One swallow does not a summer make

John Heritage

A microbiological look at genetically modified crops.

A storm over the introduction and use of genetically modified crops has been growing over recent months. The public debate, as with many controversial scientific topics, has been unenlightening and much disinformation has been promulgated by interested parties on both sides. A recent series of *New Scientist* articles provided a more balanced forum for the opposing views but they came to no clear conclusions. Public opinion polls suggest the 'Great British Public' wants nothing to do with 'Frankenstein farming'; yet the same 'Great British Public' is happy to buy genetically modified tomatoes, clearly labelled as such, by the tinful.

The public concerns over transgenic crops as food is interesting. We have been exploiting biotechnology products in human medicine for a number of years and there has been little objection to their use. For example, most insulin-dependent diabetics are happy to use cloned human insulin. There has, however, been no public outrage over the applications of biotechnology to human medicine equivalent to that seen with proposals for transgenic crops.

In a similar vein, it is interesting that people have no qualms about eating vegetarian cheddar cheese. Traditional cheese production requires the use of rennin obtained from the stomachs of calves to clot the milk in the early stages. The gene required for the production of rennin has been cloned and expressed in bacteria. Many people who have objections to the use of animal rennin will happily eat cheese that is made with the equivalent protein when produced by bacteria.

Genetically modified crops are, however, a different matter. The public does seem to view these with a degree of suspicion. Perhaps it is the nature of the crops that are currently being developed. Were a biotechnology company to produce a peanut that failed to elicit an anaphylactic reaction in those people who are allergic to nuts, the public might see this as having a real benefit, albeit for a minority of the population. The commonest genetically modified crops growing worldwide at present do not, on the face of things, seem so altruistic. Most are engineered to be resistant to herbicides. Furthermore, they are resistant to herbicides made by the companies who engineered the resistance determinants into the crops. This is an easy criticism to make of the biotechnologists but the situation is actually more complex. By engineering resistance to herbicides into crops, total herbicide usage can be reduced and a move towards more environmentally friendly chemicals can be encouraged. Issues are not clearly black and white when dealing with genetically modified crops.

Genetically modified tomato plants.
COURTESY R.S.S. FRASER

The biotechnological interests in agriculture are big business indeed. There are currently enough genetically modified plants growing around the world to cover an area the size of Great Britain. Most of these are resistant to herbicides, but crops engineered to be resistant to insect attack, if collected together, would currently cover an acreage the size of Scotland. Crops such as maize and cotton, used for oil production, have been engineered to express one of the Bt toxins produced by *Bacillus thuringiensis*. The advantages of the use of such crops are that these toxins have existed since time immemorial without selecting high levels of resistance amongst insects and without apparent toxic effects for humans. In contrast, chemical insecticides are potentially toxic to humans and are plagued by the relatively easy selection of populations of insects that are resistant to them.

Other benefits of crops that produce their own insecticides may be less tangible. Many plant infections are spread by insect vectors. By controlling the spread of vectors we can hope to control the spread of disease and of food spoilage organisms. Can we look forward to a time when mycotoxicoses are a thing of the past? Bt-producing plants may help achieve this goal. Unfortunately, however, there are early indications that the use of Bt crops may not be as successful as hoped. The sheer scale of the growth of Bt-producing plants increases very significantly the selection pressure for resistance amongst the target insects; there are suggestions from the United States that resistant insects may be emerging.

This, perhaps, should not come as a shock. We have already witnessed a similar problem with the introduction of antibiotics into clinical use. We know that antibiotic resistance genes pre-date the first use of antibiotics to treat infections but were rarely encountered. It did not take long, however, for antibiotic resistance to become apparent in hospitals once antibiotics came into use in clinical practice. As the use of antibiotics increased, so did the problem of antibiotic resistance until we have reached a stage where some infections may be untreatable, being resistant to all the antimicrobial agents currently available.

Antibiotic resistance genes are now not confined to microbes. In the construction of transgenic plants, biotechnologists employ bacterial cells for much of the early manipulation of the transgenic material. In so doing, they take advantage of numerous bacterial cloning vectors. These often exploit antibiotic resistance selectable markers and these markers do end up in the transgenic crops. The commonest encodes resistance to kanamycin due to the expression of the *nptII* gene but several other resistance markers have been used in transgene constructs.

The use of kanamycin resistance is now widely accepted: scientists disagree with the wisdom of using other markers. These include genes that confer resistance to drugs such as streptomycin and chloramphenicol. These are drugs that are rarely used these days, at least in the developed world. When they are used, however, they are employed to treat potentially life-threatening infections. In my opinion, any measure that increases the potential for the spread of these genes to serious human pathogens ought to be resisted until the benefits can be demonstrated to outweigh the potential risks. The FDA in the United States takes a much more lenient approach to the use of marker genes (see http://vm.cfsan.fda.gov/~dms/opa-armg.html).

More worrying than the use of streptomycin and chloramphenicol resistance marker genes is the exploitation of the gene encoding TEM-1 β-lactamase. This gene is commonly found in gut microbes, it is true. Indeed more than half of urinary coliforms are resistant to ampicillin because they produce this enzyme. I do not regard this as a reason why we should permit its use in transgenic plants. My concerns over the use of this marker in transgenic plants are threefold.

First, when DNA is introduced into a new genetic background, it may undergo subtle changes, more closely matching the G+C ratio of the inserted DNA to that of its new host cell. In bacteria, the TEM-1 β-lactamase has shown itself to be exquisitely amenable to such mutations. These mutations have a disastrous effect on humanity. Many change the spectrum of activity of the enzyme from a penicillinase to an extended-spectrum β-lactamase, capable of inactivating third-generation cephalosporins such as cefotaxime and ceftazidime. Other mutations render the enzyme insusceptible to β-lactamase inhibitors such as clavulanic acid. At the latest count, there were almost 70 mutations in bacteria extending the activity of the TEM family of β-lactamases (see http://www.lahey.org/studies/webt.htm). Were such mutated genes to develop in transgenic plants, and were they to find their way from plants back into the microbial gene pool, the consequences could be grave.

Second, I am concerned that the processing of genetically modified foods permits novel opportunities for human pathogens to encounter resistance genes. If a plant containing a β-lactamase gene is dry milled, for example, this will generate significant quantities of dust. This dust will be released into the atmosphere where it will be inhaled. Many bacteria in the respiratory flora, in contrast to the intestinal flora, are naturally competent. That is, they can take up and express naked DNA from their environment. What if *Neisseria meningitidis* were to acquire TEM-1 in this fashion? Or worse, what if it were to acquire a gene that encoded a mutated TEM with extended-spectrum β-lactamase activity? We would then have written off the first line of therapy for meningococcal meningitis.

Third, I am concerned about the scale of the release of resistance genes. The biomass of resistance genes growing in plants is greater than anything that we have seen on the planet to date. This problem has already been alluded to in discussing Bt-expressing plants. The rare possibility of transfer events will be much more likely if we produce sufficient resistance genes to cover the United Kingdom. In the past we have made assumptions about the behaviour of populations based upon our current knowledge. We have not, however, seen the amplification of resistance genes on this scale before and we should proceed with caution. Recent work has shown that, under laboratory conditions, acinetobacters are capable of taking up and integrating resistance genes from transgenic plants. We should not place too much reliance on scientists who say that DNA is short-lived outside of cells and that the acquisition and expression of resistance genes by human pathogens is unlikely. In undertaking risk assessment, the scale of the operation being examined cannot be ignored.

The way forward, in my opinion, is to recognize that biotechnology holds out the promise of great advances. We should not, however, surge ahead with these advances without being aware of the risks that also accompany the application of this technology. Careful consideration of each case on its merits by competent scientists from a variety of disciplines is required. The ethical considerations of cases must also not be ignored. Within the EU framework, the Advisory Committee on Novel Foods and Processes is the designated 'Competent Body' that undertakes this task within the UK. It considers applications for each genetically modified food using expert opinion from a range of scientific and other experts. If we approach this new technology with caution, then our first swallows of genetically modified foods need not be gulps.

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LEFT:
Crystals of *Bacillus thuringiensis* toxin.
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Further reading

Living in a GM world. *New Scientist* 31 October 1998.