# Clinical review

*Science, medicine, and the future*

## Genetically modified foods

Leighton Jones

The use of genetic modification in food production is proving contentious and attracting much media coverage. Despite this, it can be difficult for anyone not directly involved to know how to obtain hard facts. Genetically modified foods raise many issues—scientific, technological, environmental, social, ethical, economic, and political—too many to cover here. This article therefore paints a broad picture of genetically modified foods and provides a lead to sources of information by addressing three specific points:

- What is genetic modification and how does it relate to food production?
- What are the current and future applications?
- What concerns do genetically modified foods raise?

### Manipulating DNA

Genes change every day by natural mutation and recombination, creating new biological variations. Humans have been exploiting this for centuries—shuffling genes in increasingly systematic ways and using extensive crossing and artificial selection—to create many combinations that would never otherwise have occurred. Just about everything we eat is derived from livestock, crops, and micro-organisms bred specifically to provide food. Humans have also redistributed genes geographically: the soybean is native to Asia but is now grown throughout the Americas, and the potato, native to the American continent, is grown throughout the temperate world. DNA has never been "static," neither naturally nor at the hand of people.

Genetic modification is an extension of this. However, unlike conventional breeding, in which new assortments of genes are created more or less at random, it allows specific genes to be identified, isolated, copied, and introduced into other organisms in much more direct and controlled ways (see boxes). The most obvious difference from conventional breeding is that genetic modification allows us to transfer genes between species. For example, the gene for bovine chymosin has been transferred to industrial micro-organisms—*Kluyveromyces lactis* (a yeast), *Aspergillus niger* var *awamori* (a fungus), and *Escherichia coli* K12 (a bacterium). These microbes are grown in fermenters to produce chymosin (rennet) on a commercial scale; this rennet, which replaces the conventional form obtained from slaughtered animals, is now widely used in cheese production.[1]

### Predicted developments

- A wide range of crops resistant to pests, diseases, and herbicides
- Food materials with improved keeping and processing qualities (such as fruit much less susceptible to mould spoilage) and reduced or eliminated natural toxicants (such as glycoalkaloids in potatoes) or allergens (such as allergenic proteins in nuts)
- Better understanding of responses of crops to environmental stress and development of varieties that can grow in areas currently too inhospitable
- Production of high value drugs such as vaccines in high volume agricultural crops such as oilseed rape or livestock such as in milk of dairy cattle
- Development of renewable and sustainable sources of new materials (such as plastics based on starch or vegetable oil) in designer agricultural crops such as oilseed rape, potato, and maize

Genetic modification also allows individual genes to be specifically switched off, through the antisense approach (see box 2). For example, a tomato paste now commercially available (and clearly labelled as genetically modified) was produced with this technology. The gene that controls fruit softening was selectively underexpressed (that is, turned down) in tomatoes. This gene codes for the enzyme polygalacturonase, which digests the pectin that cements the fruit cells together and acts as a natural thickener in tomato pastes; as less polygalacturonase is produced, more of the natural thickener remains in the ripe fruit, reducing the amount of energy required to thicken the paste.[1]

It is now possible to introduce foreign genes (transgenes) into crop plants and express these in specific tissues (such as roots or leaves) and not in others (such as seeds and fruits). This is likely to substantially improve crop protection—for example, against pests that attack only roots or leaves.[2]

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## Applications of genetic modification

### Present uses

In the United Kingdom to date, four genetically modified food materials have gained full approval and are in commercial use: cheese produced with genetically modified chymosin, tomato paste from slow softening tomatoes, and genetically modified soya and maize. Many others have cleared parts of the UK approval system (for example, clearance for food safety but awaiting environmental clearance for agricultural scale production).[2] These include oil from oilseed rape, starch and oil from maize, oil from cotton, chicory, a slow softening tomato intended to be eaten fresh, and riboflavin from a microbe. In addition, other products granted full approval have not been developed to full commercial scale—for example, genetically modified brewers' yeast and bakers' yeast.[1 3]

Most applications are for crop plants, and the genetic modifications are for commercially important agronomic traits—mostly herbicide tolerance and insect resistance. These agronomic traits are determined by single genes and are therefore easiest to manipulate. In contrast, characteristics such as flavour, texture, and processing qualities tend to be determined by multiple genes and are much more difficult to manipulate.

### Future uses

Despite the technical difficulty, substantial progress is now being made with genetically modifying the compositional and processing characteristics of food crops. For example, oilseed rape can now be modified to produce oils with wide ranging characteristics through selective modification of the length and degree of saturation of the fatty acids produced—fatty acids such as laurate, typical of tropical vegetable oils, can now be produced in temperate oilseed crops.

### Box 1: Manipulation of DNA

Genetic modification is possible only because the genes of all organisms are made of the same chemical—DNA. This means that DNA from two different organisms can be cut and joined together. Restriction enzymes cut DNA at specific sequences to create "sticky ends," which, by virtue of their complementary base sequences, will tend to stick to other ends generated by the same enzyme. DNA ligase is used to re-join the DNA backbone when sticky ends pair up (fig 1).

Plasmids, short loops of DNA found naturally in bacteria, are used to genetically modify bacteria. The plasmid is cut open with a restriction enzyme and mixed with the target gene, which has been similarly cut. DNA ligase is used to stitch the gene of interest into the plasmid. This "recombinant" plasmid is then mixed with bacteria, which, under appropriate conditions, take it up. The bacterial cells are genetically modified and can be cultured, isolated, subcultured, and, if appropriate, grown in fermenters on an industrial scale (such as in chymosin production). During culturing, the plasmid is replicated at each cycle of cell division, so that the final bacterial culture contains many copies of the plasmid and its inserted gene.

To genetically modify plants or animals, the plasmid is extracted from the bacteria, and the cloned gene is excised with a restriction enzyme. The gene can then be introduced into individual plant and animal cells. For animals, this is usually done by injection of many millions of copies of the gene into the nucleus of a fertilised egg: in about 1% of cases the cloned gene will integrate into the zygote's chromosomes and, on cell division, be passed on to each cell in the embryo.

For plants, there are various ways of introducing the gene into cells. A common method is to link the gene to a plasmid of the bacterium *Agrobacterium*, a naturally occurring plant pathogen. When plant cells are exposed to and infected by a non-virulent strain of the bacterium, the plasmid transfers to the plant cells, and its DNA integrates with that of the host cells. Genes of interest can be spliced into this plasmid, which is then used as a vector to carry the genes into plant cells (fig 2). The cells are then cultured to produce a callus (an undifferentiated cell mass), which, when grown on appropriate culture media, produces roots and shoots and develops into a plant, each cell of which is derived from a single parent cell and so contains the inserted gene.

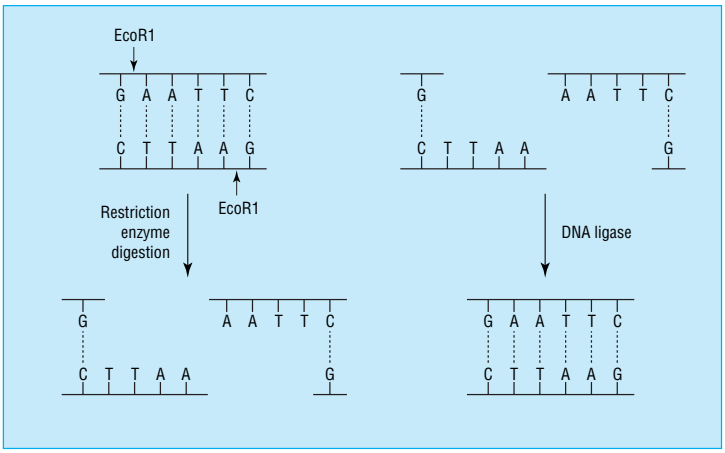


**Fig 1** Action of restriction enzymes and DNA ligase. Restriction enzyme EcoR1 cuts DNA only at the sequence GAATTC to create DNA fragments with complementary overhangs (so called "sticky ends"). These sticky ends tend to stick to each other through base pairing, and the enzyme DNA ligase can be used to reconnect the sugar phosphate backbone of the nucleic acid chains. The two DNA fragments joined by DNA ligase can be from the same or different organisms

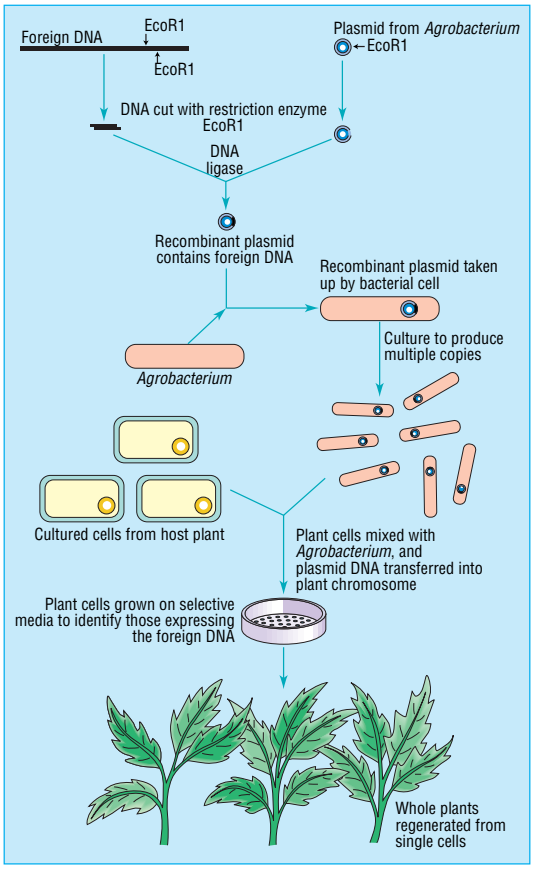


**Fig 2** Method of producing genetically modified plants using a bacterial vector

Similarly, the balance of sugar and starch in potatoes, which affects the processing quality of potatoes for snack food production (too much sugar produces a dark, poor tasting product), can also now be modified on an experimental scale.

Modern genetic techniques are being used to identify and manipulate the genes for biologically active components of food crops, such as natural toxicants (for example, potato glycoalkaloids and kidney bean lectin), antinutrients (for example, trypsin inhibitors), and allergens (for example, certain nut proteins).[3] Such developments are at early stages but in the longer term are almost certain to lead to the development of foods that lack these undesirable components.

On an industrial scale, deterioration of fruits and vegetables is a huge problem: for example, the tendency of plant tissue to turn brown at a cut or peeled surface often has to be controlled through the use of preservatives such as sulphite. Damaged cells release the enzyme polyphenol oxidase, which catalyses the conversion of monophenols (released from separate subcellular compartments) to quinones, which oxidise to form brown polyphenolic pigments. However, the gene for polyphenol oxidase has been switched off in experimental studies by genetic modification, blocking this discolouration spoilage.[4] Genetic modification and other molecular and biochemical techniques are being used to completely unravel the biochemistry of fruit and vegetable ripening and deterioration, and many new methods of preserving these foods, without the use of chemical preservatives, are likely to be developed.

Another possibility generating much interest is the use of crops to provide renewable sources of valuable materials such as vaccines, drugs, bioplastics, and other industrial materials.[5] In parallel, cattle and sheep are being genetically modified to produce pharmaceutical chemicals in their milk, so that drugs can be produced much more efficiently and cost effectively.[6] Although full discussion of this is beyond the scope of this article, there is hope that food crops such as banana could be used to produce and deliver vaccines in tropical regions.[7]

**Box 2: Marker genes, constructs, and antisense technology**

The gene of interest (such as one to delay fruit ripening) is not transferred alone but as part of a "construct." In addition to the gene of interest, the construct contains short sequences to indicate where the gene of interest starts and stops; a "promoter," which switches the gene on; and, probably, a marker gene. Typically, this marker gene will confer resistance to an antibiotic (coding for an enzyme that inactivates the antibiotic). This means that all cells containing the construct will be resistant to the antibiotic and, unlike cells that do not have the gene of interest, will be selected for on a medium containing the antibiotic.

Antisense technology allows genes to be selectively turned down (underexpressed) or switched off altogether (not expressed at all). In this approach the gene of interest is attached to the promoter, but in reverse. This means that when the gene is read (during gene expression) it is the antisense DNA strand that is read rather than the sense (or usual) strand. "Antisense genes" block the expression of "sense genes"; this might be because the sense and antisense RNAs generated during gene expression are complementary so that they associate as an inactive complex, although the mechanism is not fully understood.

## Issues of concern

In his recent editorial on genetically modified foods Burke touched on the main consumer concerns,[8] but it is worth looking further at two other closely related concerns: the safety of genetically modified foods and the use of marker genes that confer antibiotic resistance. Environmental concerns are also important[9] but are beyond the scope of this article.

### Safety

The United Kingdom has led the world in developing systems for assessing the safety of genetically modified foods.[10 11] Consequently, genetically modified foods are subject to a rigorous safety assessment, based on rational scientific evaluation by leading experts and, by definition, within the limits of current knowledge.[1 12] Within the European Union genetically modified foods are now regulated on a union-wide basis.[13]

The recently widely reported work on potatoes at the Rowett Institute shows how difficult it can be to identify the facts (reviewed by Coghlan and Kleiner[14]). Initial media reports claimed that the research proved that all genetically modified foods were inherently unsafe; subsequently it became clear that the findings related not to genetically modified potatoes at all but to potato material to which concanavalin A (a lectin and known toxin) had been added.[14] This emphasises the need to identify concerns precisely and assess claims critically.

Another case often cited as showing that genetically modified foods are inherently dangerous is that of the US company Pioneer Hi-Bred, which introduced genes from Brazil nuts into soybeans to increase the level of sulphur-rich amino acids. The soya was intended for animal feed, not human food. During tests it became clear that the nut protein that was transferred to soybean was allergenic to humans, and the company elected not to pursue the development, citing the potential difficulties of preventing the soya from entering the human food chain.[15] The point that is usually not emphasised in coverage of this case is that the problem was identified because safety checks were, and continue to be, in place to identify the unintended introduction of an allergen into a genetically modified crop.[10 15]

### Antibiotic resistance

The use of antibiotic resistance as a marker system for gene uptake (see box 2) rightly continues to generate much concern. Again, it is important to identify and deal with specific concerns and not to condemn a general approach which has been invaluable in making genetic modification technically feasible. In general, the antibiotics used in marker systems are not used for treating diseases, and the gene and its product (that is, the enzyme that inactivates the antibiotic and thus confers resistance) would usually be destroyed during heat processing of the food material.[1 16]

However, in two cases clinically important antibiotics have been used: a maize developed by Novartis contained a gene for ampicillin resistance, and a potato developed by Avebe contained a gene for amikacin resistance. A further complication with the maize is that the material was intended to be used unprocessed in animal feed and that the antibiotic resistance gene was under the control of a bacterial promoter. This led to concerns that the antibiotic resistance gene might be transferred to animal gut flora (including human pathogens), which might then acquire resistance to a clinically useful antibiotic. As a consequence, both these genetically modified crops are having difficulties gaining full regulatory approval.[17] The Advisory Committee on Novel Foods and Processes has called for the development of different marker systems,[16] and there are signs that alternative technologies are being developed.[1] In the meantime it is imperative that the clinical use of antibiotics is not compromised.

## Conclusions

Genetically modified foods have arrived. Those already on supermarket shelves have been subjected to rigorous safety assessment, as will the many more currently under development. Where genetic modification has introduced substantial changes, consumers will be informed through statutory (and additional voluntary) labelling.[11 18]

In the heat of the debate it is easy to forget that DNA is, and always has been, part of our daily diet. Daily, each of us consumes millions of copies of many thousands of genes. Many of these genes are fully viable at the point of consumption, and in most cases we do not know what they do. How many people stop to consider the viable yet unknown genes of tomato, cucumber, and lettuce in a salad, the bovine genes in a beef steak, the fragmented DNA in many processed foods, and the genes of the many micro-organisms that we breath and swallow?

We are right to take seriously the development of genetically modified foods, to debate the issues that their use raises, and to question critically the risks and benefits they present. At the same time, however, it is important to avoid hysteria, to define clearly the issues of concern, and to tackle these rationally and on an informed basis.

Competing interest: None declared. Campden and Chorleywood Food Research Association is an independent, member based, not for profit association that provides scientific, technical, and information services to the food, drinks, and allied industries and government agencies.

1 Border P, Norton M. *Genetically modified foods—benefits and risks, regulation and public acceptance*. London: Parliamentary Office of Science and Technology, 1998.
2 Jones L, Haine H. *Modern biotechnology in food production*. Bulletin No 1-5. Chipping Campden: Campden & Chorleywood Food Research Association, 1997.
3 Jones L. Food biotechnology: current developments and the need for awareness. *Nutr Food Sci* 1996;6:5-11.
4 Bachem CWP, Speckmann GJ, van der Linde PCG, Verheggen FTM, Hunt MD, Steffens JC, et al. Antisense expression of polyphenol oxidase inhibits enzymatic browning in potato tubers. *Biotechnology* 1994;12:1101-5.
5 Coghlan A. Grow your own vaccines. *New Scientist* 1995 Jan 21: 23.
6 Henninghausen L. Transgenic factor VIII: the milky way and beyond. *Nature Biotechnology* 1998;15:945-6.
7 Kiernan V. Yes, we have vaccinating bananas. *New Scientist* 1996 Sep 21: 6.
8 Burke D. Why all the fuss about genetically modified foods? *BMJ* 1998;316:1845-6.
9 Anderson A, ed. Living in a genetically modified world. *New Scientist* (special edition) 1998 Oct 31.
10 Advisory Committee on Novel Foods and Processes. *Guidelines on the assessment of novel food and processes. Advisory Committee on Novel Foods and Processes report on health and social subjects No 38*. London: HMSO, 1991.
11 Burke D. *What can biotechnology do for the food industry? 19th annual Campden day lecture*. Chipping Campden: Campden & Chorleywood Food Research Association, 1997.
12 Rossiter L. *Biotechnology factfile—a quick reference guide*. Watford: Institute of Grocery Distribution, 1997.
13 *The novel foods and novel food ingredients regulations 1997, statutory instrument No 1335*. London: Stationery Office, 1997. (EU regulation 258/97 on novel foods and novel food ingredients.)
14 Coghlan A, Kleiner K. Spud U dislike. *New Scientist* 1998 Aug 15: 5.
15 Allen AH. Biotechnology: regulations may help consumer acceptance. *Food Product Design* 1996 May: 80-5.
16 Advisory Committee on Novel Foods and Processes. *Report on the use of antibiotic resistance markers in genetically modified food organisms*. London: ACNFP, 1994.
17 MacKenzie D. Modified potato is taken off the menu. *New Scientist* 1998 Oct 17: 13.
18 *Communication and labelling guidelines for genetically modified foods*. Watford: Institute of Grocery Distribution, 1997.

*A memorable patient*

## A happy coincidence

In the mid-1960s I worked on St Helena. At that time mail came at regular but infrequent intervals on the Union Castle Line ships, which than had the mail contract between the United Kingdom and South Africa. The *BMJ* arrived at about six weekly intervals so it took some time to catch up on reading the current journals. Early in 1967 a bundle of journals arrived which included a 1966 issue in which V D Delal and D E Whittam (1966;ii:1370) describe a case of bilateral simultaneous rupture of the quadriceps tendons in a bus inspector. Their treatment regimen was described in detail.

A short time after the journals had arrived in St Helena an old man had carried a heavy basket of fish to the top of Ladder Hill and sat down on a wall to have a rest. Having recovered he eased himself down from his seat and immediately collapsed to the ground and could not get up. He was brought to the hospital and diagnosed as having bilateral simultaneous rupture of his quadriceps tendons with classical gaps in the tendons above each patella.

Fortunately Dr DSM was up to date with his journal reading and produced the *BMJ* article. We followed the treatment regimen described with Dr JSN repairing one knee, I did the other, while Dr DSM gave the anaesthetic. Recovery was uneventful and the patient returned, eventually, to his occupation.

I have not seen a similar case since and still wonder at the chance of seeing one such unusual case and having a case and treatment regimen published at the precise moment of need in a current journal.

Richard Grainger, *medical officer of health, St Lawrence, Jersey*

We welcome articles up to 600 words on topics such as *A memorable patient, A paper that changed my practice, My most unfortunate mistake,* or any other piece conveying instruction, pathos, or humour. If possible the article should be supplied on a disk. Permission is needed from the patient or a relative if an identifiable patient is referred to. We also welcome contributions for "Endpieces," consisting of quotations of up to 80 words (but most are considerably shorter) from any source, ancient or modern, which have appealed to the reader.