From Maize Transposons to the GMO Wars

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Early Days: Discovering Plant Genetics and Developing Molecular Methods for Plants

Though I didn't know it at the time, my involvement with plant biotechnology began in 1976 when I encountered Barbara McClintock by chance while visiting the Cold Spring Harbor Laboratory to give a talk. I was heading out of the Demerec Laboratory on my way to meet with then Director Jim Watson when I ran into a tiny, elderly woman. She stopped me to apologize for missing my seminar—I quickly guessed this must be the legendary Barbara McClintock, though I couldn't understand why she should be apologizing to me, as I was just a post-doc. She invited me to continue the conversation in her laboratory. On impulse, I shrugged off the meeting with Watson and followed her down to the ground floor. My recollection is that we ate peanuts and drank Cinzano—she later assured me that only the part about the peanuts was true. We talked about the usual stuff—science, science politics, a bit of philosophy.

I was puzzled. McClintock's reputation for impenetrability didn't fit with the lucidity of her casual discourse. And I was intrigued. I went back home to Baltimore, where I was a post-doc in Don Brown's laboratory at the Embryology Department of the Carnegie Institution of Washington (now the Carnegie Institution for Science), curious to know more. Since McClintock was a member of the same institution, although by then retired, she had published in the Carnegie Yearbooks, all shelved in the department's main reception area. I got them down, copied (xeroxed, in the terminology of the time) her chapters, and began to read.

It was tough going. I was a molecular biologist. Indeed, my post-doc was devoted to DNA sequencing and I'd sequenced some of the first genes ever sequenced, the 5S

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ribosomal RNA genes of South African clawed toad, *Xenopus laevis* (Miller et al. 1978; Fedoroff and Brown 1978). I'd done some simple bacterial and bacteriophage genetics, but I knew nothing about plants, much less plant genetics. Yet even if I'd had a classical genetics background, it wouldn't have helped me much. I was into genes and promoters. Publishing 30 years earlier, McClintock wrote about a position on maize chromosome 9 where breakage could occur reproducibly during development—one that could also move to a new place on the chromosome (McClintock 1987). She called it a "transposable genetic element."

By the late 70s, insertion sequences and transposons had already surfaced in bacteria and had at least a genetic identity, although their DNA sequences were still in the future. The more I read about maize transposable elements—slowly and painstakingly—the more interesting I found them. Yes, maize transposable elements could break chromosomes, but they could also jump into genes. And they could take over the regulation of a gene, making it dependent on the transposon for its expression. Or the insertion could regulate gene expression in exactly the opposite way, the insertion silencing the gene only in the presence of a related mobile sequence. Maize transposable elements could go silent and invisible, not moving for generations, then come back to an active form. And they could talk to each other, collaborating to determine how several different genes with insertions were expressed during the plant's development.

I was approaching the end of my post-doctoral tenure and was beginning to think about what I would devote my research to in the future, assuming I could land an academic post in a research institution. I kept thinking about working on the molecular biology of the maize transposable elements—and repeatedly dismissing the idea. Plant biology didn't get much in the way of public research funding and plant molecular biology didn't yet exist. The notion that I could become a plant biologist, invent the necessary technology for cloning and analyzing plants genes, and find financial support, while starting an academic career was daunting. And I was a single parent who took her parenting seriously, so I'd pretty much shelved the idea.

Quite unexpectedly, Don Brown, by then the Embryology Department's director, called me into his office one day to offer me the staff position newly vacated by the departure of Igor Dawid. Although it had previously been announced that internal candidates would not be considered for the position, Don explained that he and his colleagues had come to the conclusion that I was being discriminated against me just because I was an internal candidate. So if I wanted the job, it was mine—elegant job offer, no?

My immediate reaction was to dislodge my tucked-away fantasy of working on the maize elements so elegantly described in McClintock's genetic experiments. Staying at Carnegie would let me to devote all of my time and effort to research, so I could gamble on solving the problems that stood in the way of molecular approaches in plants. These were not insignificant. No plant genes had yet been cloned and people were saying that they couldn't be cloned.

But first I had to persuade Barbara, who didn't have much patience for slow learners, that I was serious enough for her to teach and to share some of her

precious mutant lines. I jumped right in, arranging to grow corn the following summer at the Brookhaven National Laboratories through the generosity of maize geneticist Ben Burr. Barbara did indeed give me a bit of everything she'd worked on and I probably overplanted. When pollination season came, I settled into Brookhaven housing with my son, whom I'd found a spot for in a local camp.

That summer turned into a nightmare. There's no stopping during pollination season and you have to have a pretty good idea of what you want to do—something I didn't yet have, of course, so I probably did twice as many crosses as I needed to do. My objectives and Barbara's were often at odds—her approach was that of a geneticist, while mine was that of a molecular biologist. In particular, Barbara had capitalized on the extraordinary properties of the maize kernel and its pigment-producing aleurone layer to follow the effect of the mobile elements on multiple genes simultaneously. Many of the genes she worked with coded for enzymes and—as we eventually learned—regulatory proteins involved in the synthesis and modification of the anthocyanin pigment produced by the kernel's aleurone layer. It struck me as unlikely that these would be sufficiently abundant proteins so that we could easily purify them and raise antibodies to them, the only tools then available for getting to the mRNAs encoding them and in turn to the genes. So I focused on the few genes she'd identified with insertions that were likely to encode relatively abundant proteins, such as those involved in sugar and starch biosynthesis, major biochemical activities of corn kernels.

And then there were the 5 am to 2 am days—every day! My technician Jeff had come with me to help with pollination, but it quickly became apparent that he was violently allergic to corn pollen. He was swelling up dreadfully and I sent him home to Baltimore. So all the planning of crosses, silk-trimming, tassel-bagging and pollination fell to me. I was barely managing and Barbara and I couldn't agree on anything. The summer's nadir came when my son's camp called and told me my son had impetigo—a highly contagious skin disease. I was to come and get him immediately and not bring him back for the rest of the summer.

In the end, however many wrong crosses were made, some of the right crosses were made, as well. My young son and I harvested that first crop over several brilliantly sunny warm September days. I remember marveling over each shiny, colorful ear as it emerged from is brown and shriveled husk. My knowledge of what I was looking at was improving and I was beginning to connect Barbara's inferences with the pigmentation patterns I was seeing—I still remember my constant amazement that she had figured out so much from such subtle clues. Jerry Neuffer once told me that every time he thought of a clever experiment to do with maize transposons, he found that Barbara had already done it years earlier. I felt the same way for a long time—my first single-authored purely genetic paper was still a decade in the future.

In the meantime, there was biochemistry to be done in order to get a toe-hold in the molecular realm on the way to cloning maize genes with McClintock transposable element insertions. My group was growing and post-doctoral fellows Susan Wessler and Mavis Shure took on the challenge of cloning a cDNA copy of an mRNA that looked promising both because it was likely to encode an abundant

protein and because it was produced from a gene that carried a complete McClintock-characterized transposon.

The gene we chose was the *Waxy* gene, the wildtype version of which was already known to encode a starch granule-bound UDP-glucose starch transferase responsible for the synthesis of amylose in the kernels. The fact that it was bound to starch granules and that we had both wildtype and mutant maize varieties made it relatively easy to identify an abundant 58-kD starch granule-bound protein that was present in wildtype kernels, but not in null *waxy* mutants. Though we were never able to solubilize an active protein, the genetic evidence that we'd identified the protein encoded by the *Waxy* gene was strong enough for us to raise antibodies to the protein and identify a cDNA clone using a now all-but-forgotten technique called "hybrid-selected translation."

McClintock's genetic treasury comprised basically two kinds of insertion mutations, ones in which the inserted transposon was itself mobile and others in which the insertion was mobile only in the presence of a second, mobilizing element. I named these "autonomous" and "non-autonomous" elements, respectively. These, in turn, fell into families according to which non-autonomous elements were mobilized by a given autonomous element. My first hypothesis was that the non-autonomous elements of a family were likely to be mutant elements lacking an active version of gene that encoded its "transposase," an enzyme postulated to cut and resect DNA to move the transposon to a new site. In the first transposon family that Barbara had identified, the *Activator-Dissociation* family, the *Activator* (*Ac*) element could transpose autonomously, while the *Dissociation* (*Ds*) element, first named for its ability to "break" or "dissociate" a chromosome, could only move in the presence of an *Ac* element.

I chose the Waxy locus for one of the first gene cloning efforts because McClintock had identified both an *Ac* insertion and a *Ds* insertion at the locus. Moreover, the *Ds* line appeared to have arisen from the *Ac* line, so it was a fair guess that it was a non-mobile mutant derivative of the parent *Ac*. Though it was slow going, the molecular techniques developed for other kinds of organisms worked relatively well after a bit of tweaking for Wessler and Shure to clone a cDNA copy of the mRNA encoded by the Waxy gene (Shure et al. 1983). So it should have been perfectly straight-forward to clone the gene. But it wasn't. A third post-doctoral fellow, Debbie Chaleff, had worked long and hard to clone maize DNA into the lambda vectors that were widely used at the time. She had failure after failure and finally left the lab in frustration.

And indeed, there were rumors in the plant community that plant DNA couldn't be cloned. I refused to believe them. Confident that all that was required was extreme care and attention to the success of each step in the process, I took on the project myself. I worked meticulously, devising controls for every step in the process—more controls than anyone ever used. But I, too, failed to clone maize DNA in the then widely-used lambda vectors. And I failed again. Then, for reasons I cannot reconstruct, I grew overnight cultures of all the bacterial strains in my collection and plated the packaged, recombinant, maize-DNA containing viruses on all of them. Amazingly, one strain—I even remember it was designated

K803—showed hundreds of plaques. I plated it again, and again had many plaques. The problem was solved.

Some time later, I remember receiving a call from a researcher at the Rockefeller University (if my memory serves me correctly) during this time, telling me that he had simply cried in frustration over his failure to clone maize DNA. I sent him some K803, which I had received from a laboratory at Cold Spring Harbor, and it worked for him as well. While I never stopped long enough to nail down the reasons for the earlier failure, I did carry out one experiment that strongly suggested to me that the trouble resided in the higher levels of methylation of plant DNA compared with animal, lower eukaryotic and bacterial DNAs. And that was simply to collect the virus particles grown in the K803 strain and ask whether they showed similar titers on both K803 and the other strains people were commonly using as bacterial hosts for recombinant lambda viruses—they did. I published a short description titled "Notes on cloning maize DNA" in the Maize Genetics Newsletter in 1983 in the hopes of helping others get past this cloning bottleneck (Fedoroff 1983a).

Explaining and Cloning Maize Transposons

During the period that my laboratory was struggling to develop biochemical and molecular methods for plants, Barbara was asked to write a chapter for a book that Jim Shapiro was organizing titled "Mobile Genetic Elements." During one of my not infrequent visits to her laboratory during this time, Barbara asked me to co-author the chapter with her. She was quite frustrated with her inability to communicate her science to others and blamed it on her lack of writing ability. She eventually asked me to write the chapter myself. I was not yet confident that I understood all the subtleties of the maize elements and their genetic and epigenetic behaviors, but I agreed to take on the task, assuming that she would set me straight if I got any of it wrong.

I had, by then, read and reread her papers several times and I had been through several seasons of genetic crosses. I invested a good deal of time in taking pictures of kernels from what were now my own maize stock that illustrated the pigmentation and variegation patterns McClintock used so effectively to understand the genetic behaviors of maize transposons. I wrote the draft painstakingly from a molecular perspective. Since the chapter was written before the first maize transposable elements had been cloned and analyzed in my laboratory, I relied on my knowledge of the literature describing prokaryotic transposons to interpret McClintock's genetic studies in a way that would be comprehensible to a molecular geneticist of my generation. I sent off a draft to Barbara with a request that she criticize it mercilessly. I heard nothing. When I at last summoned up the courage to call her, she declined to comment on the manuscript. When I queried her on her

reasons, she said that if she commented on it, she would have to take responsibility for it—and she refused to do so.

I was stunned. I didn't think I could have made such a complete mess of it for her to refuse any further discussion—but that was, of course, a possibility. I knew that I had used very different terminology from that she'd invented so many years earlier when people didn't have words for what she was seeing in her genetic experiments. And I had not adopted her favored hypothesis that these were misplaced regulatory elements: she had come to call them "controlling elements." (That said, I can say with all the clarity of hindsight that she was not far off the mark, as the kinds of regulatory interactions among the elements that she first identified and we later characterized at the molecular level are very consistent with the regulatory interactions among non-mobile genes. And more than that, bits of transposons are often in the regulatory sequences of genes.)

So I guessed that she was reacting badly to my rather different treatment of her intellectual construct—and decided that I had to move ahead with the manuscript. It was perhaps the most painful piece of writing I have ever done, agonizing over each inference, checking it again and again, sentence by sentence. In the end, Barbara made peace with my writing about her elements and even suggested that I'd contributed to her selection as a Nobel laureate. Though I do not believe that was true, I didn't get much wrong in that early piece, judging from the molecular evidence the accumulated over the following decades. And I do believe that book chapter, which appeared in 1983, became an accessible entry point for students to understand McClintock's work in a contemporary context (Fedoroff 1983b).

Once I'd solved the problem of cloning maize DNA, the research moved very quickly. By early 1983, the year McClintock received an unshared Nobel prize, we wrote the first paper describing the cloning of the *Waxy* gene (Shure et al. 1983) and the first *Ac* and *Ds* elements (Fedoroff et al. 1983). I had cloned the *Waxy* gene from both a wildtype revertant strain of what Barbara designated the *Ac wx-m9* allele and two strains with *Ds* insertions in the *Waxy* gene. One of these was designated *wx-m9* by McClintock and was a direct derivative of the *Ac wx-m9* allele, while the second, *wx-m6*, was of independent origin and arose by transposition of a *Ds* from another position on the same chromosome. When the wild-type and *Ac wx-m9* recombinant viral DNAs were denatured, re-annealed, and examined by electron microscopy, I saw a double-stranded molecules with a long, single-stranded loop, confirming the long-standing conjecture that the *Ac* transposon was a piece of DNA, in this case about 5 kb in length, inserted precisely into the gene. And just as I'd guessed, that first *Ds* turned out to be an *Ac* transposon with an internal deletion. The second *Ds* element, cloned from the *wx-m6* allele, contained a shorter element comprising about a kilobase from each end of the *Ac* element. It, too, likely arose by an internal deletion, although it had moved into the *Waxy* gene as an already mutant, non-autonomous *Ds* transposon.

Gene Tagging with Maize Transposons

An observation that grew out of analyzing maize DNA with the first three transposons of the *Ac–Ds* family eventually gave rise to the active transposon subfield of "tagging" using maize transposons in a number of different plants. Here's how it happened (Fedoroff et al. 1983). I used the 2-kb *wx-m6 Ds* as a probe for transposon ends and a short fragment from the middle of the *Ac wx-m9* transposon as a probe for the central part of the transposon. Importantly, the selected fragment covered the deletion site in the *Ds* element cloned from the *wx-m9* allele and therefore gave a shorter fragment. When DNA from either the *Ac wx-m9* or *wx-m9* strains were probed with the *wx-m6 Ds* probe homologous to the ends of the *Ac* transposon, I picked up many homologous fragments of many different sizes. Yet when I probed the respective maize DNAs with a probe corresponding to the middle of the element, I picked up fewer bands, only one of which was the exact size of the fragment in the cloned *Ac* element. There was also a fragment in that size range in the *wx-m9* DNA and it co-migrated with the central fragment cut from the *Ds* transposon cloned from the *wx-m9* DNA. That meant very simply that the genetic observation that there was a single *Ac* element in the genome carrying the *Ac wx-m9* allele and it was the one inserted in the *Waxy* gene!

Thus the single genetically active *Ac* element appeared to have a unique structure. The very obvious implication was that it might be possible to identify a gene in which there was an Ac insertion mutation without knowing anything about the gene product. In view of how much we know about gene structure, homology and function today, it is difficult to imagine how hard it was back then to clone a gene knowing nothing about it other than its genetic behavior. Since that was decidedly the rate-limiting step in gene isolation at the time, we decided to determine whether we could use what we knew about *Ac* structure to clone a gene whose gene product was far less abundant than that of the *Waxy* locus. We picked the *Bronze (Bz)* gene, one of the genes in the anthocyanin pigment biosynthetic pathway and one that had figured prominently in McClintock's early analyses of maize transposon behavior.

The *Bz* gene encodes a UDPglucose-flavonol glucosyltransferase whose activity stabilizes the deep purple anthocyanin pigments produced in the kernel aleurone layer. It is not an abundant enzyme and efforts to purify it directly had not gone well. But McClintock's *Ac bz-m2* allele carried an intact, autonomous *Ac* transposon and she had identified a derivative, *bz-m2(DI)*, that carried a non-autonomous *Ds* element. It had been derived from the parent *Ac bz-m2* allele and was likely to have a mutated *Ac*, much like the one I'd characterized at the *Wx* locus. We screened recombinant viruses containing fragments of DNA cut with enzymes that we knew didn't cut within the *Ac* sequence with a short probe corresponding to the center of the *Ac* element. We isolated 25 such clones; of these, 6 gave fragments of the right size for an intact *Ac* element and 4 of these 6 had the same flanking sequences, which turned out to be the *Bz* locus, as judged the comparative sizes of homologous fragments in strains with and without *Ac* insertions (Fedoroff et al. 1984).

While a number of investigators went on to use precisely these observations to clone genes from maize strains with insertions of both *Ac* and other transposons, we thought that this "transposon tagging" methodology would be even more widely useful if we could show that maize transposons could move in plants other than maize. The first step was to show that *Ac* could move in another plant and the obvious choice, for ease of transformability, was tobacco. I had raised the possibility of a collaboration during a phone call with Jeff Schell, than already Director of the Max Planck Institute in Cologne, whose laboratory was carrying out many of the pioneering studies on the plasmids of *Agrobacterium tumefaciens*. The following summer I visited the Max Planck Institute and, I began a collaboration with Barbara Baker in Schell's group.

To function in another plant, the *Ac–Ds* system necessitated correct expression of the element-encoded proteins as well as complementation by other proteins required for transposition. The first effort was quite straightforward and involved transforming the original *Ac* and *Ds* clones from the *Wx* gene into tobacco cells using *A. tumefaciens* Ti-plasmid vectors. The transformed clones were probed with both transposon probes and a probe to detect the short fragment of *Wx* DNA surrounding the insertion site. The results were positive: the empty donor site fragment was detectable in the lines transformed with the *Ac* element, but not those transformed with the *Ds* element (Baker et al. 1986). In a subsequent publication, the detection system grew more sophisticated (Baker et al. 1987), and in the ensuing years, marked transposons based on the *Ac–Ds* family and later the *Suppressor-mutator* (*Spm*) were widely used. *Ac–Ds* family transposons were even shown to transpose in organisms as varied as *Arabidopsis* and carrots (Van Sluys et al. 1987), to rice (Qu et al. 2009), tomato (Levy et al. 2000), yeast (Weil and Kunze 2000), zebrafish, and even human cells (Parinov et al. 2006).

Fortunately, I had filed a patent application on using transposable element to clone plant genes, and the patent was granted in due time. Over the years that it was in force, the patent brought in substantial licensing fees from companies, some of which have been committed to funding (upon my demise) a post-doctoral fellowship honoring McClintock within the Carnegie Institution for Science, home institution to both Barbara McClintock and me for a good fraction of our careers.

The Regulation of Recombinant DNA Research

Perhaps because I am a woman or perhaps because I was close to Washington, but most certainly because I was one of the first plant molecular biologists, I was pulled into the recombinant DNA regulatory issues early in my career. My first adventure in Washington committees was serving on a scientific advisory panel on applied genetics convened by the then extant Office of Technology Assessment of the US Congress, asked to assess the future growth of US agricultural productivity. By the next year, I was a member of the new NIH Recombinant DNA Advisory Committee

(RAC), convened by the NIH Director to provide him with advice how recombinant DNA research should be carried out (Wivel 2014).

The RAC was organized by the NIH in response to concerns raised by several prominent scientists in letter to Science (Berg et al. 1974) and following a widely publicized conference convened at the Asilomar Conference Center to discuss laboratory containment conditions appropriate to the limited state of knowledge about the then new recombinant DNA (rDNA) technology. By the time I joined the RAC, it had elaborated and published a set of guidelines for the conduct of recombinant DNA research and had established itself as the go-to place for both academic and industry scientists to present and discuss not just proposed experiments, but the containment conditions under which they were to be carried out.

The RAC was a purely advisory committee to the NIH Director and had no ability to enforce its decisions. Nonetheless, just about everyone played by its rules, both companies and academic scientists. The few discovered violators lost NIH funding, but more importantly, lost the respect of their colleagues. That said, the initial guidelines were purely conjectural and based on the guesses of Asilomar conference participants and the initial RAC members about what might be dangerous. Perhaps the most critical aspect of how the committee functioned was its ability to consider new information, propose modifications to the guidelines, publish them for public comment and finally implement the modifications. Because rDNA technology proved so powerful in understanding genes, it was adopted extremely rapidly within the scientific community, hence experience with rDNA organisms accumulated rapidly. Because none of the conjectured problems emerged, the RAC was able within a few years to decrease the stringency of the containment conditions required for experimentation with rDNA and to progressively exclude many kinds of experimentation from the requirement for more than good laboratory practice.

As well, the RAC was able to re-examine some of the total prohibitions articulated in the earliest versions on the guidelines. For example, the initial guidelines forbade the cloning of toxin genes, such as those encoding the botulinus toxin, into *Escherichia coli* vectors. However, when the RAC convened a committee of researchers who worked the organisms that produce such toxins, it became apparent that cloning a toxin gene was, in fact, the safest way of working with it in the laboratory, because the laboratory strains of *E. coli* lack the genetic apparatus to colonize the gut and deliver the toxin to target tissues.

Throughout this early period, rDNA technology received quite a lot of publicity and generated considerable controversy. Perhaps the most outspoken critic of rDNA research in that period was Jeremy Rifkin, author of a 1977 book titled "Who Should Play God" (Howard and Rifkin 1977). Rifkin came to some of the RAC meetings, always making his views known. During my final year on the RAC, I was also a Phi Beta Kappa Visiting Scholar and spoke to both academic and community audiences about the substance of rDNA science, as well as the surrounding controversies, later publishing a written version of my talk in the Syracuse Scholar (Fedoroff 1986). During a visit to the University of Ohio, I met with faculty members engaged in rDNA research in animals, in addition to giving a radio

interview and a public lecture. After my visit, letters from that part of the country began to come into the RAC expressing clear support of rDNA research, whose promise for medicine was already apparent—and would only grow in the future (I do not take credit for this, as I believe someone in the community organized the letter-writing campaign). The RAC's chairman was able to point to a stack of several hundred supportive letters in answer to Rifkin's next diatribe against rDNA research.

The first requests to field test transgenic plants began to come to the RAC in approximately 1983. The most striking result was that individuals from several regulatory agencies began to come to RAC meetings. As well, I began to be invited to attend meetings with regulators from the U. S. Department of Agriculture (USDA) and the Environmental Protection Agency (EPA). While the RAC continued to receive requests to approve research involving plants, it became evident that the EPA, the USDA, and to some extent the Food and Drug Administration (FDA) viewed transgenic plants as within their regulatory purview. By 1984, I had completed my term on the RAC and had become a member of both the Commission on Life Science and the Board on Basic Biology of the National Academy of Science (NAS), both of which had considerable interest in the regulation of rDNA research.

In due time, the Office of Science and Technology Policy convened a taskforce to coordinate the regulatory interests of the various agencies that had an interest in the use of rDNA technology in their domains, including the EPA, the USDA and the FDA. The committee produced a document titled the "Coordinated Framework for the Regulation of Biotechnology," which in 2016 remains the regulatory framework under which all three agencies continue to function (OSTP 1986). Tragically for biotechnology, particularly agricultural biotechnology, the actual regulatory practice evolved in an unintended direction.

In roughly the same timeframe, the Council of the NAS convened a small committee to produce a "white paper" expressing the NAS Council's position on the issues surrounding the introduction of rDNA organisms into the environment. I was asked to serve on the committee, chaired by plant pathologist and NAS Council member Arthur Kelman. The committee was small, but diverse, consisting of Wyatt Anderson, Stan Falkow, and Si Levin in addition to Kelman and me. After many rewrites and much discussion, we produced the promised white paper, titled "Introduction of Recombinant DNA-Engineered Organisms into the Environment: Key Issues" (Kelman et al. 1987).

The main conclusions of the white paper were as follows. First, there was then (and still is) no evidence that unique hazards attend the use of rDNA techniques or the movement of genes between unrelated organisms. Second, that the risks associated with the introduction of genetically engineered (GE) organisms into the environment were the same as those attending the introduction of unmodified organisms or organisms modified by more traditional techniques (which include chemical and radiation mutagenesis). And third, that assessment of risks of introducing GE organisms into the environment should be based on the nature of the

organisms and the environment into which it was being introduced, not the method by which it was produced.

The OSTP committee basically subscribed to the same view on GE organisms as the NAS committee and therefore felt that no new legislation was necessary for organisms modified by rDNA techniques. The committee directed each of the three relevant agencies, the EPA, the USDA, and the FDA to find existing legislation under which to oversee the introduction of GE organisms into the environment and to make it product-, and not process-based. What actually happened is that only GE organisms were subjected to a high level of regulatory scrutiny, some spending years in regulatory purgatory before being approved. Moreover, EPA regulated under laws written to regulate toxic substances and the USDA regulated them as if they were plant pathogens. Only the FDA formulated a policy that was based on composition and not on process—and may not be able to stick to that decision, as evidenced by the recent congressional directive seeking to compel the FDA to mandate labeling of genetically modified salmon, despite the FDA's clear policy that labeling is reserved for ingredients with health or environmental implications.

The GMO Wars

Following the publication of the NAS white paper, I wrote a number of editorials about GE organisms for the NAS, as well as a New York Time Op Ed piece titled "Impeding genetic engineering" that appeared in the 2 September issues of 1987. I was still naïve enough to believe that the controversies would die down as people understood the technology and began to benefit from it. I took every opportunity offered to speak and write about these new molecular techniques of genetic modification. In 2001, I began discussing writing a book about genetically modified organisms, aka GMOs, with Nancy Marie Brown, a wonderful science writer then working for Penn State. It was to be focused on food and intended for a general audience. In due time, we became a good writing team: I did the research and provided the science, while Nancy deconvoluted my sentences and wrote readable stories around the science. The book, titled "Mendel in the Kitchen: A Scientist's View of Genetically Modified Foods," was published by the Joseph Henry Press of the National Academy of Sciences in 2004.

The publication of my book thrust me deeper into the controversies, already quite fierce, which have continued to surround the use of molecular modification techniques in plants and animals destined for food, that is, agricultural biotechnology. Many, although far from all, new technologies generate some resistance and some scare stories. So, for example, cell phones were rumored to produce brain tumors and food irradiation was suspected to make foods radioactive. With time and experience, many of these early concerns die down—who even remembers the cell-phone rumors when chasing the latest Apple iPhone? This is true even in the genetic engineering realm: what would we do today without the many drugs—

perhaps most prominently recombinant human insulin—produced using rDNA technology?

I first encountered the intensity of people's feelings about GMOs when I was touring the country promoting my book in 2004. At one "science café" in Berkeley, California, an audience member rushed from the back of the room, grabbed the microphone away from me, and began to shout about how this new science was ruining the flour he used in his bakery (there was and is no GM wheat yet). The audience surrounded me, fearing that he was about to attack me. The occasional organic farmer showed up at other venues, often speaking passionately about the evils of GMOs. But what I most often encountered was people uncomfortable with new genetic "technology" in the food space and seeking to blame it for what they saw as the eroding taste of fruits and vegetables (that, of course, resulted from conventional breeding for increased yield and decreased perishability on the way to market over taste).

In hindsight, the discourse about GMOs was still relatively civil back then. The escalation of GMO discussions in the public domain from discomfort and suspicion about a new technology to a full-scale war of words happened rather gradually though the last decade of the 20th century and continues unabated in the second decade of the 21st. This happened, paradoxically, even as the GM crops were commercialized and adopted at record speeds in much of the world with substantial economic and environmental benefits and with no evidence of harm to people, animals or the environment. The reasons for the continuing chasm between how the public views GMOs and the scientific evidence on their safety and efficacy are both interesting and deeply disturbing.

First, the scientific and economic evidence on GM crops today (as of this writing, there are no GM animals in commercial agriculture or aquaculture). GM crops have been adopted at unprecedented rates since their commercial introduction in 1996. In 2014, GM crops were grown in 28 countries on 181.5 million hectares (James 2015). More than 90% of the 18 million farmers growing biotech crops today are smallholder, resource poor farmers. Farmers aren't fools: they migrate to GM crops because their yields increase and their costs decrease. The simple reasons that farmers migrate to GM crops are that their yields increase and their costs decrease. A recent meta-analysis of 147 crop studies conducted over a period of 20 years concluded that the use of GM crops had reduced pesticide use by 37%, increased crop yields by 22% and increase farmers' profits by 68% (Klümper and Qaim 2014).

The GM crop base remains very narrow, with the vast majority of GM acres devoted to corn, soybeans, cotton and canola, largely because these are the kinds of extremely widely grown commodity crops that can support the cost of both their development and the huge regulatory costs that attend deregulation. Until last year, when President Obama issued a directive to the regulatory agencies to reexamine their approach to the regulation of biotechnology, the regulation of GM crops and animals was still operating under the 1986 Coordinated Framework for the

Regulation of Biotechnology (OSTP 1986) on a case-by-case basis and applied only to crops modified by molecular techniques.

The overwhelming evidence is that the GM foods now on the market are as safe, or safer, than non-GM foods (Richroch 2013). There is still no evidence that the use of GM techniques to modify organisms is associated with unique hazards. The EU has conducted biosafety research for more than a quarter of a century, expending upward of €300 million on 130 research projects involving more than 500 independent research groups. A recent report on this research concluded simply that biotechnological (e.g. GM) approaches are no more risky than older methods of modification (http://ec.europa.eu/research/biosociety/pdf/a_decade_of_eu-funded_gmo_research.pdf). Every credible scientific body that has examined the evidence has come to the same conclusion (http://gmopundit.blogspot.com/p/450-published-safety-assessments.html).

To date, the only unexpected effects of GM crops have been beneficial. Many grains and nuts, including corn, are commonly contaminated by mycotoxins, which are toxic and carcinogenic compounds made by fungi that follow boring insects into the plants. Bt corn, however, shows as much as a 90% reduction in mycotoxin levels because the fungi that follow the boring insects into the plants cannot get into the Bt plants (Munkvold 2003). Interestingly, planting Bt crops appears to reduce insect pressure in non-GM crops growing nearby. Indeed, the widespread adoption of Bt corn in the U.S. Midwest has resulted in an area-wide suppression of the European corn borer (Hutchison et al. 2010).

While there is a global consensus among scientists and scientific organizations that GM technology is safe, the political systems of Japan and most European and African countries remain opposed to growing GM crops. Many countries lack GM regulatory systems or have regulations that prohibit growing and, in some countries, importing GM food and feed. In Europe, the regulatory framework is practically nonfunctional; only one GM crop is currently being grown and only two others have gained approval since 1990 when the EU first adopted a regulatory system (Kershen 2014).

But even countries such as the U.S. that have a GM regulatory framework, the process is complex, slow and expensive. U.S. developers must often obtain the approval of three different agencies, the EPA, the USDA, and the FDA, to introduce a new GM crop into the food supply. Bringing a GM crop to market, including complying with the regulatory requirements, was estimated to cost $135 million in 2011 (McDougall 2011). By contrast, crops modified by older techniques, including radiation and chemical mutagenesis require no regulatory oversight.

It could be argued that when the molecular modification technology was first introduced more than 30 years ago, a cautious approach that even exaggerated the potential for harm was justifiable, but it is increasingly clear that the persistence of such a highly precautionary approach is today politically driven (Smyth and Phillips

2014). Let's "follow the money." NGOs, most vocally Greenpeace and Friends of the Earth, have conducted vigorous and successful campaigns of misinformation about GMOs first in Europe, then around the world (Paarlberg 2014; Wesseler and Zilberman 2014). Patrick Moore, one of the co-founders of Greenpeace has pointed out that: "Greenpeace is clearly a big-money operation these days, as intent at feeding itself as any corporation is" (http://www.science20.com/science_20/cofounder_of_greenpeace_greenpeace_is_wrong_about_golden_rice-122754). Apel has written extensively on the economics of opposing GMOs, concluding: "The key players encompassed by the definition of 'opponent' of engineered crops reap billions annually from restricting agricultural biotechnology or the food that results. Indeed, more money can be made from restricting agricultural biotechnology than by delivering it" (Apel 2010).

Perhaps the most counterproductive—even sinister—development is the increasing vilification of GM foods as a marketing tool by the organic food industry (Schroeder 2014). The organic agriculture finds its roots in rural India where Sir Albert Howard, known as the father of organic agriculture, developed composting methods that could kill the pathogens that abound in human and animal waste (Fedoroff and Brown 2004). The organic movement grew in the UK and Europe during the early 20th century and was later championed in the US by Jerome Rodale, even as synthetic fertilizers use was increasing worldwide. With the establishment of organic retailers, such as Whole Foods and Wild Oats, the organic food business grew rapidly and certification organizations proliferated. In the 1990s, Congress established the National Organic Standards Board (NOSB) under the USDA through the Organic Food Production Act and charged it with developing national standards, which were eventually published in 2000 and often called the "Organic Rule" (http://www.ams.usda.gov/grades-standards/organic-standards). The Organic Rule expressly forbids the use of GM crops, antibiotics, and synthetic nitrogen fertilizers in crop production and animal husbandry, as well as food additives and ionizing radiation in food processing.

Organic food is food produced in compliance with the Organic Rule; the USDA's Organic Seal is a marketing tool that makes no claims about food safety or nutritional quality. But the organic food industry has systematically used false and misleading marketing about the health benefits and relative safety of organic foods compared with what are now called "conventionally grown" foods (Schroeder 2014). Indeed, organic marketers represent conventionally grown foods as swimming in pesticide residues, GM foods as dangerous, and the biotechnology companies that produce GM seeds as evil, while portraying organically grown foods as both safer and more healthful. Recent "labeling" campaigns have the objective of promoting the organic food industry by conveying the message to consumers that food containing GM ingredients is dangerous. Mainstream media frequently carry messages that are positive about organic food and extremely negative about GM foods through programs like the Dr. Oz Show and through popular food writers

such as Michael Pollan and Mark Bittman (Schroeder 2014). Simply said then, there's money and fame in being anti-GMO.

Why I Continue to Talk About GMOs

Over the almost four decades since my chance encounter with Barbara McClintock at Cold Spring Harbor focused my early career on inventing and using molecular techniques in plant biology—now, of course, called plant biotechnology—I have seen plant biologists amass vastly more knowledge about how plant genetic and physiological systems work at the biochemical and molecular levels than in all of the previous history of botany. I have appreciated contributing at many different levels, from developing techniques, to starting the whole field of plant transposon-ology, particularly transposon tagging, to explaining GMOs to anyone who would listen. In 2007, perhaps as a result of my continuing service on various Washington committees, I received an invitation from the President of the National Academy of Sciences to be a candidate for the position of Science and Technology Adviser to the Secretary of State, then Condoleeza Rice. Thinking this might give me a bit of an international bully pulpit from which to talk about GMOs, I agreed and, somewhat to my surprise, got the job. A few weeks into that new job, I was invited by Henrietta Fore, then the Administrator of the U.S. Agency for International Development (USAID) to be her science adviser, as well.

Wherever I traveled, with the noted exception of France, my scientific expertise on biotechnology was welcomed. I traveled to many countries, spoke to many audiences, and did endless press interviews on science, science diplomacy—and most of all, why GMOs and biotechnology matter to the world. My own word view expanded suddenly in 2009 when I attended a small, very international meeting on the impact of climate change on agriculture in Spitzbergen, Norway. Below is what I wrote for Andy Revkin's Dot Earth blog on the airplane coming home:

> Dear Andy, 27 February 2009
> I write you from the far frozen north of Norway. Near the village of Longyearbyen, on the island of Spitzbergen, is a remarkable structure called the Svalbard Global Seed Vault. In chambers deep in a mountain whose temperature never rises above freezing is a storage chamber, further cooled to a temperature of −15 °C. In it are seeds of some 70,000 varieties of 64 of the world's major food crops. Marking the Vault's first anniversary, a small scientific meeting focused on how climate change will affect humanity's ability to grow food.

It's cold here. But a deeper chill settled on us as we listened to the climate scientists' scenarios for the coming decades. Even if we all stopped driving, flying and turned every light out tomorrow, the CO_2 we've already poured into our atmosphere over the last 100 years means that next hundred will be much hotter than the last 100.

It seems we've begun to absorb the notion of hotter, drier summers, rising sea levels and more extreme weather—bad enough. But who's thought much about what a changing climate might mean at the grocery store? No matter whose projections, no matter whether the best, worst or most probable scenario, our crops will suffer—and I mean OUR crops, not just those in some distant land.

Here's a real example of what a higher temperature can do. In 2003, France and Italy had a summer that was just 3.5% hotter than their usual summer. It rained as usual, but the yields of major crops were still down by 20–36%. Projections show that this will be the average summer by 2090.

And within the next few decades, it's nearly certain that we'll be recording summer hotter than ever recorded. Many of our crops fail completely if the temperature goes much above 100 °F for just a few days at a critical flowering time. During my days as a corn geneticist, I watched the tassels turn brown and sterile the summer it hit 108° in Columbia, Missouri at pollination time.

To put this in perspective: the food crisis of 2008 called attention to how close we are to the limits of the global food supply. But unlike the financial one, the food crisis isn't going away. This is because the number of people on the planet is still growing and by midcentury we'll need to roughly double the food supply—which, of course, starts with growing crops, whether to feed us or to feed to pigs and cows and chickens. Yet the amount of land on the planet that's good for growing crops hasn't changed much for more than half a century.

Will the warming climate open lands for cropping farther north? Probably, though how much is uncertain. What is quite certain by now is that climate change will squeeze those farther south as soil moisture declines. This will affect the most populous countries, countries whose populations are growing fastest.

So what do we do? The Global Crop Diversity Trust (http://www.croptrust.org/main/arctic.php), which funds the Vault, is dedicated to the preservation of the genetic diversity in our food crops. They are motivated by the belief that it is this diversity that will be the source of the genes we will need to develop plants that can grow on a hotter, drier planet.

Maybe. But the fact is that over the entire (more than) 10,000 year history of agriculture, the CO_2 levels in the atmosphere were between 180 and 280 ppm. We're at 389 now. It's not unlikely that we'll hit 700 ppm before we get this problem under control. That's going to mean that it'll get hotter and drier than anything but desert plants have seen before. Desert agriculture isn't new, but scaling it up will be a challenge and may mean venturing outside the limits of our current stable of crops.

I rather think we should also be scrambling to explore and understand organisms—not just plants—that have evolved to survive and thrive in the parts of the earth that are already the hottest and driest. We'll need to understand how they survive. We'll need to capture the genes that make it possible. If we're lucky, we'll be able to use these to arm some of our super-productive crops plants to survive and thrive under such conditions. If we're lucky. And if people stop being so reluctant to use modern molecular science to enhance crops.

Cheers! Nina

Upon my return to Washington, I organized an interagency workshop on the impact of climate change on agriculture, a subject that still receives little attention, even though severe weather is making us increasingly aware that the climate is changing. The speakers ranged from climate scientists to water experts to biotechnologists to conventional agricultural experts. Together we penned a piece titled "Radically rethinking Agriculture for the 21st Century" for Science magazine (Fedoroff et al. 2010). We judged the overall challenge of feeding a still-growing human population, already numbering more than 7 billion, on a warming planet as perhaps the greatest challenge of the century.

As I approached the end of my term at the State Department, I was invited to attend the opening of the King Abdullah University of Science and Technology (KAUST), as well as to present a paper in their opening science symposium. I had participated in the early phases of KAUST's organization just a few years earlier, before I entered the State Department and had to step away from that advisory role. I attended the spectacular opening on behalf of the State Department and presented a paper that synthesized concepts about important innovations in agriculture necessary to assure a food-secure future. Upon leaving the State Department, I was invited to join the KAUST faculty. I proposed to establish a Center for Desert Agriculture (https://cda.kaust.edu.sa/Pages/Home.aspx) and spent the next 4 years doing so.

I continue to talk and write about GMOs and the future of agriculture. In 2014, I was invited to give a TEDx talk (https://www.youtube.com/watch?v=fqJAeReFr8I)

at CERN in Geneva, giving me an opportunity to assemble an overview from an agricultural perspective of what falsified Thomas Malthus' gloomy prediction two centuries ago that humanity was doomed to famine and strife because population growth would always outstrip its ability to produce food (Malthus 1798). The answer, of course, is the rapid introduction of science and technology into agriculture in the 20th century (Fedoroff 2015). And yet in some sense, agriculture is threatened in the 21st century not just by population growth and climate change, but by its very success in freeing ever more people from the back-breaking labor of agriculture and vastly increasing its capacity to produce food.

The shift of population from rural to urban has been dramatic in the developed world, with less than 2% of the population today supplying the food for the rest. Most of us are urban today and have access to food through a vast global food system that supplies our food retailers with abundant produce. We are far removed from agriculture, blind to its basics and vulnerable to the increasingly strident opponents of modern agriculture who have successfully used fear to promote their own economic interests.

It is ironic that just as we have developed methods to make agriculture more sustainable and less reliant on the kinds of chemical inputs that have collateral damage, we have begun to turn on the very science that underpins our abundant, safe food supply. We certainly have the tools to vastly improve both the productivity and the sustainability of agriculture. GPS-guided, programmable farm machinery can markedly reduce water, chemical and energy use in agriculture. But today's affluent urban dwellers denigrate efficient, large-scale farming with the moniker "factory farming." We have the tools to modify crops to meet the challenges of climate change and shifting disease distributions, but the organic food marketers are doing their best to turn consumers against foods containing GM ingredients. And the regulators are still caught in the precautionary trap, unable to convert the evidence that foods with or from GM crops and animals are as safe or safer than any we've ever introduced into our food supply. Unfortunately, belief systems, particularly those around food, are very difficult to dislodge, however large the mountain of available facts.

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