Biotechnology: A Look into the Future

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*"…**perception is reality**." Malcolm Kane, Head of Food Safety, Sainbury's Supermarkets Ltd. (1980-1999)*

***-A person who does not learn the lessons of history is doomed to repeat them. However, "What experience and history teach is this – that nations and governments have never learned anything from history, or acted upon any lessons they might have drawn from it."** G.W.F. Hegel, German philosopher (1770-1831).-*

Two issues were covered in the regional consultation. The first, Genetically Modified Cotton for Risk Assessment, potentially can have a profound effect on the second, Opportunities for Small-Scale Cotton Growers. This statement is true because regulations promulgated in the name of "biosafety" can, in effect, be barriers to implementation of otherwise beneficial biotechnical advances. This can happen when only the socioeconomic perspective is considered in the assessment process. In 1991 I wrote (Stewart, 1991) that, "Issues of concern to a society tend to be based…on perception…" rather than upon reality. Today, 16 years later, this is still true. As Michael Kane stated (Kane, 2001), "…perception is reality." In 1991, it was not anticipated that genetic engineering would be negatively perceived by some once it was understood how the process works from a scientific perspective. At the time of that review (five years before the first commercial use of biotech cotton) a process of risk assessment was in place in the USA that emphasized a scientific approach. This led to approval and the rapid adoption of biotech cotton by producers beginning in 1996. In the ensuing years, various groups, some being extremely vocal and adept at influencing public opinion, have raised objections to production of biotech foods and possible negative effects of biotechnology in general. As an example, my wife told me that she was not going to eat "rat genes" in her lettuce. When I queried her, she said that she had "heard" that rat genes were being put into lettuce but was unable to tell me the source. When I tried to explain to her that, even if it were true, a gene is only a sequence of DNA common to all living organisms. In other words, I used scientific reasoning to establish an argument against an emotional reaction. As you might expect, my "scientific reasoning" fell on deaf ears. Perception is reality.

Biotech cotton receives less scrutiny than food crops that have been genetically engineered because traditionally the fiber is made into textiles that are not eaten. Perhaps it is through lack of knowledge that extensive use of biotech cotton as a feed for dairy and beef cattle does not receive extensive notice. Also, one does not hear extensive complaint about the use of cottonseed oil from biotech cotton, perhaps for the same reason (although the amount of protein in cottonseed oil is extremely low).

One of the early complaints about biotech cotton concerned the perception that it would benefit only the large scale farmers who could afford the increased cost of seed. The argument followed that this would increase the difference in the relative well being of poor vs. rich producers. By extension, this was also applied to developing countries vs. developed countries. In 1991 it seemed to me (Stewart, 1991) that the technology would be of more benefit to the small scale farmer than the big producer. History has since shown that extensive benefits from biotechnology have accrued to the small scale producer. Many cotton producers in India and South Africa already enjoy these benefits (James, 2006). Perhaps because of the success enjoyed by these producers, today you do not hear this argument very often. In reality, the greatest disparity seems to be between those countries that have adopted biotechnology and those that have not.

Thus far, I have dwelt on the past and present situation with regard to biotechnology. My charge is to look into the future and try to offer prognostications concerning the role of biotechnology in the future. Because of the obvious benefits to cotton producers who have already adapted biotech cotton, one can predict that the application of biotechnogy will continue to expand into those areas and countries where it is not now grown. However, concerns about the safety of GMO's have slowed adoption and potentially could limit its spread into the areas where it is most needed. Hopefully, this Consultation will help provide partial, and perhaps full, answers to lingering questions concerning any environmental and socioeconomic risks associated with biotech cotton.

One of the issues that remains today, and probably will remain in the future, concerns the question of risk of environmental harm related to the release of biotech cotton into the environment. Of course, the question most at hand relates to the effect of biotech cotton expressing a Bt toxin or an enzyme that confers resistance to a particular herbicide, since these are the only biotech products that are currently commercially available. The history of the last 10 years tells us that the first generation of biotech products have not had a negative effect on the environment and will be widely grown in areas where they are currently not grown. The reasons why they are not currently grown are probably related to lack of a coherent set of approval mechanisms (country choice) or the lack of a viable method for protecting intellectual property rights (provider choice). As these various countries institute regulatory mechanisms and intellectual property rights, the technology will be made available through international trade. Part of the equation for protection of intellectual property is the establishment of a viable planting seed industry for reliable delivery of the seed to the producer.

For those countries with the capacity to develop their own biotech cotton varieties through public or private funds, the two elements of regulatory oversight and IP protection are still necessary. Pakistan is an example of this. Although it has the capacity to produce biotech cotton, only recently has the regulatory and IP systems been put into place. India, on the other hand, established its system more than 5 years ago, so that biotech cotton is now widely grown in that country.

One might ask, "Why is a regulatory system necessary if biotech cotton is not harmful to the environment?" To answer this question, one has to realize that regulation of biotechnology applies to all transgenic plants – not just to cotton. In addition, the regulatory rules must consider future genes that may be genetically engineered into cotton. As an extreme example, assume someone were to genetically engineer the botulinum toxin gene into cotton. As you know, the botulinum protein is a very powerful neutrotoxin. While cotton genetically engineered to express the gene might be grown as a specialty crop for isolation of the protein, because of the potential harm of the protein to humans, its production would have to be in isolation to prevent gene flow to other cotton. A viable regulatory system would require that the biotech cotton be grown and handled in such a way as to prevent any possible gene escape or any harm to humans.

To be commercially viable the cost of biotech cotton seeds must be priced lower than the cost of insect control practiced in that region. In this way both the developer of the biotech cotton and the producer will receive benefits. However, the late entry of some countries into the use of biotechnology in their agricultural enterprises, and especially cotton, places those counties at somewhat of a disadvantage in a global market. The cost of cotton production without the aid of biotechnology is relatively high because of losses to (or, control of) insects. In the interim, as more countries adapt to the reality of biotech cotton, yields increase, leading to higher production of cotton. Because of the increase in the world cotton supply available to the textile industry, the price received by producers could remain relatively low. Thus, the producer of non-biotech cotton will be at a distinct disadvantage.

Traditionally farmers are encouraged to produce cotton because it is a "cash crop" that provides foreign currency to the exporting country. However, in the absence of a domestic market for a cotton producer is subject to the global economy. This is very evident in the countries that historically have been dominant in cotton production and utilization. Because of the increased yield of biotech cotton, India will probably surpass the USA in total cotton production to become the number two cotton producer behind China, by virtue of the number of acres produced with increased yield. Because of the viable textile industries in both China and India, consumption of cotton will also increase as the economic status of those two countries increases. Hopefully, this will relieve some of the pressure on world cotton supplies.

Opportunities For Small-Scale Cotton Growers

The first commercially viable products in biotech cotton have been those that decreased the inputs required to manage the crop. The cheapest method to manage any insect or disease organism is through genetic resistance. By genetically engineering the *Bt* gene into cotton to resist lepidopterian insects, the cost of controlling these insects by chemicals is decreased dramatically. The developing companies recoup their investment by transferring part of the chemical management cost into the cost of the seed. In the case of genetically engineered herbicide resistance, in developed countries where labor is expensive or unavailable, the "technology fee" for the seed is less than for seed conferring insect resistance because part of the cost of development is recouped in sales of herbicide. In areas where hand labor for weeding is inexpensive and readily available, as in developing countries, it is not likely that herbicide tolerant biotech cotton will be successful.

As a result of biotechnology, farming systems have evolved. At the beginning of the green revolution, the mind-set of producers had to change in order that the technology be incorporated into their farming methods. This involved planting of genetically advanced seeds, planting at different plant densities than is traditionally done, chemical control of pests, changes in the application of fertilizers, etc. The implementation of biotechnology as an innovative method to improve production also requires a change in the mind-set of all stakeholders including the developers, producers and, perhaps for the first time, the consumer. Crop management must be accompanied by changes in cultural practices for success to be insured. Implementation of the new technology will depend upon 1) adequate education and training of producers to ensure that there is comprehension of the new technology. For example, engineered pest resistance does not mean that the crop can be planted and ignored until harvest. If anything, scouting for pests must be intensified. 2) For the technology to be useful, all of the genetic material must be adapted to the local conditions. That is, the engineered trait must be in a locally adapted variety. 3) Due attention must be given to the possibility that pests will develop resistance to the engineered resistance. Every effort must be made to delay the development of resistance so that the usefulness of the technology is not lost. 4) Ultimately the technology must provide benefits not only to the producers and developers, but it must also provide a benefit for the consumers of the raw product that can be passed to the ultimate consumers.

Both herbicide tolerant and Bt cotton are considered to be first generation products and are directed toward reducing the cost of inputs to manage the crop. Because reduction of input costs is of great benefit to producers in terms of cost of production, biotech developments have been rapidly incorporated into farming schemes. On the other hand, much of the potential benefit has been transferred to the companies developing the products at the expense of the chemical industry. While farmers have benefited from the biotech developments through increased yield and reduction in cost of managing the crops, consumers have benefited only to a lesser degree (through lower costs for textiles) because the raw product (cotton fiber) constitutes only a small part of the cost of producing and distributing a garment. A major criticism of those opposed to the biotech revolution is that producers receive only a faction of the potential benefits and the consumer receives very little.

To address this issue, the second generation of genes that will be available to the producer will probably be directed toward out-put traits, such as fiber quality and quantity and abiotic stress resistance. These are generally low value traits which, while extremely useful to producers, will not allow the biotech companies to charge high "technology fees" for seeds. In these cases, the strategy of the seed companies will be to maintain or gain "market share" for their seeds. Other low-input traits (e.g., fungal resistance; viral resistance), that may have extreme importance in a relatively small area, fall into this same category. These will have to be developed locally or regionally (depending upon biotechnological capacity). While "technology fees" at first appear to be high, as competition increases these can be expected to decrease, so that all the technology is within the perceived means of all producers. ("Cash flow" possibly could deter some producers, although by adopting the technology they would ultimately earn more from the crop.)

A new area that is receiving attention is the use of plants to produce pharmaceuticals. Plants can be genetically engineered to produce some drugs cheaper than they can be obtained from traditional sources. Although the cost of meeting regulatory requirements may be high, the high market value of the drugs could make the effort worthwhile. Part of the regulatory process will be to have absolute assurance that the trait will not be transferred to other plants not possessing the engineered gene. Of course, there are many factors that determine what the crop of choice would be for production of a specific drug, and cotton will be only one of many choices. Because of the use of cotton fiber as a wound dressing, it seems logical that it would be the plant of choice for production of antimicrobial compounds in the fiber.

The cost of meeting regulatory requirements has been, and will continue to be, a barrier to new biotech developments by academic scientists. Because of this, there has been a shift away from genetic engineering with a concomitant increase in the use of molecular markers to identify useful traits in crop germplasm. Cotton is fortunate in possessing a relatively large genetic pool from which to draw new genes (Stewart, 1995). Extensive effort is being devoted to mapping of the cotton genome and close relatives. Plants resistant to various pests and stresses that are derived from these efforts will avoid the high costs of meeting regulatory requirements since they will be developed through "natural" hybridization. A pertinent example of this would be the development of resistance to the leaf curl virus in *G. hirsutum* (4X) by introgression of resistance from *G. arboreum* (2X) While resistance probably can be developed through genetic engineering of cotton with appropriate genes that confer resistance to CLCV, in fact, it may be faster and certainly less expensive to introgress the resistance from the diploid species (*G. arboreum*), especially if a molecular marker can be associated with the area of the chromosome conferring resistance. As the molecular map of cotton evolves, selection of markers associated with particular traits will become easier, as will transfer of useful traits from exotic germplasm to elite cultivars.

In the future, biotechnology should be able to shift existing production systems to more environmentally friendly systems, especially in developing countries. Biotic resistance is just one of many traits needed to provide cotton crops that will yield more on less land. Some of the traits that are currently receiving attention are 1) increased light harvesting efficiency, 2) drought tolerance, 3) high and 4) low temperature tolerance, 5) salt tolerance and 6) fiber quality.

1) Any feature that improves the capture of light for photosynthesis would be useful in genetic engineering as a way to improve cotton yields. One way to do this would be to delay senescence of the leaves so that each leaf remains functional for a longer period of time. This seems to be a relatively straightforward method for improving light interception. Photosynthetic efficiency is a subject that has received much interest but little progress. Rubisco has affinity for both CO_2,which results in carbon fixation, and for O_2,which leads to carbon loss through photorespiration. A slight increase in affinity for CO_2 relative to O_2 would have a significant impact on carbon fixation.

2) Drought tolerance is a complex environmental parameter, that is often confounded by heat stress, or also (in the case of cotton) chilling stress. Much work has been done on model plants relative to gene expression in response to this abiotic stress. A number of genes have been increased that appear to be related to increased tolerance to water-deficit stress but they have not been reverse engineered yet, to verify a functional role in tolerance. Genes found in other plants (such as Arabidopsis) to be regulated by water-deficit, and other abiotic stresses, have also been found to be similarly regulated in cotton (e.g., DREB) (Lui, 2002). Some of these genes in model plants are claimed to increase tolerance to water-deficit and other abotic stresses (such as salt-stress). Because tolerance to biotic stress is a complex phenomenon, a single gene used to transform another plant is not expected to provide much increase in tolerance.

3) Heat stress potentially can be a limiting factor in cotton production in many parts of the world [Pakistan (Multan) is but one example where the average maximum temperature exceeds 42^0 C during June]. Wise *et al.* (2004) reported that electron transport reaches its limit in Pima cotton grown under field conditions in the USA southwestern desert. Deridder and Salvucci (2007) found that high temperature initially made Rubisco activase unstable but that it stabilized with time. This suggests that chaperon-type proteins probably stabilize the rubisco activase and that these proteins could provide a level of protection to the vital biochemical functioning of heat-stressed cells. Possibly genes coding for chaparon-type proteins could be genetically engineered for constitutive expression into cotton to increase tolerance to heat. Since these proteins play a role in enzyme protection and even in refolding of denatured protein, they would be expected to give a level of increased tolerance to most abiotic stresses.

4) Work on chilling-stress in cotton goes back many years (my graduate research), but as yet there has been no breakthrough in a viable approach to increase resistance to chilling-stress. Work at Texas Tech University suggests that maintaining a highly reductive biochemical environment improves tolerance to chilling-stress (Payton *et al.*, 2001). Transformation of cotton with superoxide dismutase increased its tolerance to chilling temperatures. Primarily, the antioxidants aid in removing damaging free radicals generated because of poor membrane function, especial in the combination of chilling temperatures and high light intensity. The cumulative information indicates that temperature membrane transition from a gel to a sol at around 12^0 C in cotton is related to its sensitivity to chilling temperatures. Genetically engineering cotton to have more flexible membranes (more unsaturated lipids) should increase its tolerance to chilling. On the other hand, this would probably also result in increased sensitivity to heat stress.

5) Salt tolerance. Many of the resistances to abiotic stress engage in “cross-talk”, that is, the resistance mechanisms draw upon a sub-set of genes that function to improve resistance to an environmental stress. For example, because of their protein-protective nature, the chaparonins function in any abiotic stress where proteins potentially can be inactivated. Cotton is considered to be relatively tolerant of salt, and its cultivation might be extended into areas when other crops cannot grow because of high salinity. Many plants are considered to be halophytes (plants that will grow under high salt concentrations.) Several genes have been identified from these plants that seem to function in salt tolerance and have great potential in genetic engineering. A Na+/H+ anti-port enzyme, which excludes Na from the plant cell, may have potential for improving the salt tolerance of cotton.

6) Fiber quality is an area that everyone recognizes as a component of production, but few workers have sufficient knowledge of the molecular biology of fiber to speculate what genes might contribute to fiber quality. Although the process has been slow, the biology of fiber is going to unravel. Of particular note are the claims that single

genes have dramatic effects on fiber yield and quality. Dr. Haigler *et al*., (2000a) transformed cotton with a sucrose phosphate synthase, while Thea Wilkins (USA) transformed extensin into cotton. In each case the claim was that the plants expressing the gene had longer and stronger fiber and increased yield (Haigler *et al*., 2000b; Wilkins, personal communication). It seems unusual that single genes would have a dramatic effect on a range of quantitative traits.

Each of these are steps toward producing more and better cotton in a sustainable way. Also, one could hope that the output traits derived from biotechnology will be viewed favorably by the general public since they will not imply the plant is producing a "toxin," as now is the case.

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