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INVITED REVIEW

Advances in insect biotechnology for human welfare

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Abstract

Biotechnology is the latest scientific breakthrough in the history of agriculture. Yet despite the promise of developing new tools for pest and disease control, transgenic organisms have encountered a mixed reception by the lay and scientific public alike. Yields are unable to keep pace with rising costs resulting in a decline in traditional farming. Switching to a new organic growing paradigm is occurring in Korea and the United States today. These new approaches ignore traditional tools that were responsible for the increased yields that support the current affluence and allowed us to protect crops while buying time to find more ecologically-friendly methods. The perception that we understand crop diseases and pests is false and those making this assumption risk destabilizing global food production. There are new pests and diseases that are very difficult to control without these traditional non-organic methods. Invasive species continue to arrive at high rates adding to the burden of farming. Global climate change is already causing changes in the pest and disease complexes and is forcing the entomologist and plant pathologist to make drastic changes to adjust to them.

Key words: biotechnology, colony collapse disorder, genetically modified organisms, organic farming, Pierce's disease, regulatory oversight.

Introduction

Biotechnology as defined currently covers a broad area. It refers to the use of microorganisms or biological substances to serve certain industrial or manufacturing purposes. The purpose can be the manufacture of drugs, synthetic hormones, and bulk foodstuffs as well as the conversion of organic waste and clean-up of industrial spills (bioremediation) or even production of new detergents and cosmetics (Anonymous 2008c). It can also refer to new types of engineering (bioengineering) that uses products of recombinant organisms for new materials.

Insect biotechnology has come to mean any of these approaches involving insects. The bioengineering of synthetic silk using genes from insects in host bacteria is an example that is not controversial and could lead to new uses for artificial silk. It is when the application involves recombinant food or crop treatments for pest and disease control that the use becomes controversial, such as new recombinant biological insecticides being developed with these new methods. Controversy results in increased scrutiny and past experiences from the introductions of other technologies often provide perspective.

Acceptance of new technology

During recorded human history, the earth was considered to be the center of the universe. Then a revolutionary breakthrough occurred when Galileo realized that Copernicus was correct and the earth revolves around the sun. By advocating this he was placed under house arrest for the rest of his life on the orders of the inquisition. Francis Bacon is credited with advocating the scientific method of inquiry by deduction. In his zeal to see if meat could be preserved by freezing in snow, he contacted pneumonia and died. Both of these scientific pioneers are associated with new ways of looking at nature. And they demonstrate that new ideas can be controversial and dangerous.

When recombinant methods were first introduced, scientists voluntarily halted research to consider implications in an extraordinary meeting in Asilomar, California in 1975 (Berg *et al*. 1975; Paul *et al*. 1975). This resulted in self-regulation of research by adoption of ethical guidelines for experiments (Anonymous 1976). The practical result of this is that no research university in the USA can obtain funds from federal grants without having a "Biosafety Committee" to screen all research being proposed.

Editorial oversight

A recent inquiry from Peter Hare, Associate Editor of *Nature Biotechnology*, asked for an ethical judgment on a recombinant biopesticide (Peter Hare, email correspondence, 5 September 2007):

> "I wonder whether you might share some of your expertise in biopesticides to help us reach a final decision on the suitability of a manuscript for publication in *Nature Biotechnology*.
> Although we would normally reserve judgment on public acceptance of a technology in deciding what is appropriate for publication, I trust that you understand that we have an ethical responsibility not to publish what may be perceived as potentially irresponsible technologies."

In reply to my request to reprint this extraordinary request in this article, Hare replied the following (Peter Hare, Email correspondence, 26 March 2008):

> "You are welcome to include the email, as written, in the PowerPoint presentation and the article. However, please ensure that it is quite clear that we only consult authorities on matters like this in exceptional situations when the contents of a paper might e.g. have adverse environmental impacts or find a dual use (e.g. for bioterrorism)."

It is clear from the email exchange shown above that scientists (including editors of top scientific journals) are continuing the effort to be responsible on two fronts: biosafety and environmental responsibility.

Oversight of new technology

The threat of losing grants is one method of forcing compliance to protocols that provide the illusion of safety. Another method of forcing compliance is the threat of trade embargo. The food we eat (from the agriculture sector) and the drugs we use (from medical research) are subject to scrutiny because both involve selling a product. Oversight extends to other products such as lead in paint and gasoline, asbestos in insulation and microbes or mercury in water supplies. How good we are at this oversight has a direct effect on the level of public confidence and therefore, acceptance of new technology.

Table 1 List of controversies involving governmental oversight

Thalidomide
Vioxx (Rofecoxib)
Mad Cow Disease (Bovine Spongiform Encephalopathy, BSE)

Some pertinent examples of oversight from non-biotechnology cases are listed in Table 1.

Thalidomide (Anonymous 2008a) was a drug marketed in Europe to relieve the symptoms of morning sickness in pregnant women. The use of thalidomide was not approved in the USA because Frances Kelsey, the Food and Drug Administration regulator, in a now very famous incident, barred approval pending further testing. She based this decision on her previous work that showed rabbit fetuses in pregnant does were unable to metabolize quinine, which thus accumulated; whereas the adult female metabolized quinine readily. With no more to go on than this observation, Kelsey held off pressure from the pharmaceutical industry to approve sale of thalidomide. In due course, disfigured children were born to mothers in Europe as a result of the exposure to thalidomide, which resulted in an immediate recall of the drug.

In a more recent incident the drug Vioxx (Rofecoxib, Mecrk & Co., Inc, Rahway, New Jersey, USA), used for pain relief, was withdrawn from the market when increased instances of heart attack and stroke were associated with Vioxx use. According to the Drugs.com website (www.drugs.com), "The manufacturer of Vioxx has announced a voluntary withdrawal of the drug from the U.S. and worldwide market. This withdrawal is due to safety concerns of an increased risk of cardiovascular events (including heart attack and stroke) in patients taking Vioxx" (Anonymous 2008b).

Bovine spongiform encephalopathy (BSE), or mad cow disease, is attributed to the effects of a "proteinaceous pathogen" named prion (Ryou 2007), an unusual protein that was traced to the use of sheep brain in cattle feed, and that can be transmitted through contaminated feed. So far only mammalian effects are known in diseases called scrapie in sheep, chronic wasting disease in deer and elk, and Creutzfeldt-Jakob disease in humans besides the BSE in cattle. Marsh *et al*. (2008) highlights the continuing effect the presence or threat of BSE has on beef sales in Canada and the USA.

Public acceptance of biotechnology

While the cases cited above do not involve biotechnology, they contribute to the mixed public acceptance of transgenic

crops and the very slow or even stagnating governmental approval process for transgenic animals. Diametrically opposed views are readily available. The non-governmental organization, Greenpeace, for example, advocates a ban on genetically modified organisms (GMOs) in the environment and a phaseout of pesticides and a reduction of synthetic fertilizers (Stokstad 2008). This severely limits development of any new tools from the only new technology available, biotechnology.

If you contrast the Greenpeace position with, "Pesticides make a significant contribution to maintaining world food production" (Pimentel *et al*. 1993) and experts estimate that anywhere from zero to 100% of crops would be lost if pesticides were not used (Pimentel *et al*. 1993) the two positions are not compatible. While it is easy to support a "phaseout of pesticides" in principle, the reality is a little different.

The main value in synthetic organic insecticides is their immediate effect. If an unexpected pest problem occurs, spraying is almost always the only solution available immediately. Spraying is costly and growers do not like to use pesticides if they can avoid them. However, the immediate part of the challenge gives no margin for error.

The most important effect of pesticide use is to eliminate fluctuations in yield to insure steady production. While the ravages of weather are still beyond the control of everyone, pest problems are controllable in the near term due to pesticides. Phasing out pesticide use altogether would mean an immediate solution is not available and a return to famine cycles that were once common in the history of the world.

Replacing modern neurotoxic insecticides with biopesticides is another laudable goal, but pales in the face of market forces. Biopesticides are widely acceptable but have two major drawbacks. The very valuable selectivity they provide necessarily means a smaller market and therefore lower income to cover costs; the more selective the biopesticide, the better for the environment but the smaller the market.

For Greenpeace to remain credible in advocating the "phaseout of pesticides" and convince me to join them, they must explain how the vital role of pesticides in food production is to be replaced and how the development of a substitute will be financed. If Greenpeace does not have a substitute technology to suggest, they are advocating a collapse of the current food production system in the world and expanding starvation.

Changing face of agriculture

Steven Blank (1998) suggested that mainline agriculture will be phased out of the USA as was the fate of many large manufacturing industries including steel and textiles. What remains is an economy based on technology and information. Many Americans have made the transition while others are struggling to adjust.

Table 2 USA Commodity prices ($US) by decade: 40 year period.

Commodity	1962	1972	1982	1992	2002	
Winter Wheat	64.7	97	113.2	131.5	129.3	$/bushel
Corn for Grain	1.12	1.57	2.55	2.07	2.32	$/bushel
Rice	5.04	6.73	7.91	5.89	4.49	$/cwt
Oranges	2.68	2.87	6.53	7.43	6.37	$/box
Sweet Cherries	288	382	699	915	1550	$/ton

Cwt = 100 lbs (pounds)
These are actual prices, not adjusted for inflation
Source: http://www.nass.usda.gov/QuickStat/
National Agricultural Statistics Service.

The stark reality for Blank's prediction is shown in the trends of income for crops at the farm gate (Table 2). These figures are not adjusted for inflation, so they are a little worse than they look. Every increase in fuel costs decreases income even further; thus it is easy to see why the trend has been away from traditional farming for the past 100 years and the trend is continuing. The price for sweet cherries is one of few having an upward projection.

Despite these bleak projections, agriculture is still a very strong force here in California. The grape and wine industry, for example, is growing, if anything. Probably because it boosts local property values and increases the standard of living, which seems to fit the move to high technology-based manufacturing and information processing. In addition, the organic food sector in California and elsewhere is still a small percentage of the whole of agriculture, but is growing.

Organic farming

The national trend in organic growing is up, driven by demand. According to the Ag Marketing Resource Center operated by Iowa State University (Anonymous 2008d) there was an increase of nearly 20% in organics in the last 7 years. The United States Department of Agriculture supports a National Organic Program that includes certification (Anonymous 2008e).

The principles of organic growing seem to fit the agenda of Greenpeace. Yet, global warming shows trends of increasing pest and disease problems in the future (Reiter 2001; Trumble & Butler 2008; Tables 3, 4). Today, a new pest or disease enters California every 60 days (Dowell 2006). A very low percentage of new pests have ever been eradicated despite dozens of attempts (Dowell 2006). We barely cope with invasive species and we seem unable to stop the incursion.

Colony collapse disorder

Two examples will serve to illustrate the challenges facing agricultural researchers. Colony collapse disorder (CCD) has

Table 3 Increasing CO_2 in atmosphere

Increases:
Food consumption by caterpillars
Reproduction of aphids
Predation by a lady beetle
Carbon-based plant defenses
Effects of foliar applications of *Bacillus thuringiensis*
Decreases:
Insect developmental rates
Response to alarm pheromones by aphids
Parasitism
Effects of transgenic *B. thuringiensis*
Nitrogen-based plant defenses

Table 4 Consequences of global temperature increase

Increases:
Northward migration
Migration up elevation gradients
Insect developmental rates and oviposition
Potential for insect outbreaks
Occurrence of invasive species introductions
Insect extinctions
Occurrence of human and animal diseases
Decreases:
Effects of biocontrol of insects with fungi
Reliability of economic threshold levels
Insect diversity in ecosystems
Parasitism

recently been in the news. It describes a disappearance of honeybees. The cause of CCD is hotly debated, but unknown (Cox-Foster *et al*. 2007). Given that the almond crop in California depends 100% on pollination by honeybees, their absence and lack of a substitute would be a disaster for that industry. CCD is not a new phenomenon, a general disappearance of honeybees happened before in 1973. The intervening 30 years have not brought us any closer to understanding this syndrome, nor having a clue what to do about it.

The occurrence of rice stripe virus in east Asia is a similar threat. Ten percent of the rice crop in China is reportedly lost to rice stripe virus. While the pathogen and vectors are both known, there is an absence of interventions tool to stop the loss.

Pierce's disease in California

CCD illustrates how little we know about common agricultural pest and disease problems. The same is true of plant diseases caused by pathogens carried by insects. The second example. Pierce's disease (PD) in California is caused by a strain of the bacterium, *Xylella fastidiosa* that is transmitted physically by xylem-feeding leafhopper insects. Although the pathogen has been present in California for well over a hundred years, native leafhoppers seem reluctant to feed on European grapevines, so PD remained a nuisance confined to local areas (Redak *et al*. 2004; Miller *et al*. 2006).

A new leafhopper pest, *Homalodisca vitripennis*, the glassy-winged sharpshooter (GWSS) arrived in California and after several years, began transmitting a number of *Xylella* strains to cause oleander leaf scorch in ornamentals, phony peach disease in ornamental plums and PD in the wine growing area of Temecula, California in a now famous epidemic in the late 1990s. GWSS remains largely confined to southern California by efforts of the United States Department of Agriculture and California Department of Food and Agriculture.

Despite a large investment in research funding over the past 8 years, there are new theories about cause of PD with some suggestions for remedy, but an exact cause and effect of PD still eludes us while the grape and wine industry signaled that recombinant grapevines will not be accepted as a strategy. However, Don Hopkins is planning field tests in California based on a relatively simple process he discovered in Florida (Hopkins 2005). This is based on the simple principle of competitive displacement of the PD pathogen by an avirulent strain of *X. fastidiosa* that Don isolated from elderberry in Florida. Since this is a biological control method and does not involve recombinant methods, it is compatible with the organic industry; indeed his field trial is set in an organic vineyard in the Temecula growing area.

Clash between organic and non-organic growers

Throughout 2007 we monitored the presence of PD pathogen in vineyards in Temecula, California with Barry Hill, a plant pathologist with the California Department of Food and Agriculture. Barry operates the state plant pathogen diagnostics laboratory in Sacramento. He picked suitable plants from cooperating growers in the early summer in Temecula. We collected leaf and petiole samples from the selected plants through the season and sent them to Sacramento for analysis. Table 5 shows the results.

The one data point standing out from the others is field W, which is a commercial chardonnay vineyard. W is treated with imidacloprid systemic insecticide early in the season. It remains effective through the summer and is typical of the absence of pathogen in most viable vineyards in the Temecula area. The numbers of replaced grapevines is around a normal 5% or less, and some of that is due to rodent damage, so the

Table 5 Percentage of *Xylella*-positive of petioles from selected grapevines in Temecula, California during summer of 2007 by enzyme-linked immunosorbent assay (ELISA) test

Field	# of vines	Apr 1, 2007	Apr 15, 2007	Apr 29, 2007	May 12, 2007	May 26, 2007	Jun 10, 2007	Jun 24, 2007	Jul 9, 2007
CL	41	0%	0%	0%	0%	0%	0%	0%	2.5%
CZ-1	19	0%	0%	32%	32%	32%	37%	79%	84%
CZ-2	28	0%	0%	4%	4%	4%	11%	50%	86%
ZSR	24	0%	0%	4%	4%	4%	42%	67%	92%
W	3	0%	0%	0%	0%	0%	0%	0%	0%
9F	8	0%	0%	0%	0%	0%	38%	38%	66%

incidence of PD in commercial vineyards is low and the epidemic is considered under control.

By contrast, field ZSR was an abandoned vineyard. Although the drip irrigation system still functioned, the vineyard contain a large number of grapevines stunted and many removed and it was full of weeds that were not cultivated the entire summer. That data clearly shows the pathogen present.

Both CZ fields were adjacent to one another and well-cared for organic vineyards of mixed varieties, some cabernet, some orange muscat and others. In field CZ-1 perhaps 80–90% of the grapevines had been replaced. Some of the remaining old plants appeared healthy and others exhibited symptoms that could be PD, but was not confirmed. The plants we sampled in CZ-1 tested positive for the pathogen and the data was parallel that obtained in the neighboring CZ-2 cabernet vineyard.

The part of CZ-2 that we sampled was located near a corner of the much smaller CZ-1 field, but the remainder of the much larger CZ-2 vineyard showed signs of hundreds of replaced grapevines presumably due to PD. It was difficult to understand how the grower could continue to operate at that level of loss, which appeared to be at least 50% in some of the blocks.

However, the most interesting result was from field CL, an organic vineyard of old Petit Shirah grapevines about a kilometer away from W chardonnay field and 5 kilometers from the CZ and ZSR fields. When Barry Hill first surveyed CL early in the season, he was convinced it had *Xylella* because the early season shooters appeared stunted. When the test results were obtained, we were all a little stunned that vineyard CL appeared to be largely free of the pathogen.

We concluded, despite the CL result, that organic vineyards act as reservoirs for the PD pathogen, *Xylella* and could act as a source of inoculation for surrounding vineyards. We also concluded that the commercial vineyards were adequately protected from PD by the imidacloprid treatments. The pathogen also resides in weeds outside of the vineyards, so the source of pathogens cannot be attributed just to the organic vineyards. However, the situation is not lost on the commercial growers.

Organic citrus orchards in Temecula are also not treated and while these are not good sources for the pathogen, they attract the vector insect. GWSS oviposits in citrus leaves and tends to overwinter in citrus orchards in the adult stage. The GWSS that molt from the eggs in citrus disperse in the spring to surrounding areas; another source of irritation to the non-organic grower because treatment of non-organic citrus drastically reduces the presence of GWSS and the oviposition.

Summary

Biotechnology is a new field offering tools for pest and disease control. We know very little about either pests or diseases; certainly not enough to readily control them by other than the brute force methods of pesticide spraying. We are also unable to stem the tide of invasive species that seems to be getting worse with global climate change. Yet some advocate a move away from pesticides and recombinant methods in crop protection. This view seems unaware of our inability to understand agricultural pest problems, much less deal with them and could be seen as advocating a return to cycles of famine and resulting chaos that were common before modern methods of farming were developed.

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