Chapter 2
The Global Importance of Transgenic Cotton

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Abstract The origins of transgenic cotton are reviewed including the original objectives, early efforts to establish the technical capabilities, selection of initial traits for development, market place benefits, and global acceptance of the technology. Further consideration is given to cotton's place in the effort to meet the projected demands for food and fiber over the next 50-year horizon, traits and technologies under development, and the need for close public and private research collaboration in order to address the issues facing the world's farmers as they work to meet those demands. Impact of transgenic cotton on global economy, environment, genetic diversity, and safety is also highlighted.

Keywords Cotton · Transgenic cotton · Cotton traits · Global economy · Genetic diversity

2.1 Historical Perspective

In a book published in 1957 (Brown et al. 1957), James Bonner emphasized that significant problems would face the world's agricultural producers as they sought to keep pace with the needs of the growing population. First, James envisioned ongoing pressure on agricultural productivity and an elevation of the costs of production as a consequence of industrialization attracting more and more of the world's labor force at the expense of farm labor. Science and technology were posited as the most likely means of increasing overall farm output in order to produce the food (calories) and fiber required to feed and clothe the world's

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increasing population. Bonner also foresaw a second challenge to agricultural output in the form of public resistance to the adoption of those very technologies that would be essential to achieving the necessary gains in per acre productivity to feed the world's growing population. On this point, James cited a commonly encountered public sentiment of his day that chemical fertilizers would be poisonous to plants if used to replace manure. The more the things change, the more they stay the same? Cotton biotechnology is nothing more, or less, than developing and applying technology to improve farm output in the face of decreased labor availability and increasing costs of same, reducing costs associated with controlling yield-reducing pests, and improving the value of the fiber cotton farmers produce. In many respects, the problems foreseen by James Bonner 58 years ago are where our present writing begins and ends.

It is appropriate that 23 years after the publication of "The Next Hundred Years," James, along with the J.G. Boswell Company, became a co-founder of the plant biotechnology company Phytogen. Phytogen was an early entrant in the field of plant biotechnology with a primary focus on developing and deploying biotechnologies in the improvement of cotton through increasing output per acre, reducing costs of production, and in improving the overall value received by farmers for the seed and fiber produced on a per acre basis. Phytogen was very successful both in the development of many of those technologies and in the commercialization of transgenic cotton, mirroring the advancements made by many researchers across other major row crops in elevating productivity per acre and delivering on-farm economic improvement through the development and deployment of various biotechnologies.

In our discussion of transgenic cotton and its global impact, it is useful for us to establish what we do and do not mean by the phrase "transgenic." The Dictionary of Botany published in 1980 (Little and Jones 1980), which sat on the corner of the laboratory bench at the time Phytogen began laboratory operations, did not define the term. Clearly, when this dictionary was published, the same year in which Phytogen was founded, the science underlying transgenic plants was yet to be created. It is worth noting the remarkable advancements that have been made in the very short intervening period since those very first days in the laboratory. The online Oxford Advanced Lerner's Dictionary (2015) defines the term as "having genetic material introduced from another type of plant or animal." This definition underscores the advances made in the development and application of biotechnologies and the general public awareness of same as the referenced dictionary is a Web-based resource used by the general public. This definition does have its limitations for our purposes here, as transgenic plants in general, cotton included, can and do carry genetic material from bacteria, fungi, animals, or other plants. Transgenic cotton can also carry genetic material from other cotton plants which has been removed, altered in some particular way, and then reintroduced. One such example would be cotton plants resistant to sulfonylurea herbicides created by isolating a cotton gene for acetohydroxyacid synthase (AHAS), introducing point mutations at particular serine (653) or tryptophan (574) codons, and then reintroducing these same mutated AHAS genes back into cotton to create cotton plants

resistant to certain sulfonylurea and imidazolinone herbicides (Grula et al. 1995; Rajasekaran et al. 1996a, b). For the purposes of this discussion, we will consider a transgenic cotton plant as one which carries a heritable foreign gene construct irrespective of the source of the foreign DNA. Excluded will be cotton plants carrying heritable traits resulting from the use of other means of altering the genome such as somaclonal variation, EMS mutation, or site-directed in situ modification via technologies such as zinc finger nucleases (Rajasekaran et al. 1996a; Cai et al. 2008; Shukla et al. 2009). In each of these latter examples, heritable alterations in the genome can be introduced and/or useful phenotypes selected, but no foreign DNA per se remains in the resulting plant. Hence, they will not be considered transgenic.

The development of transgenic cotton began in earnest in 1980 in parallel with the broader focus by many private and public organizations in development of transgenic plants per se. It is also of note that this is the year in which the United States Supreme Court ruled that living organisms could be patented so long as it could be demonstrated that they were the products of man and not naturally existing in nature (Diamond v Chakrabarty 1980). This ruling opened the way for infusions of research dollars from private industry as patent protection was necessary to ensure the commercial success of transgenic plants. Protection of technology is essential to business success as it enables shareholders and the investing public the opportunity to recover and then profit from the large dollar investments that are required to develop and bring biotechnologies to market. Such traits must be delivered in the best germplasm (seeds) available in order to be useful to farmers, and most seed companies are privately held. Private industry was thus best positioned to carry the weight of both trait development, introgression of those traits into leading cultivars, and subsequent delivery to farmers in the form of seeds. Partnerships between public and private institutions were viewed as essential to the entire endeavor. Creative scientists armed with unbounded optimism took on the challenge of solving some of the globes' most difficult crop production problems by developing and then applying plant biotechnology.

Those of us working in the field of plant biotechnology in general, and cotton biotechnology in particular, recognized the need to (a) develop gene constructs that would function in cotton plants; (b) establish methods for introducing heritable foreign gene constructs, including selectable markers, into cotton cells; (c) select cells that had been genetically altered and which were expressing the introduced genes ("transformed"); (d) establish the ability to regenerate fertile cotton plants from cells; and (e) build useful libraries of regulatory sequences and genes, thereby enabling the development of multiple generations of cotton plants with combinations of useful traits. While there were relatively few laboratories focused on cotton in the early 1980s, competition to establish these capabilities for plants in general from both private and public sector laboratories was spirited. All things considered, progress came remarkably quickly, both for plants in general and for cotton in particular. Davidonis and Hamilton (1983) reported the important finding that at least one Coker cultivar was amenable to somatic embryogenesis, while parallel work extended regeneration success to other commercial cottons including high

fiber quality Acala and Pima varieties and a broad range of additional Midsouth upland cotton varieties (Rangan and Zavala 1984; Trolinder and Goodin 1987; Shoemaker et al. 1986; Rangan and Rajasekaran 1997; Sakhanokho et al. 2001; Sakhanokho and Rajasekaran 2016). The development of vectors, selectable markers, and transformation in plants emerged from a period of intense, creative public and private research on a global scale in the early 1980s, both for *Agrobacterium*-mediated (Fraley et al. 1983; Hoekema et al. 1983; De Block et al. 1984; Horsch et al. 1985; An et al. 1985) and for transformation with "naked" DNA per se (Anderson 1985; Potrykus 1991). Successful cotton transformation was achieved during this same period (Firoozabady et al. 1987; Umbeck et al. 1987; Chlan et al. 1999; Rajasekaran 2004; Rangan et al. 2004). Selectable markers initially included genes conferring resistance to antibiotics such as kanamycin (Fraley et al. 1983) and hygromycin (Waldron et al. 1985). For many practical reasons, public researchers still make wide use of antibiotic resistance markers for selection, while private companies now typically avoid antibiotic resistance markers and use genes for resistance to various herbicide tolerance traits such as glufosinate (Thompson et al. 2005), AHAS inhibitors (Rajasekaran et al. 1996b) and on occasion glyphosate (Rathore et al. 2008).

2.2 Initial Traits and Trait Development

For the farmer, viability of his or her farming operation is driven by three simple factors including (a) total productivity per acre, (b) costs of production on a per acre basis, and (c) the market value for what is produced. Put simply, and this is a global reality, the grower needs higher yield, lower costs of production and a good price for what he produces. From the very beginning, the objective of cotton biotechnology across programs (public and private) has been to deliver against those three primary grower needs. Our own approach has been to view yield and stability of yield as best addressed initially through genetics, capturing of native traits from race stocks and diploid species, and the development of marker-based breeding tools and deployment of genome-wide selection capabilities to enable efficient and cost-effective introgression and stacking of those traits into high-yielding cultivars. The per unit value for what is sold depends largely on the quality of the fiber. The spinning performance of the fiber produced from a cotton crop, driven by its individual fiber properties such as length, strength, fineness, and maturity, will determine the extent to which farmers receive discounts or premiums for the harvested crop and hence drive output trait value. Given the complexity of the genetics conditioning overall spinning performance, and the relatively untapped reservoir of genetic resources for fiber improvement in cotton breeding populations, accessions, and race stocks, we likewise viewed fiber quality and output trait value as being best addressed initially by the aforementioned genetic tools. It is our perspective that single-gene (transgenic) constructs will not likely add sufficient economic value

to the complex genetic systems undergirding spinning performance within the foreseeable future.

For our program, it seemed apparent that the largest near-term opportunities for improving on-farm economic return utilizing biotechnology would come from developing in-plant resistance to lepidopteran insects and tolerance to broad-spectrum herbicides. Clearly, researchers in other companies reached the same conclusions. Namely, that insect resistance would reduce costly spraying to control insects, reduce the labor costs associated with said applications, and have the benefit of driving yield improvement in situations where weather conditions precluded field application or insect attack was below the treatment threshold but still negatively impacting yield. Concerns regarding increasing costs of production driven in large part by increasing labor costs and a shrinking pool of agricultural labor echo the theme voiced by Bonner in 1957 referenced earlier. With respect to herbicide tolerance, weeds compete for sunlight, water, and nutrients, harbor insect pests, host pathogens, and create trash that can end up in the lint, thereby reducing crop output trait (fiber) value. We, along with others, saw that resistance to environmentally safe, broad-spectrum herbicides such as glyphosate would simplify control practices and reduce overall labor costs. Personal conversations with cotton growers in 1981 reinforced these conclusions, both for insect resistance and for glyphosate tolerance.

The first glyphosate-tolerant plant was developed at Phytogen in the early 1980s resulting in the patent now owned by Dow AgroSciences which issued covering same (Rangan et al. 2004), while the first commercial glyphosate-tolerant ("Round-up Ready™") cotton variety was developed by Monsanto and introduced in 1997 (Rathore et al. 2008). US acres planted to glyphosate-tolerant cotton reached 65 % by 2006 and 93 % by 2009, and at present, approximately 98 % of US cotton acres are glyphosate tolerant (Roundup-Ready Flex and Glytol from Bayer Crop Sciences) (Fig. 2.1). Glyphosate tolerance has been a compelling tool in the hands of US cotton growers. It is important to note that the first transgenic cotton commercialized anywhere was developed by Calgene and was resistant to the herbicide Bromoxynil (BXN™ cotton; Stalker et al. 1988). The BXN™ cotton system, introduced in 1995, was excellent technology but ultimately lacked extensive uptake by growers due to its relatively narrow weed control spectrum versus glyphosate along with uncertainties for the future of the technology regarding a potential ban on BXN cotton due to certain environmental concerns (Kamalick 1997).

While herbicide tolerance in cotton is seen to be of keen importance to US cotton growers, the development of in-planta lepidopteran insect resistance has been even more crucial not only to US growers, but has been breakthrough technology globally. Monsanto lead the way in the USA with the introduction of Bollgard™ cotton in 1996, which comprised a gene for a single active component, the delta-endotoxin Cry1Ac from *Bacillus thuringiensis* (Perlak et al. 1990). Since the introduction of Bollgard™ cotton, the number of US trait providers has increased

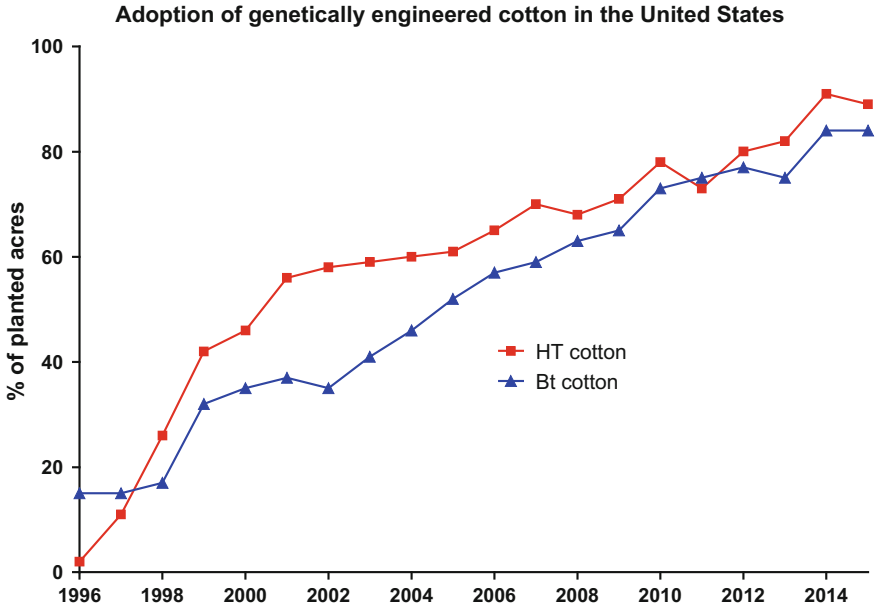

Fig. 2.1 Adoption of GM cotton in the USA from 1996 to 2015. Redrawn using data from USDA, National Agricultural Statistics Service

with a concomitant expansion of the spectrum of insects controlled, more effective resistance management, as well as giving farmers freedom of choice when determining trait and germplasm combinations best for their individual production needs. US growers now select between trait providers including Monsanto (Bollgard™ and Bollgard II™) and Dow AgroSciences (WideStrike™ and WideStrike 3™, and Bayer Crop Science (TwinLink™). Globally, Monsanto's Bollgard™ cotton has been of keen importance in Australia, India, and China. Dow AgroSciences' WideStrike™ trait is the preferred insect resistance technology in Brazil. Early assumptions that insect resistance and herbicide tolerance would deliver the most near-term value to cotton growers been borne out. In the USA, and Australia, where these technologies were first introduced in combination, varieties "stacked" with both insect resistance ("IR") and herbicide tolerance ("HT") dominate the market (Fig. 2.2). Clearly, growers have spoken very clearly as to the importance of these technologies in improving productivity while managing costs. For them, it is not an intellectual debate. In many cases, access has been the difference between prosperity and loss of one's farm and livelihood. Regulatory restraints have slowed the pace at which growers have had access to these technologies outside the USA, but IR traits have enjoyed rapid uptake when made available and have delivered excellent value to those growers fortunate enough to have access.

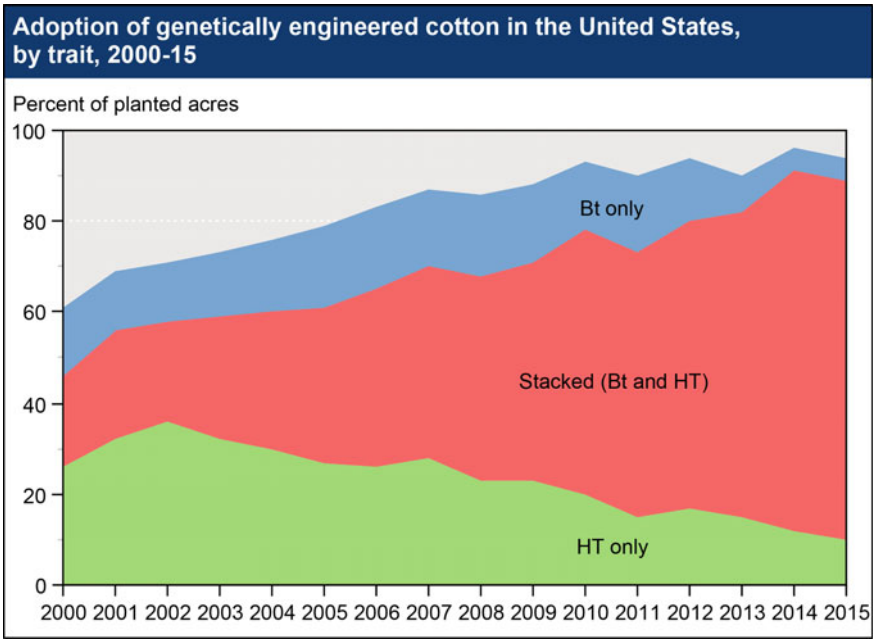

Fig. 2.2 Adoption of GM cotton in the USA, by trait, 2000–2015. *Source* USDA-Economic Research Service using data from USDA, National Agricultural Statistics Service, June Agricultural Survey

2.3 Global Adoption Is Driven by Benefits

In 1995, zero percent of global cotton production was planted to transgenic cotton. Twenty years later, it is estimated that roughly 25 million of the world's 37 million hectares of cotton production is planted to varieties carrying one or more biotech traits (Fernandez-Cornejo et al. 2014; James 2014). If accurate, then cotton (68 %) stands second only to soybeans (82 %) in terms of global hectares planted to transgenic varieties, and the same studies indicate that the adoption of transgenic cotton is increasing at about 5 % per year. Clearly, adoption of transgenic cotton varieties has proceeded quickly whenever transgenic cotton varieties have become available. US cotton growers went from 0 % planted to transgenic cotton to 85 % in 4 years. China went from 0 to 65 % in 4 years. India went from 0 to 90 % in 8 years (Fig. 2.3). Bt cotton has resulted in a virtual doubling of the national production of cotton fiber in India with almost no new hectares added under cultivation. India is now a major exporter of cotton fiber rather than a net importer, driving significant value back to the individual cotton farmer. There are approximately 6.3 million cotton farmers in India with an average cotton farm size of about

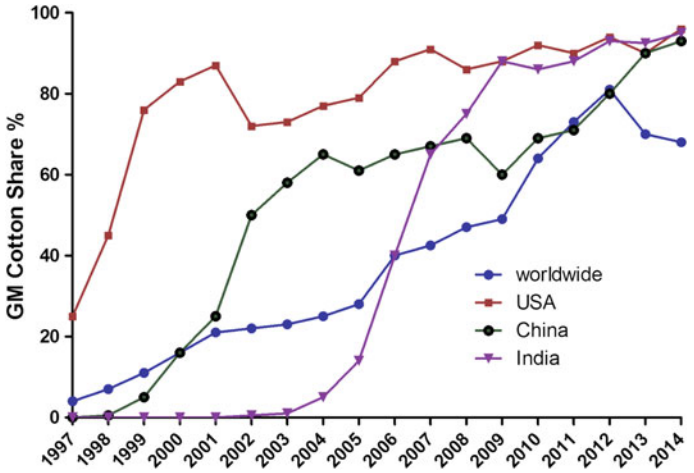

Fig. 2.3 Transgenic cotton share (%) in the total global cotton acreage and in three selected countries. Redrawn from data provided by GMO-Compass.org, ISAAA, and USDA-ERS

1.5 ha. Historically, these have been some of the world's poorest farmers, with cash from operations rarely meeting yet alone exceeding costs of production. For them, Bt cotton has been a revolution in productivity and economic opportunity. Cotton is an important cash crop for them, and one estimate places the economic benefit back to the India's cotton farmers at $5.1 billion (Choudhary and Gaur 2010). Furthermore, Bt cotton significantly reduces pesticide spraying, thereby increasing the safety of their farming activities. A similar story has unfolded in Burkina Faso, where Bt cotton was introduced in 2008 and now represents more than 70 % of the nation's production. Yields have increased an estimated 20 % over conventional cotton, and profitability to growers has increased by 50 %. Several authors have analyzed the benefits of GM crops, and they concluded that on average, GM technology adoption has reduced chemical pesticide use by 37 %, increased crop yields by 22 %, and increased farmer profits by 68 %. Yield gains and pesticide reductions are larger for insect-resistant crops than for herbicide-tolerant crops. Yield and profit gains are higher in developing countries than in developed countries (Brookes and Barfoot 2014; Klümper and Qaim 2014). As is the case in India, Burkina Faso's cotton farmers are smallholder farmers with an average of 3 ha or less under production. Bt cotton has meant lower costs of production, greater crop safety, higher yields, and improved economic returns to Burkina Faso's smallholder cotton farmers. With the recent passage of the biosafety law in Nigeria (All Africa 2015), it is anticipated that Bt cotton will reach growers there, exhibit a similar rate and extent of adoption, and deliver the same benefits to Nigeria's smallholder cotton farmers that are being experienced by growers of transgenic cotton the world over. One of the important aspects of transgenic cotton globally is that it is one of the first, if not the first, transgenic crops to gain wide acceptance. Because of the demonstrated value delivered, transgenic cotton paves the way for

similar technologies in other crops to enter these geographies. China, India, Brazil, Burkina Faso, and Australia are good examples. Nigeria will soon be another.

Those of us involved in the early days of plant biotechnology were intrigued by what we perceived to be an opportunity to increase global farm productivity, reduce costs of production, increase the safety of farming practices, and enable the production of food and fiber to keep pace with the world's growing population. Yes, we thought we could eliminate world hunger. Clearly, the industry is on its way toward delivering against that promise far beyond our wildest imaginations. When cotton farmers have been allowed to vote, and they do so with their livelihoods, they have voted overwhelmingly in favor of the benefits delivered by biotechnology. As James Bonner so aptly perceived in 1957, technology is absolutely required to deliver the on-farm productivity that will certainly be essential over the next 50 years in order to feed and clothe the world's population. We are well on our way toward achieving that objective, and the alternative is unthinkable.

2.4 Trait Pipeline

As of this writing, transgenic events comprising 16 traits and trait combinations have achieved non-regulated status for cotton in the USA and one additional trait is pending final assessment and decision (USDA APHIS data). Of these, six are insect resistance (IR) only, eight are herbicide tolerance (HT) only, and three are IRHT molecular stacks. The years ahead will see an array of new transgenic traits working their way into cotton. Some will serve to broaden the efficacy of insect resistance actives as well as fortify pest resistance management strategies. Multiple Cry and Cry-like Bt endotoxin genes encoding proteins with alternative binding sites to those presently in use will be stacked to forestall development of resistance in targeted insect pests. Additional actives will target other non-lepidopteran insects including plant bugs. New transgenic cottons developed in the USA will have the opportunity to move into other markets globally, which dictates that new IR actives in new molecular stacks will need to address potential resistance management questions on a global as opposed to a local level. The new HT traits such as 2,4-D (Enlist Duo™) from Dow AgroSciences and Dicamba (Extend™) from Monsanto are designed to provide broader efficacy, broaden the application window, and deliver better control for glyphosate-tolerant species such as pigweed.

Longer term, the industry will have the opportunity to move its focus from input (production) traits and seek the manipulation of output (fiber, oil, and meal) traits with the intention of opening up new end uses by exploring ways to alter cotton fiber to enable new end uses on a global scale as well as expanding the use of cotton meal for wider human and animal (non-ruminant) nutrition (Sunilkumar et al. 2006). In the end, the path to higher prices and better economic return to the world's cotton growers will be to create new end uses for the oil and meal and by ensuring that a higher share of the world's spinning system is devoted to cotton. This would likely have to be at the expense of man-made fibers, principally

polyester. Clearly, this will require altering fiber attributes to enable new functionalities, likely via rationally designed alterations in fiber structure in order to enable new end uses. But what are those new end uses, what are the attributes that will enable them, and what alterations in fiber structure might be required? Consumers consistently identify significant unmet needs in cotton fabrics and articulate desired new functionalities including modified permeability, improved durability, shrink and wrinkle resistance, shape retention in fabric, and fire retardation. Each of these individual categories has an estimated potential market impact of $5 billion or more and, if achieved in cotton, could significantly elevate cotton's share of the global spinning system, thereby creating more value for the world's cotton growers. Given the incredible molecular complexity of a cotton fiber (see, e.g., Rapp et al. 2010), there may become apparent practical ways to rationally design and then manipulate fiber structure to either deliver the desired attributes directly, or lend themselves to post-spinning treatments that will achieve the desired performance. We will need to define what needs to be done prior to designing alterations to accomplish same. In our view, these are all improvements that can be enabled in cotton, but developing fibers that address these consumer demands will require a proactive, coordinated public and private cooperation in order to make them a reality.

2.5 Preserving Genetic Diversity

Genetic diversity is clearly desirable for long-term crop improvement, and simple sequence repeat analysis presents a picture of a cotton germplasm pool that is relatively narrow (de Magalhães Bertini et al. 2006; Liu et al. 2000). This situation will not improve in the near term due to the nature of the transgenic event regulatory approval process. The exact numbers are difficult to come by, but present estimates are that it costs somewhere between $75 million and $100 million to register a single event in cotton and bring it to market. Accordingly, the only economically viable approach to trait development is to transform a single cotton variety, examine the structure and complexity (single versus multiple copies) of the "events," measure expression of the transgene, characterize the surrounding chromosomal environment, and then pick the best event to use as the initial trait donor. Backcrossing and forward-crossing are used to move deregulated traits into new genetic backgrounds and develop cultivars with suitable agronomic and fiber properties. This approach works well to a point, but there will always be some flanking DNA from the original transformed variety (typically a Coker variety) traveling along linked with the trait of interest. A "construct-" versus "event"-based approach to deregulation would be helpful in broadening the genetic diversity of the world's cultivated gene pool. Greater than 95 % of the US cotton crop is transgenic, as much of as 68 % of global production is transgenic, and virtually all transgenic cottons cultivated globally share in part a common Coker genetic background. This is due in part to the recalcitrance of most cotton cultivars except Coker to regeneration with the methods being

employed (Chlan et al. 1999; Mishra et al. 2003; Wilkins et al. 2000). Two major exceptions are the Dow AgroSciences' WideStrike™ Cry1Ac and Cry1F events referenced earlier which were generated in the Acala cotton variety GC510. This variety was selected because acceptable regeneration protocols existed and GC510 was an Acala cotton variety with superior fiber quality (Rangan and Rajasekaran 1997). As anticipated, these GC510 events carry linkages to improved fiber quality and *Verticillium* tolerance far superior to those found in Coker backgrounds. Nevertheless, the cost of registering new events mandates that the single background most amenable to transformation and regeneration must be used for initial event generation. With the high cost of new event registration, trait providers are engaging in trait cross-licensing agreements which are having the unfortunate consequence of spreading the Coker background broadly. A construct-based registration policy would allow any registered and deregulated construct to be used widely across multiple genetic backgrounds and help alleviate some of the negatives associated with event-based deregulation. Better yet, we should view transformation as one more natural breeding process and embrace new technologies that are making real strides in helping to achieve the rate of productivity required to feed and clothe the world over the next 50-year period.

2.6 An Inconvenient Truth

It appears that we have all been consuming transgenic food for thousands of years. One could say that what we did not know was not hurting us. Quoting from Kyndt et al. (2015), "This finding draws attention to the importance of plant-microbe interactions, and given that this crop has been eaten for millennia, it may change the paradigm governing the 'unnatural' status of transgenic crops," so reports Kyndt et al's fascinating paper which details the observation that domesticated sweet potato (*Ipomoea batata* L.) is transgenic, carrying expressed bacterial genes, the product of horizontal gene transfer involving *Agrobacterium* which may have occurred 8000 to 10,000 years ago. The persistence of transgenes in the selected, cultivated clones versus non-cultivated wild unselected clones is at least partly suggestive of a potential selective advantage for transgenic sweet potato, at least in the eyes of the early consuming public. Chilton et al. (1977) demonstrated that *Agrobacterium* employs a natural system for genetically transforming host plants cells. Gladyshev et al. (2008) demonstrated extensive horizontal gene transfer in rotifers. Moran and Jarvik (2010) documented horizontal gene transfer between fungi and aphids. Li et al. (2014) showed the horizontal transfer of a functional receptor from a bryophyte to ferns. McClintock (1953) described the existence of mobile genetic elements in the maize genome playing a significant role in chromosome rearrangement as well as gene expression, and there are now studies describing same across a broad range of dicots and monocots (Bureau and Wessler 1994). Rob Schilperoort's laboratory (Hooykaas van Slogteren et al. 1984) described the ability of *Agrobacterium* to infect monocots, and

Agrobacterium-mediated transformation is now a preferred method for the transformation of cereals. All this to say that we have every reason to believe what Kyndt et al. have described will prove to be a general occurrence across all plants. Some will consider it to be inconvenient, but we deem it likely that the next 10 years will witness a plethora of studies finding similar results across the breadth of crop species driving us to the inescapable conclusion that we have all been consuming a host of transgenic foods in addition to sweet potato for millennia. Indeed, based on Kyndt, it may well be determined that these natural transgenes persist because they confer a selective advantage. Certainly, that argument might be made for *Ipomoea*. "What has been will be again, what has been done will be done again; there is nothing new under the sun" (Ecclesiastes 1:9).

Organisms have been exchanging DNA since there was DNA in organisms to exchange. Biotechnologists have not invented genetic recombination, and we have not invented the recognition signals, the enzymes that cut, splice, and rejoin DNA, the regulatory elements associated with regulated transcription of genes, the ability for elements to hop in and out of genomes horizontally as well as vertically, nor the mechanisms that allow genes to rearrange or those that allow one organism to move functional genes into another. Nor are biotechnologists the inventors of horizontal gene transfer taking place in plants intra- and interspecifically around the globe 24/7. What we do is to study natural systems and then determine ways to take advantage of, improve on, or otherwise speed the pace of developments that would likely be achievable by other means but only over a much greater time frame. It might be plant molecular breeding, but it is plant breeding nonetheless built on a foundation of mechanisms established thousands of years ago. Mules can still pull plows, but tractors make it possible to feed the world. Over time, mankind might possibly develop immunity to smallpox, but we are better off having the vaccine. Cotton biotechnologists use natural systems to assemble genes for resistance to pests, transfer them into cotton plants, and in so doing increase productivity per hectare, enable safer production practices, and improve the economics of farming, particularly for the smallholder farmers that have been proven to be those that benefit most from access. These efforts should be embraced if for no other reason than the humanitarian good served by so doing.

Approximately 175 million hectares of transgenic crop production is underway globally in 2015, 25 million hectares of which are cotton, and the industry has had an incredible record for increased safety and increased farm productivity. We have already seen that transgenic cotton raised productivity in Burkina Faso by 20 % and in the country of India by 100 % (James 2014). These are the kinds of gains that need to be made to keep pace with the world's increasing population and accordant need for food and fiber. It is indeed an inconvenient truth that transgenic plants including cotton, in spite of their record of safety and productivity gains, have been subject to much public scrutiny, debate, and incredibly costly regulation (borne primarily by US farmers and US consumers). This even while other approaches to food production make claims that go untested scientifically, stand virtually unregulated, and have resulted in thousands of foodborne illnesses and several deaths on a global scale (Hanola and Pauly 2011; Popoff 2011). Biodynamic

farming and organic production practices might feed the affluent, but cannot provide for the 9.5 billion people expected to live on earth by the year 2050. The relatively good times we presently enjoy with respect to food availability on a global scale may in fact also be feeding the complacency which drives our dalliance with regulatory processes that restrict genetic diversity and slow the deployment of new technologies that will be essential to expanding the production of food and fiber at a pace required by the increasing population (Hoisington et al. 1999). Feeding and clothing the additional 2.5 billion people that will arrive over the next 35 years will require an increase in food and fiber production of 35.7 %. The realistic options are to (a) increase productivity of existing farmland by 35.7 %, or (b) bring a minimum of some 3.6 million km^2 of new land under production. That number would surely be a minimum because the most fertile land is already being tilled. Considering the fact that 70–80 % of the new farmland brought under production takes place by deforestation (Kendall and Pimental 1994), the selection of option b would have devastating environmental effects. Increasing overall agricultural productivity will not be solved by any single approach. The best existing farming methods must be coupled with the best new developments in farming practice including technology. Rather than embracing technology, there has been created an enormous regulatory bureaucracy, spending billions of dollars annually to regulate that which is going on naturally across the plant kingdom, which restricts access to technology and results in a narrowing of the germplasm base, and which is slowing the rate at which gains in per hectare productivity could and should be achieved. And for what real purpose? Perhaps Andersen (1909) said it as well as anyone. Given the fact that we have been consuming transgenic plants for as long as man has been consuming plants, we can hope that at some point in the near future, molecular breeding including the creation of transgenic plants will be looked at as any other breeding process and no longer be subject to the kinds of regulation being faced today.

2.7 Back to the Future

We began this writing referencing projections made by James Bonner some 59 years ago with respect to what one might expect the future to hold for agriculture as the world becomes industrialized and more populated. His observations remain spot on. Increasing agricultural productivity on a per hectare basis is critical, reducing costs of production is essential to maintaining the economic incentive to keep fertile land under production, the quality and value of what is produced must be elevated in order to keep pace with rising costs and drive that same economic return, and we must continue our development of technologies resulting in safer farming practices. This was an appropriate foundation on which to build our discussion of the global importance of transgenic cotton. It has been just 36 years since we and others began in earnest to invent, refine, and deploy cotton biotechnologies. We have made tremendous strides in understanding and utilizing what

plants already understand and utilize with respect to optimizing gene expression, shuffling coding regions, exchanging regulatory elements, and effecting advances in overall environmental fitness. In these relatively short years, we have seen transgenic cotton go from 0 to 68 % of the world's cotton acres and the safety and performance record is remarkable. No one is forcing smallholder cotton farmers to plant transgenic cotton, but there are many using misdirected law and regulatory processes to forcibly prevent many from doing so. We have achieved productivity gains as measured in yield per hectare between 12 and 100 % depending on the country. Safer production practices have been enabled by in-plant insect resistance and the poorest of the world's smallholder cotton farmers have benefitted the most when they have been allowed access to the technology. These are accomplishments which the entire industry and public institutions are and should be proud of. We do not live in an either/or world. It will take far more than biotechnology to enable cotton to keep pace with the increasing need for natural fiber, vegetable oil, and meal, but biotechnology is surely needed. Marker-based technologies and genome-wide selection, for example, are enabling the capture and movement of native traits from race stocks and diploid species as well as allowing us to do a far better job of selecting parents in our crossing programs. Advances in how we break negative linkages are allowing extremely high-quality fiber to be carried in high-yielding cultivars. A significant portion of yield improvement in cotton production comes from the development of better systems for planting, cultivating, and GPS guidance for the purpose of "surgically" applying fertilizers, nutrients, and controlling pests. All of that notwithstanding, there remain many traits that can and will be brought into cotton via transgenic methods much more efficiently than by any other of the means just described. All of these cross-functional approaches must be embraced and deployed if we are to meet the demands of the world's population in the year 2050.

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