 1 in maize showed dosage compensation for the *Adh1* gene, which is encoded therein. I made the connection between the inverse dosage effect and dosage compensation in an "aha" moment as I was reaching into the bushes for some ripe raspberries on the IU campus one summer day on my way back to the lab from lunch.

Rhoades was Schwartz's adviser and a member of my PhD advisory committee. Rhoades retired during my early graduate years and, being freed of responsibilities, would wander into my corn plot in the summer and give me tips and suggestions. With no one in his lab, he welcomed me to visit, and when I did, he would reminisce about many geneticists, particularly Barbara McClintock and Theodosius Dobzhansky. He had his favorites—and otherwise. Rhoades provided a classical emphasis to my training, compared with the biochemical genetics of Schwartz.

For postdoctoral work, I ventured into Drosophila genetics. After realizing the prevalence of the inverse gene dosage effect in maize, studying papers on locating enzyme structural genes in flies via segmental aneuploidy revealed the same effect, but it had been generally ignored. I applied to work with Ed Grell at the Oak Ridge National Laboratory in Tennessee because he had worked on gene dosage effects. Ed readily grasped the idea of the inverse effect and dosage compensation and was highly supportive. At the end of my two-year fellowship, I transferred to the lab of Bruce Jacobsen at Oak Ridge and studied the dosage compensation of tRNA genes. With my lack of any success in job hunting, I needed an option. Bruce had learned that Ken Paigen at the Roswell Park Memorial Cancer Institute in Buffalo, New York, was looking for a Drosophila geneticist and suggested that I inquire. The Paigen lab worked on mouse genetics, but Ken was interested in expanding to Drosophila. I visited the Paigen lab and was offered a position.

Ken had accepted an offer to be chair of the Genetics Department at the University of California, Berkeley, but had not yet moved. So I spent nine months, including a winter, in Buffalo before moving to Berkeley. The small department at Roswell made for lively interactions. As part of his chair offer, a junior faculty position was included. Ken asked me to stay in the lab in order to apply, which I did, but the department wanted no part of it. So the next year I sent out a number of applications to other universities and got an offer from Harvard in the Department of Organismic and Evolutionary Biology. I now joke that I was a postdoc for eight years before it was popular, but my postdoc years were valuable experiences, adding Drosophila and an exposure to mouse genetics to my graduate training in maize.

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At Harvard, I wrote grants on both maize and flies, and both got funded. My next-door lab neighbor was Rodney Honeycutt, a molecular cytogeneticist. We pooled our resources, set up a common equipment room, and threw open the doors of the two labs to all members. This was unheard of at Harvard at the time. We cotaught cytogenetics, and I taught plant genetics. Dick Lewontin, Laurie Bogorad, and Matt Meselson were particularly welcoming, inviting me to their lab meetings and dropping by my office to chat. Although Rodney and I enjoyed our time at Harvard as we started our careers, we both chose to leave for other universities, as did many other junior faculty members at the time, rather than try for a tenured position, which at Harvard involved competing with outside candidates for a slot.

In 1991, I joined the Division of Biological Sciences at the University of Missouri. Missouri had a distinguished history in plant genetics, and so it was an attractive place to settle. I worked on maize genetics and genomics, as well as Drosophila studies on individual regulatory genes that produce dosage effects, effects of retrotransposons, transcriptional silencing of transgenes, cell death inhibition of RNAi, and X chromosome dosage compensation. In the mid 1990s, as a by-product of gene dosage studies, we discovered cosuppression in Drosophila, which seemed reasonable to us given its discovery in plants in the late 1980s by the Jorgensen and Matzke groups. An early reviewer likened the Drosophila cases to "cold fusion," but the work was eventually published in a couple of papers in *Cell* and other journals.

What do you consider to be your most important contributions to plant science?

Studies of the effects of gene dosage on expression and regulation, formulated as the gene balance hypothesis, is the longest standing of my interests. As a graduate student, I found that changing the dosage of maize chromosome arms would modulate the expression of genes encoded elsewhere in the genome. Basically, any chromosomal region, when changed in dosage, can alter the expression of genes across the genome. Any one gene could be modulated by several genomic regions for which dosage was changed. Whereas these modulations could be positive or negative, the most prominent change is an inverse dosage effect. When an inverse dosage effect is caused by a particular chromosomal region and affects target genes on the same varied segment, dosage compensation results, because the change of target gene dosage is cancelled by the simultaneous inverse dosage effect. From work in Drosophila, the dosage effects were found to be caused by changing the number of single genes encoding transcription factors, signal transduction components, and chromatin proteins.

Whereas altering the dosage of parts of the genome causes expression modulations, altering the whole genome, as in a ploidy series, has much less effect. RNAseq studies in maize, Drosophila, and Arabidopsis (in collaboration with Jack Cheng's lab, and the latter also in collaboration with the Matzke lab) established all these effects on a genomic global scale. Classical studies in many eukaryotic species, but first in plants, had shown that partial genome changes (aneuploidy) were much more detrimental than whole-genome changes (ploidy). Classically, this was referred to as *unbalanced* and *balanced* genotypes. Our studies provided a molecular basis for this phenotypic phenomenon.

When evolutionary genomics emerged as a discipline, it became evident that there is a history of whole-genome duplication in most plant lineages. As the duplicate genes from these events become deleted over long periods of evolutionary time, there is a preferential retention of transcription factors, signal transduction components, and other genes encoding members of macromolecular complexes. We postulated that the similarity between the classes of retained genes and those that show a dosage effect supports the hypothesis that the balance of these genes is instrumental in their prolonged maintenance. Loss of one member of an interacting set of proteins would have a detrimental fitness effect, similar to the classical gene balance phenomena, thus maintaining the composition of the interacting set.

As predicted from gene balance, segmental chromosome duplications in plant (and animal) genomes have an underrepresenta-

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tion of the same classes of genes that are overrepresented following whole-genome duplication. It was also noted that because most aneuploids of any significant size have recognizable phenotypic effects, and because different aneuploidies can affect the same plant characteristic, it was postulated that there exists a coincidence of genes causing the gene balance effects and those contributing to multigenic quantitative effects. There is still much to be learned about how genomic balance affects gene expression and quantitative traits.

In 2002, Reiner Veitia at the University of Paris wrote an article about macromolecular stoichiometry and gene dosage effects with regard to tumor suppressor genes. This theoretical work dovetailed with the gene balance and dosage studies we had been doing, so I wrote to him and suggested we communicate about the topic. We eventually met when I attended a conference in Paris; subsequently, over a 15-year period we have written many articles together about gene balance, haploinsufficiency, and the kinetics involved in these effects. Before we met, I wondered who he might be. As it turned out, he was a young Cuban who had gone to France for his education and had recently started his own lab. Reiner must have been wondering about me as well, because as we parted from our first meeting he said, "I envisioned someone much taller." Many people inquire about and are amazed by this out-of-the-blue collaboration, but it is just what a maize geneticist would do.

A test of whether there is a dosage component to heterosis, which we found there is, led us into studies of hybrid vigor. This initial foray into heterosis pulled us into additional studies of hybrid vigor in various polyploidy configurations. It is a challenging scientific problem with a magnetic attraction that is difficult to resist.

Early in my career, one of my graduate students cloned a specific repeat sequence from the supernumerary B chromosome of maize. It turned out to be at the centromeric region of the B chromosome, which led us in the direction of studying maize centromeres, which were little explored at the time. Artificial chromosomes had been assembled in yeast, and so with the identification of plant centromere sequences, we set out to attempt to produce them in plants. Our work, however, found that the functionality of maize centromeres was epigenetic, as is true of most other eukaryotic centromeres with the exception of yeast, so the yeast paradigm did not work for maize. Not to be discouraged, we turned to telomere-mediated chromosomal truncation, which occurs when telomere sequences are introduced into chromosomes. Using this approach, we were able to produce engineered minichromosomes from both A and B chromosomes that can serve as the foundation for building artificial chromosomes. We have transformed several site-specific recombinases and other transgenes into maize for targeted integration, excision, and inversion of sequences in engineered minichromosomes.

With this venture into maize chromosomes, we sought a means to identify the 10 chromosomes in somatic root tip metaphase spreads. This was previously possible at the pachytene stage of meiosis but basically impossible in somatic cells. Because maize chromosomes are decorated with various types of tandemly arrayed repeat sequences, we developed a fluorescent in situ hybridization cocktail that would paint these sequences different colors and allow each chromosome to be distinguished. This technique allowed cytological studies examining chromosomal variation, chromosomal behavior, transposable element dynamics, and organellar DNA insertions into nuclear DNA, the latter in collaboration with Kathleen Newton. Later a collaborative effort with Jiming Jiang's lab produced whole-chromosome paints that facilitate recognizing translocations, insertions, and chromosomal domains in interphase for each of the 10 chromosomes.

Using the B chromosome for centromere and minichromosome studies led us into collaborative work with the labs of Jan Bartos and Fangpu Han to sequence this bizarre chromosome. It is nonvital, and most lines of maize have been purged of it after its descent from teosinte. It is maintained in populations by a "drive" mechanism and has additional strange properties to perpetuate itself, such as increasing recombination in heterochromatic chromosomal regions and a unique mechanism to help itself transmit as a univalent during meiosis,

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which for regular chromosomes often results in loss. The sequence of the B chromosome revealed several hundred genes, many being expressed. These genes have paralogues scattered all over A chromosomes with widely varying divergence times, indicating that the current gene repertoire of the B is basically composed of genes transposed there from the A chromosomes. Most of these genes show evidence of relaxed purifying selection, but some appear to be selected for functions related to its perpetuation.

Having served on an NSF panel in which other members denigrated maize as a genetic model because of its longer generation time, I was inspired to initiate the development of a fast-flowering line. I knew of maize lines that flowered quickly but did not produce particularly robust plants. I gathered several of them that were early flowering and conducted a crossing scheme to select a workable line with early flowering. This endeavor resulted in the development of Fast Flowering Mini Maize (FFMM), which can produce six generations a year in the greenhouse. Interestingly, when I proposed the completion of FFMM in an NSF grant, a reviewer dismissed it as basically useless because "maize is person height for a reason." Nevertheless, it continues to expand in use in industry and academia for innumerable studies and has greatly expedited maize transformation.

In the above narrative I have not mentioned lab members' names because so many have contributed to these studies, and I do not want to slight anyone by mentioning only a few. A literature search will reveal their significant contributions.

When did you become a member of ASPB?

2005

How did the Society impact your career, and what motivated you to become a Founding Member of the Legacy Society?

My contribution to the Society has been through being a member of the editorial board of *The Plant Cell.* I have now served in this capacity in various titles for 15 years with four different editors-in-chief. It seems that I am incapable of being fired, although that might be the wish of some authors. Yet I view my role as being an advocate for authors and for evidence-based manuscript reviews. I try to support discovery science and to eschew the fads of the field, especially if an important new discovery emerges, which often will hit roadblocks in review. Being an editor forces one to stay current in the field and to broaden one's horizons by handling papers tangential to one's own field. *The Plant Cell* is run by practicing scientists, and the editing staff is spectacular in producing excellent final manuscripts, so by becoming a member of the Legacy Society I can help ensure the continuity of this journal, as well as the other excellent journals published by ASPB.

What important advice would you give to individuals at the start of their career in plant science?

- Work on the most challenging and important questions that your talents allow.
- Keep your eyes and your mind open.
- Follow the data, not fads or the famous.
- Discovery comes before mechanism!
- All of science is "descriptive"; it is just a matter of at what level and how thorough.
- Others will love your technical advances but argue to their death about conceptual ideas.
- Let your lab members flow to projects that best fit their talents.
- The best thing you can teach your students is to continue to learn for themselves.
- Tell your students that they should be dragging you into new intellectual territory with their work. They will roll their eyes at you at first, but when it happens, you will know you have succeeded.
- It is not possible to understand all of the nuances of multidisciplinary collaborations, but it is good to appreciate the promise and pitfalls of each.
- Enjoy the excitement of being the first human being to know a newly discovered scientific fact.
- Have humility in the face of Mother Nature.

Academic Family Tree

https://academictree.org/cellbio/tree.php?pid=655210