5 Future Applications of GMOs

5.1 Second Generation GM Plant Products

Gert E. de Vries

Genetic traits in modified plants can be grouped into three categories:

1. Input traits, which enhance agronomic value such as herbicide tolerance, pathogen resistance or abiotic stress/yield
2. Output traits for increased quality such as modified nutrients, improved industrial use, or health-related compounds (molecular farming)
3. Traits for technological purposes such as genetic markers or gene switches

We have chosen an alternative classification following the development of GM crops in order to show the progress of this technology. A first generation of GM plants therefore received traits from the first and the third category to prove the principle of genetic modification and to acquire new agronomic traits. Second generation GM crops, to be discussed in this section, have increased agronomic and nutritional properties by inclusion of traits from both the first and second category. Third generation GM crops are modified with traits to improve their use in industrial processes, and these are discussed in the next section.

5.1.1 Introduction

The health and well-being of humans are entirely dependent on plant foods either directly, or indirectly when used as feed for animals. Plant foods provide almost all essential vitamins and minerals as well as a number of other health-promoting phytochemicals. Plants also provide the primary source of energy in the form of carbohydrates or lipids and the building blocks for proteins.

The technology of genetic modification has been used initially to produce a variety of crop plants with distinct traits to enhance their agronomic properties, such as the resistance to insect pests or viruses and the tolerance to specific herbicides. While this first generation of GM plants has benefits for farmers, it is more difficult for the consumers to see any benefit other than, in limited cases, a possible decreased price owing to reduced cost of production. This may be one of the most important reasons why today's transgenic plants are under permanent fire of criticism. This situation may change in the near future when transgenic crops of the so-called second generation enter the market. A key to the success of such GM plants is metabolic engineering: the in vivo modification of cellular processes in specific plant cells resulting in the production of modified and/or increased amounts of non-protein products. The creation of these novel crops is a more ambitious and technically challenging task since it involves the modification of plant physiology and biochemistry rather than the overproduction of a single protein.

5.1.1.1
What are Second Generation GM Crops?

Genomics-based strategies for gene discovery, coupled with high-throughput transformation methods and miniaturised, automated analytical and functionality assays, have accelerated the identification of valuable genes. The discovered genes may change the compositions of carbohydrates or the functionality of proteins and radically modify the properties of crop plants. Therefore, the real potential of GM technology to help address some of the most serious concerns of world agriculture has only recently begun to be explored. Modified crops resulting from plant biotechnology have the potential of providing major health benefits to people throughout the world. Examples include enhancing the vitamin and mineral content of staple foods, eliminating common food allergens, developing higher protein quality and quantity in widely consumed crops. The trend for this second generation of GM plants therefore is the development of GM foods with enriched nutrients, with improved functionality, and with health-promoting activities, which will all be of direct benefit to the consumer.

The third and so far the most recent generation in plant biotechnology is characterised by the use of GM plants as biofactories for the production of specialty (such as vaccines or other pharmaceuticals) or bulk products that cannot be produced in conventional crops (such as industrial oils) These developments are discussed in Sect. 5.2.

5.1.2
Examples

Detailed examples are given from an area that may appeal to consumers most – health. The development of golden rice has met a lot of debate and is therefore discussed in greater detail. The wide range of traits which are employed or considered in GM plants preclude extensive discussion here, but a useful overview is given in the first reference of under "Essential Sources".

5.1.2.1
Processing: the FlavrSavr Tomato

The first GM whole product, marketed under the brand McGregor, was introduced to the US market by Calgene in May 1994. It is interesting to note that it was in fact a second generation GM plant, producing tomatoes with delayed ripening properties. A tomato gene had been silenced that normally causes the breakdown of pectin in cell walls, resulting in a softening and eventual rotting of the fruit. This was thought to be a useful trait for two reasons. Tomatoes could be picked ripe, transported and stored for up to 10 days, providing plenty of time for shipping and sale. Secondly it was expected and advertised that the FlavrSavr tomatoes, due to the arrested loss of structure, would develop a superior taste. This was not perceived so by consumers and the first GM tomato did not meet its expected commercial success. Nevertheless, research efforts on improving the taste of tomatoes is continuing, although the majority of GM tomatoes are currently processed to ketchup and tomato paste.

5.1.2.2
Oils

Fats and oils, in particular vegetable oil sources, have been a topic of keen research interest over the past 20 years. The role of dietary fats in human nutrition has created widespread interest among consumers, clinicians and food producers. Concern with the type of fat, as an important dietary risk factor in coronary heart disease, has been a major impetus for the development of specialty modified fats and oils from plants. Consumers want oils that are low in saturated fats and low in trans-fatty acids. The food industry also requires that the oils have a high stability to oxidative changes as these can result in off-odours. The natural health products market for the omega-3 fatty acid and α-linolenic acid, found to be effective in lowering blood cholesterol levels and reducing the clotting of blood platelets and lowering blood pressure, is well established. Opportunities also exist to produce elevated levels of nutraceutical products such as vitamin E (the antioxidant α-tocopherol) in oils from plant sources. New findings in diet formulations and health-promoting substances will certainly drive further research and breeding of specialty crops that will be suited to fill such needs. A detailed knowledge of the chemistry of lipids in plant cells is an essential starting point for these studies and the identification of candidate genes with novel functions is a next step.

Oil crops are one of the most valuable traded agricultural commodities and are probably worth over 100 billion €/year. Despite the large volume of globally traded vegetable oil, only four major crops (soybean, oil palm, rapeseed and sunflower) contribute about 75% of this production. The vast majority of vegetable oils are currently used for edible commodities, such as margarines, cooking oils, and processed foods. Only about 15% of production goes towards the manufacture of oleochemicals, i.e. industrial commodities derived from oil crops (a third generation GM product, see Sect. 5.2).

In addition to the technical problems of producing useful GM oil-producing crops for all these different markets, there are considerable challenges involved in the management of such crops. Since all resulting cultivars will appear identical and the only differences are in their seed oil compositions, segregation and identity preservation of such incompatible commodity streams will turn out to be essential.

5.1.2.3
Starch

Starch is a polymer, or chain, of glucose molecules containing both amylose and amylopectin. Amylose is the straight-chain form of this polymer, while amylopectin is the branched form. Starch is the main carbohydrate food reserve in plant seeds and tubers and while it forms an important part of human nutrition, it also provides a useful raw material for industry. Amylopectin has unique physicochemical properties that makes it attractive for a vast range of non-food purposes. Most industrial uses normally involve modification by physical, chemical or enzymatic methods to alter its properties for specific purposes. There is an advantage, however, in producing a wider range of natural starches or derivatives to circumvent the need for processing steps since this is expensive and some constitute an environmental load. Transgenic potatoes and maize producing amylose-free starch have indeed been developed and are ready to enter the market. Even the creation of transgenic plants with more complex genetic changes, which would result in the production of bio-degradable plastics (a third generation GM plant product) instead of starch, are well underway. Transgenic potatoes have also been modified to prevent starch degradation resulting in sugar formation during cold storage to prevent browning (due to the presence of reducing sugars) of french fries and chips. Other potatoes with a modified high-density starch absorb less oil when deep-fried, resulting in chips containing less fat. These and other lines of research have the potential of producing healthier foods or increasing the role of agriculture in replacing limited natural resources. Again, the design of such GM plants requires a detailed understanding of the chemistry of starch synthesis in plant cells and an extensive search for suitable traits that will not disturb the physiology of the host plant.

5.1.2.4
Yield

Rice, a staple food crop for nearly half of the world's six billion population, is a key target for molecular research aiming to develop improved varieties to feed the world's expanding population. The rapid population growth, especially in developing countries, has caught up with the achieved advances in cereal yields in the past decades. To meet expected demands, according to the International Rice Research Institute experts, a 40% increase in rice yield is needed by 2020. Researchers have therefore turned their attention back to basis of crop yields–carbon fixation.

Photosynthesis is the process in green plants that uses the energy of sunlight to convert carbon dioxide and water into glucose, while releasing oxygen to the atmosphere. Glucose and derived sugars are essential for plant growth and the build up of storage compounds such as starch and oils. All animals, including humans, depend either directly or indirectly on photosynthesis, the most important chemical process on Earth. Increasing the efficiency of photosynthesis and carbon metabolism in crop plants would increase yield in agriculture and is therefore an important way to help feed the world's ever-growing population.

The process of photosynthesis is not similar in all organisms, and rice happens to employ a less efficient system of carbon dioxide fixation. Indeed, by introducing two specific maize genes that are involved in photosynthesis into rice, it was demonstrated that the new rice strains could boost photosynthesis and grain yield by up to 35% under laboratory conditions. Trials are underway for rice plants with a further enhancement of the photosynthetic capacity, requiring simultaneous expression of three key enzymes in proper cellular compartments. It is expected that the technology can also be applied to other crops with the less efficient type of photosynthesis, such as wheat.

Even plants with the efficient type of photosynthesis may be target for improvement. GM plants are being developed that need less light by increasing the amount of chlorophyll, the protein that grabs the energy quanta from light. Other opportunities to increase agricultural yield, not necessarily requiring genetic modification, can be found in improvements that influence the growing season or harvesting methods. One particular observation is worth noticing: in the Philippines a rice variety has been developed that does not die at the end of one season. Moreover, it can be grown in virtual hedgerows across mountain slopes. This perennial rice plant can be harvested again and again, while providing living barriers to soil movement on sloping land. This would help reduce loss of precious topsoil in upland regions, the silting of rivers and irrigation systems downstream, and the intensive inputs and hard labour of annual rice crops. While some of the plants have also survived experimental drought stress and yield more grain than expected, further breeding and multiplication may take five years or more before these plants are available to farmers.

5.1.2.5 *Health*

It is common knowledge that plants form an immensely rich source of health-promoting substances, but it is often difficult to pinpoint the true effectors, especially if combinations of substances are doing the job. Differences in requirements may exist among individuals, at what level active substances may be found in different crop varieties, how storage affects their functioning, etc. Vitamins, while essential, should not be overdosed and the recommended daily allowance (RDA) gives an indication of an average safe level. Also, there are many plants that harbour less healthy or even toxic compounds. While we have great working experience with the plants we use for food, the attention that is being given to less desirable compounds such as allergens has never been so great since the advent of genetic modification and its application to the production of food. Other health-related compounds include the production of antibodies, pharmaceutical proteins and/or (edible) vaccines. This agronomic practice, not expected for another 10 years, is often referred to as molecular farming.

5.1.2.5.1 Allergy

Our knowledge of food allergies is far from complete. It is still unclear, for example, why only certain individuals are affected and why, even among them, the problem is often restricted to childhood. It is also not clear why the allergies caused by various nuts and aquatic animals tend to persist and be lifelong. Milk, egg, soy, and wheat are the major causes of food allergies in children, whereas peanut, tree nuts, shellfish, and fish are the most prevalent causes for allergies in adults.

Virtually all allergens are proteins and food allergens typically represent 1% or more of the total protein. The question of whether a novel (transgene) protein would render a food product more allergenic than its conventional counterpart can be addressed by:

1. Comparing the predicted amino acid sequence of the novel protein with that of known food allergens
2. Examining the protein for characteristics often associated with known food allergens, such as sugar-like side-chains and heat stability
3. Monitoring the digestibility of the novel protein

Since any outcome from these comparisons would not be conclusive, a (ideally, animal) model test system would be needed to show potential evidence of allergenicity. Such a system could also be used to answer questions such as whether it is possible that the process of genetic modification renders existing proteins allergenic, or even gives rise to unintended protein products with toxic properties.

In quite a reverse line of thought the question can be asked whether genetic modification might be able to remove allergens from food, yielding for example non-allergenic cereals, dairy products and seafood. Indeed researchers in Japan are developing a variety of rice that is allergen-free and US colleagues are working on peanuts to get rid of the two main allegenic proteins responsible for a potentially life-threatening swelling of the lips and airways in sensitive individuals (estimated to affect approximately 1% of the Western population). It is not unreasonable to expect that basic research and a good understanding of the chemical processes in plant cells will deliver maize, soybean and rapeseed with a healthier fat profile and cereal grains with better nutritional value but low in measurable toxins or allergens.

5.1.2.5.2
Plant Nutraceuticals

World consumption of natural health products, nutraceuticals, and functional foods is estimated to be between $140 and $250 billion and growing at an annual rate of about 10%. Nutraceuticals, also referred to as functional foods, are ordinary foods that have components or ingredients incorporated into them to give them a specific medical or physiological benefit, other than a purely nutritional effect. A good example comes from the so-called French paradox: Epidemiological data prove that France has a low morbidity through cardiovascular coronaries (infarctus) despite the fact the diet is rich in lipids and risk factors in arteriosclerosis (think of the French cheeses and cigarettes). Polyphenols in red wine are now thought to play a role in the prevention of heart disease. Polyphenols inhibit the production of a peptide by blood vessel cells, a small protein called endothelin-1.

Endothelin causes blood vessels to constrict and overproduction of this protein compound is thought to be a key factor in why arteries clog with fatty deposits. Genetic modification may thus find ways to overproduce polyphenols, and possibly other compounds. Crops with nutraceuticals may thus help in reducing chances of developing specific diseases.

5.1.2.5.3
Vitamins: Golden Rice

A vast range of scientific studies are concerned with the role of enhanced levels of vitamins and trace elements. Vitamin E, zinc and selenium are suggest to lower the risk of heart disease and possibly improve immunity, as well as fight against Alzheimer's disease. A consensus still seems far away and a healthy, diverse diet would probably be the best choice. However, it is quite possible that certain individuals, or population groups, would benefit from foods with health-promoting elements or defined formulations. As golden rice has been such a debated subject in this respect, it useful to expand on the history of its creation and future.

Millions of people in the world suffer from vitamin A deficiency (VAD), which leads to vision impairment and increased susceptibility to diarrhoea, respiratory diseases, and measles. In Southeast Asia it is estimated that five million children develop xerophthalmia (alteration in the structure of the conjunctiva and cornea found predominantly in children) every year. This problem may be equally severe in certain areas of Africa, Latin America and the Caribbean. Overall, around 500,000 children annually become irreversibly blind as a result of VAD.

Because rice accounts for the majority of the world's diet, it was only natural that it became the focus of an intense research effort that began in 1982. Plants are usually rich in the provitamin A precursor (beta-carotene or other carotenoids) that the body converts into two vitamin A molecules (retinol), an organic compound that is soluble in fats. In the rice crop it resides mainly in the greener parts of the plant, which are discarded, and not in the endosperm, i.e. the part of the rice grain that remains after it has been polished. Traditional breeding methods have been unsuccessful in producing crops containing a high vitamin A precursor concentration and most national authorities therefore rely on complicated supplementation programs to address the problem.

By inserting three foreign genes – phytoene synthase (from daffodil), phytoene desaturase (from the bacterium *Erwinia uredovora*), lycopene beta-cyclase (from daffodil) – Dr. Ingo Potrykus of the Swiss Federal Institute of Technology and Dr. Peter Beyer of the University of Freiburg in Germany managed to engineer a full biosynthetic pathway for beta-carotene into Taipei 309, a japonica rice variety. In August 1999, they unveiled the fruit of their research and named it "golden rice." because of its colour. Golden rice varieties can easily be integrated into the farming systems of the world's poorer regions, therefore the technology promises to help solving Asia's vitamin A deficiency problem in an effective, inexpensive, and sustainable way. But how effective is golden rice really? How much carotene is needed and how much can be supplied through rice?

The FAO/WHO recommended daily amount (RDA) for vitamin A in children aged 1–6 is 400 µg. To be active, beta-carotene -(a pro-vitamin) must be split by an enzyme in the intestinal mucosa or liver into two molecules of vitamin A. Like vitamin A, the pro-vitamin is fat-soluble and requires dietary fat for absorption. Thus, digestion, absorption, and transport of beta-carotene require a functional digestive tract adequate energy, protein and fat in the diet. Therefore the RDA for carotene in healthy persons has been set to 2.4 mg. The current varieties of golden rice contain approximately 1.6 µg of beta-carotene/g dry weight. Using the standard beta-carotene-to-vitamin A conversion, 30 g of current golden rice would contain 8 µg of vitamin A activity, less than 1% of the RDA. Many children exhibiting symptoms of vitamin A deficiency suffer from generalised protein-energy malnutrition and intestinal infections that interfere with the absorption of beta-carotene or its conversion to vitamin A. Therefore, at first glance, golden rice does not seem to contribute a great deal. On the other hand, RDA values are to some extent luxurious recommendations, representing a "nice to have"-supply, which also considers the multiple effects of vitamin A and especially of provitamin A, beta-carotene. The latter, besides being a provitamin, has one additional effect, which is to act as a free radical scavenger, thus preventing typical diseases in developed countries (diseases of the cardio-vascular system and some sorts of cancer). There is consent that the amounts required in the prevention of those severe symptoms of vitamin A deficiency in developing countries are significantly lower than given by RDA values. Furthermore, it is expected that future varieties of golden rice will contain increased levels of carotenes – carrots accumulate approximately 100 µg or more of beta-carotene/g fresh weight! We will therefore know a correct answer only after having data from the varieties bred by the plant breeders, from bioavailability studies and from nutritional studies on vitamin A-deficient people.

What about patent rights and the costs of using the GM rice varieties? Will golden rice be available to farmers and thus the population of Third World countries?

The inventors, Potrykus and Beyer, were determined to make the technology freely available and since only public funding was involved they initially considered this should not be too difficult. However, at least fifteen technology property (TP) components went into the three different genetic constructs that were used to generate golden rice. Many of these TPs were acquired by ETH-Zürich under Material Transfer Agreements or by the use of licenses. Transfer and use of golden rice therefore, depending on the country in which it is to be deployed, would, at a minimum, require agreements from a dozen or so entities (public and private, institutes or companies) for the TP transfer and use. In addition, again depending on the country of use, between zero and 40 licenses for IP rights would be required, from a dozen or so entities. However, thanks to the public pressure it turned out that there was a lot of goodwill in the leading companies to come to an agreement on the use of IPR/TPR for humanitarian use that does not interfere with commercial interests of the companies. Therefore, the delivery of golden rice from the inventors' laboratories in Europe was possible as a result of the donation of intellectual property licences from a range of legal entities, including companies such as Syngenta, Bayer and Monsanto. Each company has licensed free-of-charge technology used in the research that led to the invention. Subject to further research, initially in the developing countries of Asia, as well as local regulatory clearances, golden rice can thus be made available free-of-charge for humanitarian uses in any developing nation.

To date, golden rice is a popular case supported by the scientific community and official developmental aid institutions, but equally strongly opposed by the opponents of GMOs. The first groups think it is an excellent example of how genetic engineering of plants can be of direct benefit to the consumer, especially the poor and the disadvantaged in developing countries, where GMOs offer many more opportunities for the improvement of livelihood than for those living in well-fed developed nations. The opposition, however, is concerned that golden rice will be a kind of Trojan horse, opening the door to other GM applications and leading to improving acceptance of GM food.

It is argued that vitamin A deficiency is accompanied by deficiencies in iron, iodine and a host of micronutrients, all of which come from the substitution of a traditionally varied diet with one based on the monoculture crops of the Green Revolution. Poor people do not eat plain rice out of choice, they just do not get enough to eat and are undernourished as well as malnourished. In numerous countries where vitamin A deficiency is endemic, food sources of beta-carotene are plentiful but are believed inappropriate for young children, are not cooked sufficiently to be digestible, or are not accompanied by enough dietary fat to permit absorption. In addition to doubts about cost and acceptability, biological, cultural, and dietary factors act as barriers to the use of beta-carotene, which explains why injections or supplements of pre-formed vitamin A are preferred as interventions. Opponents therefore reject the notion that golden rice could play a significant role to alleviate the VAD problems and dismiss the enthusiasm by others as a publicity campaign for the application of genetic modification.

5.1.3 Information Sources

Agricultural molecular biology laboratory (AgMoBiol) of Peking University has set up a database of food allergens. http://ambl.lsc.pku.edu.cn

Global status of approved genetically modified plants. Agriculture & Biotechnology Strategies (Canada) http://64.26.159.139/dbase.php

Information systems for biotechnology lists databases of international field tests of GMOs and commercialised GMOs http://www.nbiap.vt.edu

ISAAA brief on GM rice: Will this lead the way for global acceptance of GM crop technology? http://www.isaaa.org/Publications/Downloads/Briefs%2028.pdf

James C (2002) Global status of commercialised transgenic crops: ISAAA http://www. isaaa.org/Press_release/GMUpdate2002.htm

Lheureux et al. Review of GMOs under research and development and in the pipeline in Europe. IPTS ftp://ftp.jrc.es/pub/EURdoc/eur20394en.pdf

Prototype database for products derived using modern biotechnology. OECD http://webdomino1.oecd.org/ehs/bioprod.nsf

5.2 Third Generation of GM Plants: Biofactories

Anne-Katrin Bock, Janusz Zimny

Plants are known as sources for a variety of different pharmaceutically or industrially used substances. Modern biotechnology makes it possible through the targeted modification of plants to enlarge the spectrum of products and to generate new biofactories. It has been found that GM plants can produce vaccines and antibodies protecting against human and animal diseases such as cholera, cancer, diarrhoea or dental caries. The application also includes industrial raw materials that in future might replace petroleum-based substances. The potentials of future utilisation of products obtained from GM plants are discussed in this section.

5.2.1 Introduction

The application of modern biotechnological techniques in plant breeding promises new advances in the production of food as well as non-food products. Continuous development in these areas of research has so far resulted in three "generations" of GM plants. The first GM plants contained genes responsible for agronomically important traits, such as herbicide tolerance or insect and disease resistance, which provide advantages for farmers by reducing the necessary input of herbicides, pesticides or manpower. The second generation of GM plants are those with improved end-use quality traits (see previous section). These plants are supposed to provide improved (food) products for consumers. The introduced genes change the composition of carbohydrates, fats or the functionality of proteins. Improved amino acid composition or vitamin content (for example golden rice, a GM rice with enhanced levels of pro-vitamin A) could enhance food quality (nutraceuticals). An increase in shelf life could lead to fresher products in supermarkets and to less spoilage during transport. Also, the taste of fruits and vegetables and the decrease of allergen content in food can be influenced by genetic modification.

The third, and so far the most recent, generation of GM plants are those to be used as biofactories producing non-food fine chemicals or raw materials. Researchers may choose genetic modification of plants, but micro-organisms or animals can be attractive hosts as well. Substances to be used for diagnosing diseases or for therapy have already entered the market place. Researchers are also looking for new ways of immunising people and animals against viral and bacterial diseases. Apart from medical applications, GM plants with altered patterns of fatty acid contents find uses in the production of technical oils. GM plants may also be used to produce biopolymers replacing petroleum-based compounds in the plastics industry.

Well over a 100 compounds directly derived from plants are currently used by industry to produce pharmaceuticals. Many investigations have been carried out in recent years to improve plants as a source for such organic substances. The production of specific secondary metabolites from plants or tissue or cell culture has become routine, and genetic transformation methods have been used to increase the production of such substances.

5.2.2 Plants as Biofactories

Novel biocompounds produced by or extracted from GM plants can be used as pharmaceuticals, e.g. edible vaccines, specific antibodies or human proteins. While monoclonal antibodies, blood proteins or hormones are currently produced using biotechnological methods using animal or human tissue cultures, plants have a distinct advantage. The use of substances from human or animal sources carries a risk of contamination with pathogens while the use of GM plants would practically eliminate such risks. Furthermore, large-scale production of biocompounds from plants may be easier and less expensive.

5.2.2.1 *Plant-Derived Injectable and Edible Vaccines*

The immune system of humans and animals reacts against viral and bacterial pathogens by producing antibodies that are specific for certain proteins of these pathogens (immunogenic proteins). Antibodies are able to recognise these proteins, attach to them and thus initiate the destruction of the pathogenic organism. To avoid an outbreak of a known disease among human or animal populations, vaccination can be used as a precaution. Conventional vaccines usually consist of a killed or weakened form of the targeted pathogen and are usually administered by injection. The subsequent immune response will secure immunity against the disease for a defined period of time. Vaccines are currently produced by infecting human or animal cells in appropriate culture media.

Modern biotechnological methods, especially genetic modification, provide powerful possibilities for the development of new strategies for vaccine production. GM plants may serve as biofactories producing vaccines free from any potential human or animal proteins or diseases. Transgenic plants, when supplied with specifically selected genes, are capable of producing immunogenic proteins. Such plants can subsequently be grown on a large scale and can be used for isolation of pure vaccines in large quantities.

Three GM vaccines have currently been approved for commercialisation in the EU. The genetic method that was chosen relied on the production of a weakened versions of a virus after deletion of specific genes (such as the animal vaccine against Aujezky's disease) or rely on the production of a harmless host virus containing a few specific genes from a pathogenic virus (such as vaccine for foxes against rabies). While these particular vaccines are not produced in GM plants as yet, a range of vaccines from GM plant sources has been developed and produced in research laboratories.

An important factor for an effective vaccination is that the vaccine contains a protein that is specific for a certain pathogen and that the immune system will subsequently recognise the live pathogen. It was found that particular proteins provoke strong responses from the immune system when taken orally. Therefore, when searching for new forms of immunisation of humans and animals to viral and bacterial diseases, researchers have identified pathogen proteins with such properties for developing edible vaccines from plants. In order to achieve this, genes coding for such immunogenic viral or bacterial proteins have been introduced and expressed in plants. Oral delivery of vaccines is a very attractive alternative to injection. Production in GM plants is comparatively inexpensive, it can be done in any country, including developing countries, purification of the vaccine is not necessary and administration is easy.

So far research has predominantly been carried out with plants that are easily modified, such as tobacco, potato and tomato. After testing the reliability of the system, other plants will be used that can be eaten raw or that are suitable for storage as such as banana, lettuce, wheat, rice and maize. Therefore, oral vaccinations against common diseases such as flu, hepatitis B, tuberculosis, malaria and cholera might indeed become a reality in the future.

5.2.2.1.1
Examples of Vaccines Produced in Plants

Several strategies to produce effective vaccines in plants have been developed. One of them makes use of a plant virus, harbouring the gene for a protein of a human virus. After infection of a plant with this GM plant virus, the human virus protein is produced and can be isolated, purified and used as a vaccine. Indeed, animals, when vaccinated, developed antibodies that would react with the human virus. Vaccines for the human immunodeficiency virus (HIV) and the human rhino virus (HRV) have been developed following this method.

In potatoes, an orally active vaccine against cholera has been developed. Cholera-causing bacteria produce two types of toxin proteins but only one of them is toxic for humans. The harmless protein can therefore be used to induce immunity. A part of this protein was produced in potatoes after introducing a gene fragment coding for the toxin. Mice that were fed with the GM potatoes, were found to produce antibodies that would neutralise the activity of both cholera toxins.

Another important target for vaccine production is hepatitis B, a virus that is responsible for the majority of chronic liver diseases. Vaccines that are effective against hepatitis B infection have been produced in yeast, but these are expensive to produce and need stringent storage conditions. Therefore novel vaccines have been developed using potato and lettuce plants. Mice fed with GM potatoes producing one of the hepatitis B virus proteins showed an immune response. Future efforts will include banana as a vaccine source since such a pharmaceutical crop can easily be grown and administered in developing countries.

The Norwalk virus is responsible for most non-bacterial gastroenteritis. A protein that forms the coat of the virus, the capsid, has been expressed in transgenic tobacco and potatoes. After injection of these purified antigenic proteins into mice, protein-specific antibodies were produced.

Not only fruit or leaf tissue but also plant seeds offer potential advantages for the production of vaccines that can be administered orally. For example, a glyco-

Table 5.1. Examples for vaccine production

Expressed protein	GM plant host
Heat-labile toxin enterotoxic *E. coli* (humans)	Tobacco, potato, maize
Cholera toxin of Vibrio cholerae (humans)	Potato
Envelope surface protein hepatitis B virus (humans)	Tobacco, potato, lettuce
Capsid protein of Norwalk virus (humans)	Tobacco, potato
VP1 protein of foot-and-mouth disease virus (agricultural domestic animals	Arabidopsis, alfalfa
Glycoprotein S from transmissible gastroenteritis coronavirus (pigs)	Arabidopsis, tobacco, maize
Epitope gp120 and gp41 human immune deficiency virus (humans)	Tobacco, black-eyed bean, cow-pea
Epitope protein of human rhinovirus	Black-eyed bean
Glycoprotein B of human cytomegalovirus	Tobacco

protein of the human cytomegalovirus (a widespread virus, that causes pneumonia in immune-suppressed patients) that was expressed in GM tobacco seeds proved to be immunologically reactive.

Immunisation by edible vaccines of animals also has an economically attractive potential. For instance, vaccines active against a transmissible gastroenteritis virus of pigs, when produced in maize, were successful in protection against the disease (Table 5.1).

5.2.2.2
Therapeutic and Diagnostic Antibodies

An alternative to immunisation, and thus to relying on antibody production in the patients, is the direct administration of appropriate antibodies to treat a disease (passive immunisation). Such antibodies can also be used for diagnostic testing. The ability of plants to produce functional monoclonal antibodies, so-called plantibodies opens the way for the establishment of an efficient and inexpensive method of immune protection against a number of diseases.

Only a limited number of antibodies that could be used in human medical applications have so far been produced in plants. Antibodies against the bacterium *Streptococcus sanguis* have been obtained from GM tobacco. Oral application of these plantibodies in clinical trials showed prevention of the formation of tartar on the teeth and, consequently, of dental caries. Plantibodies that inactivate *Streptococcus mutans*, another caries-causing bacterium, are at the stage of clinical testing. The expression of monoclonal antibodies against the herpes virus, causing fever blisters, has been reported for GM soybean. Rice and wheat plantibodies against a cell surface protein typical of tumours (carcinoembryonic antigen) have been produced and can be used for diagnostic purposes as well as in tumour therapy.

Table 5.2. Examples of plantibody production

Application for the plantibody	GM plant host
Dental caries (against streptococci)	Tobacco
Cancer treatment/diagnosis (against carcinoembryonic antigen)	Wheat, rice, tobacco
Herpes treatment (against herpes virus)	soybean

Because of the production in plants, plantibodies show slight modifications in molecular composition as compared to human antibodies. Although these differences do not influence their effectiveness, there is the potential of an allergic or even immunogenic reaction. Novel human therapeutics must be carefully checked and for this reason plantibodies are not yet produced commercially. Although it is expected that production costs from plants will be much lower, the cost of purification will still be comparable to current practices. But, purification might be avoided if antibodies were produced in seeds and oral application proved effective (Table 5.2).

5.2.2.3
Other Biopharmaceuticals

Apart from vaccines and human antibodies, other human proteins or pharmaceuticals may also be produced using GM plants. Several GM plants have already been developed for the production of, e.g. interferon, human serum albumin, haemoglobin, blood coagulation factors etc. (see Table 5.3).

Human haemoglobin as well as blood coagulation factors have been synthesised in GM tobacco plants. Glucocerebrosidase, an enzyme that is deficient in patients with Gaucher's disease, is an expensive drug since 10–12 tons of human placentas are used to isolate and purify the enzyme each year for a single patient. The enzyme has now also been obtained from GM tobacco, where it is expressed after harvesting the plants in order to limit accidental environmental exposure to pharmaceuticals.

Hirudin is a protein that is obtained from leeches and is used for its anticoagulant activity in the treatment of thrombosis. GM oilseed rape that produces

Table 5.3. Examples for protein/biopharmaceutical production

Application	GM plant host
Anticoagulant (hirudin)	Oilseed rape
Hepatitis B and C treatment (interferon)	Rice, turnip, tobacco
Blood substitute (human haemoglobin)	Tobacco
Gaucher's disease (glucocerebrosidase)	Tobacco
Wound repair, control of cell proliferation (human epidermal growth factor)	Tobacco, kiwi, potato, orange
Liver cirrhosis, burns, surgery (human serum albumin)	Tobacco

hirudin is already cultivated and commercialised in Canada. The plant produces a hirudin-oleosin fusion protein, a trick which results in storage of the hirudin protein in seed oil-bodies, thereby facilitating purification. Hirudin is recovered after enzymatic cleavage of the fusion protein. Apart from an improved purification procedure, the chosen approach also leads to hirudin only being activated after harvest and purification, thus limiting potential environmental impacts.

The gene of a mussel glue protein has also been introduced into plants. The water-resistant adhesive, which has a breaking load twice that of most epoxy resins, does not attack human cells or provoke an immune response, therefore it could be ideal for repairing soft tissues and bones inside the human body. Finally, expression of the human epidermal growth factor was reported in GM kiwifruit, potato and trifoliate orange. The application of these and other human growth factors may be useful to support the repair of tissues such as skin, bones or nerves (Table 5.3).

5.2.2.4
Biopolymers from Plants

The manufacture of plastics and polymers from petroleum-derived chemicals has a negative environmental impact, apart from the fact that this practice relies on the use of non-renewable resources. Plants would be a much more acceptable source of biodegradable polymers for the plastics industry. Genes responsible for the production of a certain type of polymer were identified in bacteria, isolated and introduced into mustard thale cress (*Arabidopsis thaliana*) and maize plants. Maize was modified in such a way that the required polymer was produced in leaves and stems but not in grains. Thus, the grains could potentially continued to be used as food, and the rest of the plant as a resource for the chemical industry. However, thus far the production of plastics from GM maize is still too costly and therefore the process has not been commercialised. Nevertheless, field trials are underway with oilseed rape and soybean as well.

Spider silk is known to be a very strong and flexible fiber. Increasing knowledge about its structure and the identification of the genes that code for the proteins involved facilitated the production of spider silk in GM plants (“biosteel”). Applications include fishing lines, ultra-light protective vests or stitching materials in the medical field. While tobacco and potato plants were modified to produce the spider silk proteins, success was also reported when GM mammary cells in cows and goats produced the proteins in milk and the proteins could actually be spun into fibres.

5.2.2.5
Oils for Food Production and Technical Use

The possibility of the genetic modification of the oil content and fatty acid composition in plants and seeds can play an important role in the production of healthier foods as well as in finding new or improved materials for industrial use. A large proportion of this type of research focuses on oilseed rape, the third most important oil-producing crop in the world. GM varieties with high levels of stearic acid or high myristic-palmitic acid as well as high erucic acid content have been developed. A variety with high levels of laureate oil is available commercially under the brand name Laurical. Its oil products are used in coffee creamers, in whipped toppings and in the confection industry. GM soybean and sunflower varieties gain interest because of the high quantities of oleic acid in these plants, which are important in the food industry.

There are also expectations for vast new markets for non-food bio-oils. World crude oil production from petroleum reserves will probably peak at some time between the years 2000 and 2020. Crops like sorghum, soybean and rapeseed are being developed and used for the production of fuels like ethanol, diesel petroleum or for fuel additives and lubricants.

New vegetable-based oils can also serve as a source for a wide range of biodegradable petrochemicals, which are the raw materials for products such as plastics, textiles, lubricants, paints and varnishes. Once non-renewable hydrocarbon resources such as petroleum and coal are exhausted, there will be no other source of such products. An example is oleic acid that can be converted into estolides to be used in production of hydraulic fluids. Researchers have also developed transgenic plants expressing enzymes that convert oleic acid into vernolic or crepenynic acids for the production of environmentally friendly paints.

5.2.2.6 Production Methods

5.2.2.6.1 Field-Grown Plants

GM crops can easily be grown in the field to produce specialty or bulk substances on a large scale. It must be kept in mind, however, that non-food producing crops may need to be segregated from other crops. Pharmaceutical substances may be quite toxic in large doses and therefore GM crops for these purposes should be stringently controlled. GM crops for the production of industrial bulk compounds should not be allowed to mix with food or feed crops. Indeed such segregation is already standard practice for (non-GM) rapeseed crops with enhanced levels of erucic acid, which has anti-nutritional characteristics and is used as an industrial raw material for, e.g. lubricant production.

The possible persistence of novel plant products in the environment and their possible effects on non-target organisms must also be examined carefully. Out-crossing to other crops or related weeds may be undesirable and must therefore be prevented. Therefore, depending on the nature of the product and the characteristics of the crop, the degree of containment needs to be decided upon. It may be necessary to employ genetically sterile plants, restrict the activation of the desired product to the laboratory setting or to physically confine growth and harvest in specially equipped greenhouses.

5.2.2.6.2
Plant Cell Culture

An alternative to crops that are grown and harvested from an open field or in greenhouses might be the use of suspension plant cell cultures. Plant cells can be multiplied very efficiently in liquid media. Cell suspension cultures can be used as biofactories to produce substances of interest without any contact with the environment and without risk of mixing with feed or food. An illustration of such a set-up is the production of recombinant human interleukin using GM yeast or tobacco cells that are cultured in a suspension culture. The plant cells are able to excrete interleukins through the plasma membrane and cell wall into the medium, from which isolation and purification of the substance is relatively easy. Interleukins play a role in the regeneration of tissues, are involved in immune regulation and are used for the treatment of diseases such as asthma and cancer.

A successful method for generating large cell suspension cultures with identical genetic makeup, employs the bacterium *Agrobacterium rhizogenes*. These bacteria are able to reliably transfer a small and distinct fragment of DNA into the nucleus of a plant root cells, causing tumour-like effects and the formation of hairy roots. The plant root cells can be grown in a controlled way, using specific growth substances, and can be induced to produce specialty secondary plant metabolites such as phenolics, alkaloids and terpenoids. The amount of secondary metabolites developed in hairy root cells can be regulated by certain supplements added to an in-vitro culture medium (e.g. plant growth hormones or ammonium) or other culture conditions (e.g. light intensity, temperature).

The biosynthesis of geranin, which is used to fight diarrhea, can thus be increased in the hairy root culture of geranium (*Geranium thunbergi*). The medical plant great burnet (*Sanguisorba officinalis*) is a source of the compound sanguiin, which has hemostatic and anti-inflammable activity. Hairy roots produced twice as much sanguiin as the conventional plant. Scopolamine (used as a tranquiliser as well as for diagnostic purposes) was produced with high efficiency in the deadly nightshade (*Atropa belladonna*) root cultures after *Agrobacterium* mediated transformation.

Other pharmaceutical substances, like piperidine and lobeline, were isolated from the hairy root cultures of lobelia (*Lobelia inflata*) and henbane (*Hyoscyamus albus*). Another example is the production of glycosides, used in cardiology, in hairy root cultures of foxglove (*Digitalis purpurea*). Cancer fighting substances were isolated from the hairy root cultures of yew (*Taxus*), platycodon (*Platycodon*) and lobelia.

5.2.3
Information Sources

Arkansas Agricultural Experiment Station, University of Arkansas Division of Agriculture. Using plants as biofactories is made possible by the increasing understanding of the genetic structure of organisms. http://www.uark.edu/depts/agripub/Publications/Agnews/agnews01–47.html

Biofactories. Within the plant biotechnology sector there is great interest in expressing mammalian proteins in plants, in a way that would allow their commercial exploitation. http://www.dcwi.com/~pnpi/Biofactories.htm

Daniell H et al. (2001) Medical molecular farming: production of antibodies, biopharmaceuticals and edible vaccines in plants. Trends in Plant Sci 6:219

Giddings G et al. (2000) Transgenic plants as factories for biopharmaceuticals. Nature Biotechnol 18:1151

Giddings G (2001) Transgenic plants as protein factories. Curr Opin Biotechnol 12:450

Sheller J, Gührs K-H, Grosse F, Conrad U (2001) Production of spider silk proteins in tobacco and potato. Nature Biotechnol 19:573–577

The Canadian Food Inspection Agency organised a public forum on plant molecular farming http://www.inspection.gc.ca/english/plaveg/bio/mf/mf_come.shtml

The Pew initiative on food and biotechnology hosted a workshop exploring the potential risks and benefits of bioengineering plants to produce pharmaceuticals http://pewagbiotech.org/events/0717/ConferenceReport.pdf

5.3 Biotechnology for Food and Agriculture: Global Issues

Gert E. de Vries

Current and future developments in agricultural biotechnology may contribute to prevent local food shortages and improve its quality. Technological progress will nevertheless neither be a major solution to current problems nor can it be ignored because immediate solutions are not manifest. In this section a range of issues are described that are closely connected to, or interfere with, a successful deployment of improved crops that will arise from biotechnological research and development.

5.3.1 Hunger and Poverty

The number of chronically malnourished people in the world in 2001 was estimated to be 840 million, roughly equivalent to the combined population of the United States, Canada, Russia, France, Germany, the United Kingdom and Japan. Of these people, 95% live in the developing world. There is enough food produced for the whole world community, so why is it so difficult to curb malnutrition and famine? Is food security basically a distribution problem, as often advocated? Food is handled as a mere commodity in world trade, therefore adequate distribution would require overseeing and a change in policy. As long as food is not recognised as a basic human right, improvements in agricultural technologies and the stimulation of fair trade seem to form the best options. Among reasons for the existence of hunger are:

1. Unstable governments and political unrest
2. Lack of infrastructure and distribution systems
3. The toll placed by tropical diseases and HIV on the agricultural work force
4. Increased frequency of occurrence of natural disasters like earthquakes, extensive periods of drought, hurricanes or mudslides which partially may be connected to effects of global warming

These and other effects of human intervention in the environment may become a trend and will probably intensify over the next 30 years.

The greatest problem for the inhabitants of the developing world is poverty; having no financial reserves nor technology to curb any of these misfortunes makes them increasingly dependent on populations in rich countries. These disparities are growing. The richest 15 persons in the world have more wealth than the combined yearly gross domestic product (GDP) of all of sub-Saharan Africa with its 550 million people. There are more numbers for reflection: the world's richest countries, with 20% of the global population, account for 86% of private consumption while the poorest 20% account for just 1.3%. A child born today in an industrialised country will add more to consumption and pollution over his or her lifetime than 30–50 children born in developing countries. Half the world, nearly three billion people, live on less than $2 a day and 30% of them are unable to read or write. To place this situation in another perspective: the costs for schools for all children equals 1% of the money spent on weapons in the world. The condition of hunger in a world of plenty is seen by some to be as equally monstrous and unconscionable as slavery has been in the past. Therefore every effort should be done to open eyes to these dramatic events which claim tens of thousands of hunger-related deaths every day.

Lack of food is an obvious condition, but deficiencies in micronutrients such as vitamin A, iodine, iron and zinc are widespread with equally serious consequences for health. The World Bank's World Development Report 1993 found that micronutrient programs were among the most cost-effective of all health interventions. This general problem of poor dietary quality has been dubbed "hidden hunger".

At present, one-third of the population of sub-Saharan Africa falls below the poverty line and, according to USAID data, an estimated 50% of the world's hungry will reside in this region in 10 years from now. Experts say that there cannot be a long-term solution to famine without significant investment in education and agriculture, which is the foundation of most economies in Africa. Farming supports more than 70% of the population and contributes about 30% of gross domestic product. However, African farmers face stiff competition: per capita world food production has grown by 25% over the past 40 years and food prices in real terms have fallen by 40%. While current practices of small scale agriculture may be more acceptable to support the local social fabric of life, it may not be an economically viable option to compete at a world scale.

5.3.2
Problems Facing World Food Production

Despite steadily falling fertility rates and family sizes, the world population is projected to grow from 5.6 billion in 1994 to up to 9 billion in 2050. The population in the 50 least-developed countries will nearly triple in size in 50 years and by then, 84% of the world population will live in what we call today developing countries.

According to the FAO more than 800 million people around the world currently do not get enough to eat. On average an adult needs 2,200 kcal/day. According to UN data, the world food supply in 1970 represented 2,360 kcal per person each day and has risen to more than 2,750 kcal today. The rate of increase in food supply is expected to exceed that of population growth until 2010, suggesting that sufficient food is available to feed the world population.

So far, predictions that the human world population would multiply beyond their capacity to feed themselves have repeatedly been proven wrong. Thomas Malthus predicted famine in 1798, just as farm yields were taking off. Similarly, Paul Ehrlich in 1969 gave up hopes of continuing to feed India and concluded that hundreds of millions of people would starve to death in the 1970s. Indeed, the world's population grew much as expected, but food output more than kept pace. The Green Revolution brought novel crop varieties that farmers rushed to adopt.

Research that was exclusively undertaken by institutions in the public sector during the years 1960–1980 introduced semi-dwarfed wheat and rice varieties to parts of Asia and Central America, together with well-functioning systems of irrigation. Millions of farmers started using higher-yielding hybrid seeds for the production of staple foods, chemical fertilisers, pesticides and weed-killers. These agronomic technologies even allowed India to export surplus grain. Chinese rice farmers also raised production by two-thirds between 1970 and 1995, but these increases largely bypassed sub-Saharan Africa. While the new technologies may still have saved a billion people from starvation in the past, the subsequent population growth, changing demographics and inadequate poverty intervention programs have now probably levelled most of its gains.

It is sometimes argued that agricultural technology merely postpones an inevitable next famine. By making more food available, the world population will grow further, leading to additional demand for agricultural lands and a further conversion of wildlife habitat. However, agricultural technology not only results in larger quantities but also enhances food quality, helping to reduce general misery, maternal and infant mortality rates, and thus directly improve human well-being. A better quality of life may very well slow down population growth, as witnessed in the developed countries.

The pledge made at the 1996 World Food Summit to reduce by half the number of hungry people in the world by 2015 is far behind schedule. Therefore, the FAO concluded that the world lacks the commitment to ensure that all of its population has enough to eat and that poor countries must do more to stimulate their own agro-economy rather than rely on foreign aid. It is indeed conflicting wisdom to note that subsidised farmers in rich countries produce enough surplus food to feed the hungry, but not at a price they can afford by regular trade. Much food is therefore donated. However, since most poor people earn their living from agriculture, quantities of donated food negatively affects their livelihoods and the build-up of market economies in the target countries.

The world's population is expected to almost double between 1990 and 2050, making food security one of the most important social issue for the next 30 years. Food production will have to be doubled or preferably tripled to meet the needs of the expected 9 billion people, 90% of whom will reside in the developing world. However, natural resources, necessary to feed an extra 250,000 world citizens/day, are declining: the availability of productive new croplands is decreasing, there is a lack of fresh water for irrigation expansion and crops show only limited response to additional fertilisers. The climatic conditions in developing countries, mainly in the tropics and subtropics, favour insect pests and disease vectors causing significant crop losses only to be worsened by poor soils, low productivity levels and post-harvest losses. Poor farmers lack economic resources to purchase high quality seeds, insecticides, and fertilisers. The only answer to world hunger, aside from necessary political and infra-structural reforms and assuming that population growth cannot be curbed, is to improve the productivity of farmlands in poor countries and support poor farmers when adopting successful technologies. In addition, there is a need for rich states to open up their markets to poor nations. Poor countries currently cannot compete fairly in agricultural markets because of a trade imbalance caused by liberal subsidies to agriculture in the countries of the Organisation for Economic Cooperation and Development, compared with marginal farm aid programs to developing nations.

Apart from improvements of political issues and resolving unstable situations, there are a number of technological options to improve food production:

1. Increase local farm productivity in the countries that most need the food
2. Work hard on new technologies to improve or modernise existing agricultural practices
3. Expand the area of farmland at the cost of forests, grasslands and risk losing areas of important biodiversity
4. Intensify production in agricultural exporting countries and distribute the products to where they are needed

There is not one single answer and any theoretically sound solution may have far reaching effects on economy, security, food quality and environment. A number of issues will be dealt with below.

5.3.2.1
Food Distribution and Aid

It is an embarrassment that in today's world, when global food production should suffice to feed everyone, so many people are malnourished or starve to death. It is therefore often argued that food security is a distribution problem rather than a production problem. Indeed if the world's food supply were equally distributed everyone could have an adequate diet.

In developed countries people prefer types of food that use lots of agricultural resources for a given level of nourishment. A serious redistribution effort would therefore require convincing about a billion people in developed countries to change their eating habits and give up certain types of food. Furthermore it can be questioned how long-term shipments of food can be financed or compensated by trade.

It is therefore not easy to imagine how such a change would take place while preserving democracy based on capitalism in food-producing countries. This culture is in many ways the most successful that has ever been deployed in terms of accommodating large numbers of individuals in comfort and luxury. However, it has not been as successful in integrating all in equal measure. While it has solved the problems of feeding large numbers of people, its failure in achieving equality on a world scale remains one of its major problems.

Solving food security by equal distribution therefore is clearly too idealistic for the current political world situation. Also, one cannot argue that there is enough food, for instance, in the continent of Africa and that it is merely a matter of distribution to prevent mass starvation. Above all, Africa has inadequate infrastructure for the transportation of food since only 20% of roads are paved, making transportation of perishable goods difficult. Africa is plagued by political unrest in different regions, which prevents food from reaching the poorest of the poor. Many of the world's poor, in fact, live in countries where governments lack either the will or the ability to raise living standards on their own. The Food and Agriculture Organisation (FAO) of the United Nations (UN) has listed wars and other forms of armed conflict as the exclusive cause of food emergencies in 10–15 developing countries during the last three years. Financial assistance to such governments, therefore, has often not helped their neediest citizens. Foreign aid has even worsened the worries of the poor by sustaining the corrupt or otherwise inefficient governments that caused their misery in the first place.

The best way, therefore, to combat this inequality is for rich countries to increase foreign aid budgets and initiate new, Marshall Plan-like, initiatives to fight poverty and improve local production systems. However, for such plans to succeed there must be an existing infrastructure where aid can flourish. It is sad to note that in the poorest regions of the world there is either little infrastructure, or existing (political) systems actually cause poverty. For instance, the future will tell how serious the consequences will be after Zimbabwe's president Mugabe ordered the confiscation of white-owned farmlands in the year 2001, thereby dismantling the existing agricultural infrastructure without providing adequate alternatives.

In the following year, US relief food packages were rejected in Zimbabwe since the unmilled maize seeds were genetically modified. It was argued that farmers would use the food as planting material and fields would be contaminated with GM maize. This would potentially render a large portion of the nation's future maize harvests to be unexportable to Europe and other nations that restrict imports of GM foods. It is likely that such problems will reoccur in other parts of the world, since GM foods continue to be produced in increasing quantities. In reaction, the USAID and the World Food Program, while not specifically referring to GM foods, claimed that they never have or will distribute foods that are not fit for human consumption or which might damage people's health in any way. However, since seeds from food aid donations are likely to be planted by poor farmers, it is not wise to introduce GM crops, against prevailing regulations, into any country by this route.

5.3.2.2
Climate, Soils, Nutrients, Water and Yields

In developing countries in the tropics and subtropics, crop losses due to pests, diseases, and poor soils are augmented by unfavourable climatic conditions such as droughts and by the lack of economic resources to purchase high quality seeds, insecticides, and fertilisers. In addition to low productivity levels there are high post-harvest losses due to the lack of appropriate storage facilities to prevent fungal and insect infestations. Indeed, pests destroy over half of all world crop production.

5.3.2.2.1
Water

While approximately 50% of the world's food production is fully dependent on timely precipitation, up to 40% of the crops are irrigated with water collected from rainfall and 10% is grown using groundwater or water from wells. There is growing competition for this water between cities and industry, with agriculture often getting the worst quality of water, if any remains. While supplies of water are generally adequate to meet demand for the foreseeable future, water is poorly distributed across countries, within countries and between seasons. Modern agriculture is by far the largest consumer of water, accounting for 70–80% of all water use. Lack of available water will seriously limit the expansion of food production when using current crop varieties. World water use has risen sixfold over the past 70 years, therefore the rapidly growing domestic and industrial demand for water will have to be met by reducing the use in the agriculture sector. A projected doubling of food production in unfavourable climates must therefore largely take place on the same land area while using dramatically less water.

Photosynthetic carbon dioxide fixation by plants is associated with a large amount of water loss through transpiration. The growth of quality crops requires considerable and varied amounts of water. For instance, the production of 1 kg of cotton by irrigated agriculture currently requires 17,000 L of water while growing 1 kg of rice requires about 5,000 L. The improvement of water delivery equipment may help to drive these figures down, since most of this water does not reach the plants but evaporates. There are also biotechnological solutions. To prevent desiccation-induced growth arrest and injury, most plants require a constant level of adequate soil moisture. However, recent advances in understanding the genetic control of drought tolerance offer new opportunities to develop crops that are less damaged by short periods of low soil moisture. This might enable the use of less water for irrigation and reduce drought-induced yield reduction caused by unfavourable climatic conditions. More effective management of water can therefore be reached through a series of institutional and managerial changes, in addition to a new generation of technical innovations that may also include the exploitation of advances in genetic modification of plants.

The costs of developing new sources of water are high and rising, and non-traditional sources such as desalination, reuse of wastewater, and water harvesting are unlikely to add much to global water availability in the near future, although they may be important in some local or regional ecosystems. A Blue Revolution, complementing the past Green Revolution, may be badly needed if we are to reform the usage of land and water while meeting required environmental and economic conditions.

5.3.2.2.2
Soil Fertility

Improved soil fertility is a critical component of increased sustainable agricultural production. Reduced use of fertilisers is warranted in some locations because of negative environmental effects. But, in countries where soil fertility is low and a large share of the population is food insecure, fertiliser use may need to be expanded. Locally available organic materials are usually insufficient by themselves and while nitrogen fixation by legumes may help, inorganic fertiliser will continue to be an important plant nutrient supplement.

Abiotic stress is a major limiting factor in agricultural crop production in many countries. The major abiotic stresses of economic importance include drought, cold, heat, salinity, soil mineral deficiency, and toxicity. Combined with chronic shortage of water, the results of poor soil fertility for African farmers is easy to predict. A study on vegetable production in South Africa showed that soil acidity and drought stress accounted for over 80% of all crops that were lost. Diseases and pests accounted for the remaining 20%.

Salinity is usually worsened by intensive irrigation. Agricultural lands that repetitively need extra water due to drought periods, or lands that experience high water losses due to evaporation run the risk of accumulating salts. Rice fields, which are mostly irrigated, are declining in productivity in many Asian countries because of increasing salinity levels. It is estimated that 25 million ha of agricultural land in the world suffers from excess salinity, and approximately 10 million ha can no longer be used for agricultural production. In 30 years, about 10% of all arable land will be contaminated with salt concentrations that will seriously affect crop yields.

Traditional plant breeding has had almost no success in creating crops with sufficient resistance to increased salt concentrations, but there is some progress in wheat breeding. Although some wheat cultivars are considered moderately tolerant to high salinity, they are still less salt-tolerant than many wild *Triticeae* species, especially those in the genus *Thinopyrum*. A long-term effort by plant breeders may lead to the transfer of salt tolerance from such species into wheat. However, genetic modification promises to be a much more powerful approach. In 2001, Chinese researchers reported to have isolated GM plants of tomato, eggplant, and hot pepper that even can be watered with seawater after introduction of genes from salt-resistant plants such as mangrove.

Soil acidity is the term used to express the quantity of hydrogen (H^+) and aluminium (Al) in soils that are highly weathered (leached) because of excessive rainfall. This process has depleted nutrient elements such as calcium (Ca^{2+}) and magnesium (Mg^{2+}) from naturally occurring minerals by chemical reactions involved in the nitrogen cycle and breakdown of organic matter. Soil acidity is a major problem for about 30% of all arable land in tropical regions. The presence of aluminium at levels exceeding 200 ppm presents a serious abiotic stress for most crops. The most important symptom of aluminium toxicity is the inhibition of root growth, caused by inhibitory effects on calcium and magnesium import at the level of the cellular membrane. Long-term exposure of plants to aluminium also inhibits shoot growth by inducing nutrient deficiencies, drought stress and phytohormone imbalances. Metal toxicity and nutrient deficiency problems in acid soils are investigated by only a handful of scientists in developed countries and this topic has thus far been largely neglected by large agrochemical companies. Sub-Saharan Africa has some of the oldest and most depleted soils in the world. Thousands of years of weathering have leached the nutrients, leaving the soil highly acidic, causing aluminium and manganese to become soluble and thereby toxic to plants. Together with high levels of iron, the aluminium oxides also hinder plant growth by chemically locking up phosphates. So far, traditional plant breeding has produced few answers for this global problem.

5.3.2.3
Impact on the Environment

Human activity is altering the planet on an unprecedented scale. More people are using more resources with more intensity and leaving a bigger "footprint" on the earth than ever before. Humans have become a major force of nature, largely because of the success of science-based technologies in extracting the earth's resources without proper concern for the environmental consequences. Science, though, also has a crucial role to play in helping us avoid the impeding catastrophe that is partly of its own making. Paul Ehrlich, author of the book *The Population Bomb*, developed an equation in the 1970s to describe the impact of human population on the environment. The population-resource equation puts the challenge that faces agriculture into perspective by saying: (Natural resource use)×(technology)=(population)×(per capita consumption). It would mean that, unless plant science and agricultural technologies can bring significant progress, natural resources will be increasingly employed to feed a growing world population with rising demands.

Agriculture accounts for 38% of land use, for some 75% of water consumption and it is responsible for most of the habitat loss and fragmentation that threaten the world's forests and biodiversity. Pesticide or fertiliser runoff and soil erosion threaten aquatic and avian species from sweet and coastal waters. But, paradoxically, if agricultural technology had been frozen at 1961 levels, the level of agricultural production in 1998 would have required more than a doubling of land devoted to agriculture: an extra area approximately the size of South America. Since the best agricultural land is probably already being cultivated and new cropland is unlikely to be as productive, this may even be a conservative estimate. Thanks to improvements in productivity this could still be avoided, but, as the human population rises from 6 to 9 billion people in the next 50 years, the environment may be further stressed by necessary increases in agricultural farmlands. There are still areas, mainly in Africa, where the techniques of the Green Revolution have yet to be tried, but in most of the developing world the gains in productivity are tailing off. Perhaps again we need a new impulse from science in developing sustainable agricultural systems that will curb the trend.

5.3.3 Strategies for the Improvement of Agriculture

There have been a number of ingenious suggestions for changes in agricultural practices that would improve the environment, while at the same time increase the efficiency of fertiliser and pesticide use, thus maximising crop yield. One example is “precision agriculture” in which the state of the soil and crop is monitored, sometimes by satellite, so that sowing and treatment rates can be adjusted accordingly. Such state-of-the-art agriculture technologies require high investments and are still out of reach of most farmers today. Alternatively, easy-to-use electronic tools, such as soil nutrient detectors or leaf chlorophyll measurements, could also play an important role in the improvement of current conventional methods in agriculture. Another method is the no-till strategy, combining organic and conventional methods and dubbed “integrated agriculture”, in which soil structure and biodiversity is conserved by obviating the need for ploughing and natural predators are employed to ward off plant pests.

Growing crops organically, a third strategy, means not using synthetic fertilisers and only a few selected pesticides of natural origin. Proponents argue that organic agriculture maintains a better soil quality, increases biodiversity in the field, produces equal or better food qualities and lowers the vulnerability of crops to pests. While conventional agriculture is seen to deplete resources and is susceptible to plagues or introduces unwanted chemicals in food products, organic agriculture is advocated to guarantee sustainability and to respect nature. Sustainable farm practices must nevertheless lead to adequate high-quality yields, be competitive and profitable, and in addition protect the environment, conserve resources and be socially responsible in the long term. Specific indicators used are soil quality, performance, profitability, environmental quality and energy efficiency.

Organic agriculture is not all as rosy as it seems since natural pesticides contain compounds that can be as poisonous as man-made chemicals. In addition, if farmers do not effectively treat fungal infections in their crops, mycotoxins may be produced which rank very high on the list of carcinogenic compounds. It is often questioned whether natural pesticides and organic methods will continue to sufficiently ward off plant diseases or whether a combination with biotechnological solutions should be sought.

Other problems would arise if it were decided to grow all food according to organic standards. Approximately 40% of the world population of 6 billion use crops grown using synthetic ammonia fertilisers. An extra 5 billion cattle would be required to supply the manure needed to produce the yearly 80 million tons of nitrogen nutrients used globally each year. There are no clear predictions what the consequences would be for the less precise applications of fertiliser, for hygiene, for environmental pollution due to runoff or for the increase of volatile ammonium loss in the atmosphere. Because organic crops require nitrogen obtained from supplementary farm practices rather than manufactured in a factory, organic farming is also land-hungry. If the current 6 billion people were to be fed using the technologies and crop yields of 1961, which were mainly organic, it would now require an approximate tripling of land area to be cultivated.

This assessment is, however, somewhat inadequate since organic farming has improved since then and agricultural techniques in 1961 were not fully organic.

Studies on the actual energy consumption of organic, conventional and integrated agriculture also point out that organic agriculture may use more energy and produces more carbon dioxide and ozone layer damaging nitrogen oxides. The higher energy consumption was due in part to the need for mechanical weeding and cattle-rearing activities, which easily exceeded the amount of energy needed to produce nitrate fertiliser in non-organic systems.

In developing countries organic agriculture is practiced in many places, not because of choice but because of lack of resources. Farmers in developing countries may, in comparison to large capital-intensive farms in developed countries, use inefficient methods but these are directly responsible for preserving vast amounts of plant biological diversity. Developing countries possess the largest plant biological diversity on earth, as well as the largest problems of soil depletion and environmental degradation. It is likely that agricultural production will increasingly specialise, with exports from countries that focus on particular products and types of agriculture. Many developing countries may well hold a comparative advantage in producing high-value, labour-intensive specialty crops and horticulture, while land-abundant countries may be better at producing bulk goods such as wheat, maize, and soybeans. It may neither be efficient nor environmentally sound for developing countries to seek food security by becoming self-sufficient in the production of all food crops, particularly when such production involves inefficient, unsustainable methods on fragile lands.

There are numerous ways by which agricultural productivity may be increased in a sustainable way, including the use of biological fertilisers, improved pest control, soil and water conservation, and the use of improved plant varieties, produced by either traditional or biotechnological means. Of these measures, biotechnological applications, especially transgenic plant varieties and the future products of functional genomic projects, probably hold the most promise for expanding agricultural production and productivity when properly integrated into traditional systems. It can therefore be expected that local food production will need to depend on non-organic methodologies unless conventional breeding techniques overcome limitations for fertiliser demand and yield in the very near future, or organic agriculture embraces genetic modification to speed up its development.

5.3.3.1
Role of Plant Biotechnology

There is considerable debate about whether conventional plant breeding can continue to generate yield increases and provide farmers with ways of reducing input constraints. So far conventional plant breeding still leads in contributing to yield increases. Farmers were modifying plant genomes long before they knew anything about genes. For thousands of years, they sought to transfer desirable traits from one plant species to another by cross-breeding. This was how wheat was obtained from wild grasses. Modern plant breeders further developed these crops with additional desirable traits, such as disease resistance. When crossing two plants, hybrids are formed and their genetic materials will be fully mixed. After subsequent rounds of self-crossing of the progeny and selection of promising candidates, a new and stable variety may be obtained with a set of desired characteristics. It typically takes 8–12 years to produce an improved plant variety by way of conventional cross-breeding.

Now, using techniques of molecular biology, scientists can identify traits from similar species or even from unrelated organisms and, basically in a single step, transfer those desirable genes into agronomically important crops. Therefore, as an extension of traditional plant breeding, plant biotechnology or genetic modification uses genetic knowledge and scientific techniques to add specific traits to crops, such as an ability to fend off pests, survive droughts, delay ripening, or require less pesticides. Such traits specifically benefit farmers, including those in developing countries where crop losses due to weeds, pests and diseases are high and conventional tools to ward off those problems are unavailable or unaffordable. Other traits, such as disease resistances or less dependence on fertilisers also have benefits for the environment, while crops with enhanced levels of health-promoting substances or improved taste benefit the consumer.

A major advantage of GM technology is that it allows the transfer of traits between unrelated species, something that is not possible through breeding. Additionally, these plant biotechnological techniques offer strategies for crop improvement that can be applied to many different crops. A typical example includes resistance to leaf or yellow rust, a disease caused by a fungus in wheat, which has eluded science and plant breeders for a long time. Yet one grain, rice, is rustproof and it is hoped that the genetic basis for that resistance in rice can be found and transferred to other grains, like wheat. With 70% of the world's food coming from grains, such disease-free transgenic crops would be an important step towards preventing famine and producing high quality food, with additional benefits for the environment.

There are also a number of uncertainties that accompany the introduction of GM technology. There may be environmental risks involved when releasing GM organisms and there are concerns about human and animal health when new GM products are used in food or feed. Furthermore, it may turn out that farmers of the developing nations will not be able to afford the new crop varieties since GM is an expensive technology, which can only be carried out in well-equipped laboratories and needs further development and marketing by efficiently organised companies.

Also, if a limited number of successful GM crops are accepted universally, crop uniformity may reduce genetic diversity and introduce the risk of explosions of specific pests. The need to use successive novel crop varieties may prevent farmers from relying on their current practice of saving seeds for planting the next year's crop. It is feared that patenting laws work against the poor around the world and allow biotechnology companies to benefit from patenting indigenous knowledge or materials, often without consent of the original owners of the land where the valuable genetic materials were collected. Enforcing intellectual property rights over living organisms would further divert Africa's resources from where they should be directed – to feeding the poor.

Agriculture in most parts of the world is more than 5,000 years old and mass introduction of non-local high-technology crops may cause the loss of the traditional knowledge base of farmers. GM has had more to offer to the developed world than to the developing countries. So far, a restricted number of life-science companies have delivered a limited number of transgenic crops with a small number of different traits to the market place. Most of today's GM crops carry traits that are of minor importance in developing countries, or concern crops that have economic value in feeding livestock, instead of providing food for hungry people. Because companies have the task of making a profit, their primary focus is not likely to be on the needs of people that are not able to pay. Therefore, in order to serve poor farmers, plant science, breeding and genetic engineering research also needs to be directed at the staple crops they grow and which are their main source of nutrients. These include white maize, cassava, sorghum, millet and sweet potato. Improvements would also need to include adapting crop species to the adverse environments the farmers face, be applicable for small farms and not require expensive inputs farmers cannot afford.

It must be realised, however, that GM crops cannot solve the problems of improper distribution of food resources that are due to political conditions or inequalities of trade. The purpose of plant biotechnology is to enhance the ability to increase food production relative to population growth, to cope with changes in climatic conditions, to continue to outpace pests and diseases, to provide environmental improvements and to extend crops into ecologically challenging areas, such as those with acid or saline soils. It would also be sensible to use GM crops in conjunction with the practice of organic agriculture and take advantage of the best elements of two currently opposing agricultural methodologies.

Often the debate between the proponents and opponents of GM plants circles around very simplified statements. This can to some extent be attributed to its broad spectrum, involving a mixture of technological, political, economic, ethical, environmental and health issues – but this is also a reflection of a confrontation between fundamentally different ideologies and approaches. It must be realised that the transgenic crops being cultivated today will constitute only a small part of the rapidly expanding plant biotechnology portfolio with, before the end of this decade, the expected availability of many novel plants and plant products. In the future GM crops will certainly play a role in the delivery of medicines, vaccines, and improved nutrition. Thus, it would not be an exaggeration at all to conclude that new GM crops and products will display increasing consumer and environmental relevance.

In general, the proposed risks of employing GM crops is rather speculative. It is for instance impossible to prove conclusively that GM foods are 100% safe, but this is also true for food products from conventional or organic agriculture. Still, it is essential to carefully predict and test the effects of employing novel GMOs in agriculture, and to keep monitoring possible offspring afterwards. But so far, there is no evidence that GM crops are prone to cause damage to the environment or endanger human health.

Should the agricultural sector remain unchanged while every other aspect of life is changing? While not many experts suggest that transgenic crops are the single magic bullet to solve the future food problem, many scientists find it is one tool among many that can help reduce poverty and provide new innovative products. Transgenic crops can substantially contribute to improve agriculture in parallel to the needed changes at the socio-political level. Benefits and risks associated with particular GM crops can only be assessed on a case-by-case basis when employed in the field. A fair comparison to other alternatives would be the right attitude to evaluate novel crops. To do nothing, as has been the case during the European de facto moratorium on GM market introductions, is itself not without risk. An unfounded restriction of further development and employment of techniques and results from molecular biology may do more harm than good.

5.3.3.2
Role of Global Policies

More than half of the world's poorest people have little alternative but to continue to rely on agriculture for their livelihood and try to increase productivity to secure continued existence. In a global sense, the most effective strategy to ensure sufficient levels of food production would be to raise productivity in areas of subsistence farming, where an increase in food production is urgently needed and where crop yields are significantly lower than those obtained in other areas of the world. In most of these environments, crop failures are frequently due to drought and other natural catastrophes. The new tools of biotechnology, in particular genetic modification, promise the potential for creating crop varieties that are more tolerant of drought or saline soils and meet the challenges of farming.

Consumer groups claim their right to avoid GM food and see no reason for GM technology since there is sufficient food already. Will the poor have the choice to use plant biotechnology and possibly decide whether they will have food to eat or not? Will political and economic interests, for or against GM food, allow us to reach the levels of food production necessary to feed the growing world population? GM crop technology development is likely to benefit the poor only if proper technology is developed in a responsible manner and put into the right hands. The potential of GM crops should therefore not imply rejecting organic agriculture, nor disregard the value of indigenous knowledge.

Consumer resistance to GM crops in Europe, the subsequent moratorium on GMOs and dramatically reduced numbers of GM crop field trials have had an indirect effect on exporting countries in the developing world. Some countries could benefit in the short term by staying GM-free and retain their access to European markets. The needs of Europe, having surplus food, are different from Africa where we witness hunger and starvation. The priority of Africa is to feed its people with safe foods and to sustain agricultural production as well as the environment. Over the long run, when markets have harmonised and GM products find more acceptance, it may become essential for Africa and economically necessary for its farmers to reap the benefits that GM crop innovations provide.

Investing in more research and development of improved crops therefore is a promising avenue for accelerating progress and reducing global poverty. Public institutions can help in doing quality research that will benefit poor farmers, alleviate food shortages and reduce poverty. However, an ultimate failure to end hunger in developing countries will arise not from technological limitations but from political and/or economic decisions and the disinterest of governments and corporations. There is no question that the primary responsibility for dealing with poverty actually belongs to developing countries themselves and that the establishment of a fair trade regime is in the hands of the developed countries.

Self-sufficiency of developing countries can only be reached if there are no restrictions on export markets for agricultural products under equal competitive conditions. Currently, the total subsidies to agriculture in developed countries are six times the amount of development aid that is given to poor countries. Developed countries therefore produce surplus food and readily supply this in the form of aid, as a result of which the developing countries do not get adequate pressure to adopt effective food policies themselves. The anomaly of this agriculture policy is that rich countries tend to subsidise a declining agricultural sector, which may contribute less than 5% to GDP, while poor countries, where agriculture is the dominant sector, are limited in possibilities to expand economically.

Globalisation is not an automatic blessing and will certainly not eradicate poverty on its own. While international trade and investment have increased vastly over the last decade, this process has not really been global enough. Two billion people live in countries where trade is diminishing in relation to national income, economic growth has stagnated, and poverty is on the rise. Most people in Africa, Latin America, the Middle East, and Central Asia are poorer today than they were 10 years ago. In many of these countries the systematic restriction of economy and political freedom are caused by any of the following: an over-regulated economy, corruption, repression or war.

In theory, sound macroeconomics and market liberalisation, as proposed by the World Bank and the IMF, together with freedom and democracy seem to form the complex recipe for a globalised capitalist economy to provide opportunities for developing countries to improve integration with the rest of the world. It is unfortunate that, in practice, these arrangements tend to be bent to favour specific market niches or political goals and, of course, by the most powerful parties. Nevertheless, people in Asia have enjoyed a big improvement in living standards, especially since the 1980s, when China and India began to adopt market reforms. Much of the improvement in Chinese economic performance can indeed be attributed to liberalisation since its international trade expanded when the economy became market-oriented and less regulated.

While globalisation may have diminished a rising inequality between participating nations, it requires a significant policy change to properly exploit the strategy. Nations that did not adopt these changes, or were too isolated to do so, were left behind. In theory, globalisation should give small farmers access to lucrative world markets, but it is equally possible that in a number of countries they lose much of the urban markets of their major cities to imported goods from other continents.

5.3.3.3
Role of Companies

The top ten global seed companies control almost one-third of the $25 billion commercial seed trade. The concentration of patents and plant variety ownerships make it difficult for small start-up companies or public sector researchers to compete or gain access to new agricultural technologies. The multiplicity of patents embedded in a GM product can make the product expensive. It is also possible that the holder of a single piece of intellectual property right (IPR) decides to block the commercialisation of a rival product. The costs associated with transacting IPRs can be quite substantial and may give private companies considerable power because of their strategy of building up defensive patent portfolios. Critics claim therefore that poor countries have no chance to benefit from plant biotechnology or that poor farmers will only be exploited by multinationals. The current patent system, in addition, does not offer sufficient protection for the genetic material of local varieties and local community-based innovations.

It is, however, not very likely that patents in biotechnology will be used to seriously frustrate indigenous plant breeding. There is a misplaced concern that patents and other forms of intellectual property constrain the freedom to operate of plant science researchers in developing countries. For most IPRs in plant sciences that are held by life science companies, no protection has been sought in the majority of such countries. Crop breeders are free to produce any crop as long as the inputs and processes used and the crop varieties grown are not protected under local intellectual property laws. The restriction is that those crops cannot be legally exported to countries where they fall under intellectual property protection. Intellectual property rights assigned to the key enabling technologies, for instance those used to transform crops, are primarily relevant to rich-country jurisdictions. For many of the crops that matter in poor countries and of which little is exported (e.g. cassava, coconut, groundnuts, beans, sorghum, lentils) much of the needed technology is not covered by intellectual property rights locally and can be employed without much restriction for local use.

For researchers and farmers in less-developed countries it is therefore much more important to gain access to technologies in plant biotechnology than to worry about possible, future, IPR problems in international trade. Failure to attract investments in domestic expertise, needed to evaluate, access, and regulate the new technologies, is currently a far greater constraint. Poor people rely for sustenance on crops that are largely beyond the focus of the private research sector and that have modest future commercial prospects. In addition, poor producers often face production problems different from those of commercial farmers in wealthier countries. Companies are producing and marketing new crop varieties for a profit and therefore have shown little interest in developing the crops most often grown by subsistence farmers (such as millet, sorghum and rice) or design others that would survive the harsh weather and soil conditions in needy countries.

As in the case of medicine and pharmacology, major advances have often come from large corporations with an eye firmly on a return on investment and share-holder dividends. In the past few years a number of large life science companies nevertheless have shared information or donated intellectual property for use in certain non-commercial crops. Monsanto shared its draft rice genome sequence data with public researchers involved in the International Rice Genome Sequencing Project. Syngenta, among others, donated IPRs relevant to vitamin A rice to allow free licensing to farmers so long as they do not export such products or profit excessively from it. These well-publicised donations left a strong impression that a large number of crucial patent rights were transferred in favour of the poor in developing countries. But, in fact, in some major rice-consuming countries, there are no relevant valid patents and in most countries there are very few.

In any case, companies have seen it in their own interest to develop partnerships with the public sector that will help bring benefits to developing countries. An initiative by the Rockefeller Foundation, known as the African Agricultural Technology Foundation (AATF) will function as a broker of public–private partnerships, and will act as a focal point for materials and information on technologies. Monsanto, DuPont, Syngenta and Dow Agrosciences have announced that they will donate research tools, seed varieties, patent rights and laboratory techniques free to African scientists through the AATF being established in Kenya. Among the aims of the organisation are:

1. Involvement of farmers in the design of new crop varieties
2. Find effective combined use of organic with inorganic fertilisers
3. Make African products more competitive in global markets
4. Implement the new technologies of plant biotechnology

5.3.4 Regulation

The global debate about the acceptability of GM foods came to international attention when a number of African countries that, although suffering famine, refused US food aid in 2002 because it included GM maize. The USA food aid program uses commodity maize, which typically includes the GM maize that is widely grown in the USA. This situation highlights the global ambivalence over a technology that some have touted as a tool to end world hunger and others have criticised as providing no benefits to consumers while posing significant risks to the environment.

The reluctance of some African governments to accept GM maize is not representative of the attitude of developing countries towards biotechnology. Ethiopia is wary of GM while Kenya, its neighbour to the south, is actively pursuing the technology as a means to increase food security. South Africa and Argentina have embraced GM agriculture. China is actively pursuing its own GM research programme and India has just approved GM cotton. In 2002 nearly 10% of the global acreage of transgenic crops was planted in the developing countries. This fact would negate the argument that plant biotechnology is a tool of the industrialised countries for the exploitation of the developing world, although it must be realised that most GM crop seeds currently originate from western breeders.

5.3.4.1
Towards Consensus

How could world wide consensus on the regulation of agricultural products be achieved? The World Trade Organization's (WTO) legal framework regarding trade in GM products only includes the Sanitary and Phytosanitary (SPS) Agreement and the Agreement on Technical Barriers to Trade. The SPS Agreement says that WTO members have "... the right to take sanitary and phytosanitary measures only to the extent necessary to protect human, animal or plant life or health, and based on scientific principles ...". The SPS Agreement stipulates that food safety regulations be scientifically justifiable and requires WTO member governments that violate the SPS Agreement to modify or withdraw their non-compliant food safety regulations. In 1995, the SPS agreement conferred on the Codex Alimentarius commission the responsibility for defining international food safety standards that would be recognised by the WTO.

In the absence of agreed-upon international standards, some countries invoke the precautionary principle that allows them to rule provisionally where relevant scientific evidence is lacking, although they are supposed to do the necessary research within a reasonable period of time. Other countries argue that the precautionary principle is being abused in order to protect less efficient domestic producers from foreign competition. Europe has adopted the precautionary principle as a means for determining whether GM crops can be planted or whether a food product is safe enough to eat. The principle states that when an activity raises threats of human health or harm to the environment, precautionary measures should be taken even if cause and effect have not yet been scientifically established.

The WTO Agreement on Technical Barriers to Trade (TBT) aims to ensure that WTO members do not use domestic regulations, standards, testing, and certification procedures to create unnecessary obstacles to trade. The TBT rules encourage countries to use international standards as a basis for national laws and these include provisions for labelling. Since the WTO SPS or TBT rules do not interpret the precautionary actions taken by Europe and some other countries to restrict or label GM food imports, there is room for conflicting interpretations. More than 30 countries currently require labelling of GM foods. Europe has one of the strictest labelling standards, requiring labels if more than 0.9% of the ingredients in foods are GM. It is this labelling standard that motivated the African countries to refuse the US food aid that contained GM maize. There was concern that farmers would plant the maize instead of using it as food, resulting in cross-pollination of native maize seeds. If that should happen the European standards would no longer be met and the countries would no longer be able to export surplus maize in the future. The US government has brought a dispute against the EU's refusal to accept GM crops and products to the WTO and this procedure may clarify the grey areas in WTO rules one way or the other.

The United Nations-sponsored Cartagena Protocol on Biosafety (CPB), which was adopted in January 2000 in Montreal, regulates the trade of living GM organisms (LMOs) and requires member nations to establish strict controls over many aspects of research and development on GM crops, animals, and micro-organisms. Article 1 of the CPB refers to the precautionary approach and to "…ensure an adequate level of protection in the field of safe transfer, handling, and use of living modified organisms resulting from modern biotechnology…" Article 2 emphasises the right of states to enforce more stringent protection goals for the "…conservation and sustainable use of biological diversity than called for in this Protocol". For exporters, the protocol is potentially troublesome because it allows importers to refuse LMOs on a precautionary basis, without a scientific demonstration of risk. The United States, which is not party to the Cartagena pact, treats GM grains no differently from conventional crops and says they pose no threat.

Close to 200 countries and regions have signed the Cartagena protocol, and as soon as 50 ratifications are completed, it will come into force. The CPB will be the first legally binding international agreement that will make use of the precautionary principle as a policy instrument for the conservation and sustainable use of biological diversity and the protection of human health, if relevant to the trans-boundary movement of GMOs. Risk assessment remains the primary tool under the CPB for competent authorities to "…identify and evaluate the potential adverse effects of living modified organisms on the conservation and sustainable use of biological diversity in the likely potential receiving environment, taking also into account risks to human health". The precautionary principle is concerned with possible unacceptable risks and threats and calls for risk assessment to be carried out. Both measures are compatible if risk assessment can provide some indication as to the proper degree of precaution that is warranted and if precaution can be used to audit and refine risk-assessment assumptions.

While many countries have biosafety regulations or laws on labelling, the majority of them do not. Building strong biosafety capacity with clear guidelines, systematic assessment, public consultation and product labelling can help countries to make informed decisions. Many developing countries do not have the multiple- and inter-disciplinary personnel needed to carry out risk analyses and risk management within a methodological framework, as stipulated by modern regulations. Assistance to such countries that attempt to establish a national biosafety capacity therefore deserves priority support. It remains to be seen whether the world community will be able to accept modern plant biotechnology in some regulated form or whether reservations, prevalent at present in Europe, will continue to slow down the development and assessment of its potentials.

5.3.4.2
Intellectual Property Rights: Patents and Plant Variety Protection

If information, new ideas or inventions are published without proper protection, these will then enter public domain, meaning that anyone can use the information without asking for permission. Developments in technologies that are based on public knowledge will not be supported by large investments because the possibility of imitation creates a discouraging commercial future. For this reason, a number of different mechanisms have been established for the protection of, for instance, information (copyright), inventions (patents) or brand names (trademark).

When corporations or, increasingly, also public agencies develop new crop varieties, they often seek intellectual property right (IPR) protection on these innovations. Inventors and researchers seeking these rights must then disclose the new knowledge they have obtained, which will stimulate further rounds of innovation and technological advances. Patents and other IPRs are awarded by national governments or common trading blocks. To obtain patent protection in more than just one country, innovators must separately apply and gain such rights in additional nations.

Similar restrictions apply more or less for protection through the plant variety protection laws (PVP, or plant breeders' rights), which are generally based on the UPOV Convention. To be granted protection, a variety must fulfil criteria governing novelty, distinctiveness, uniformity and stability while allowing farmers to save seeds for their own use. PVP also defines "breeders exemption", which allows any plant breeder to use the protected variety as a basis to develop a new one without previous consent of the owner of the original protected variety.

IPR regimes tend to be weak in developing countries, but the WTO agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) prepares for increased global harmonisation. This international agreement is binding on all WTO members and sets minimum standards for the implementation of IPRs at the national level. While some argue that the agreement favours the biotechnology industry in developed countries, an important provision is that plants and animals may be excluded from patentability by national governments. Although WTO members are therefore not required to allow patents on living organisms, a minimum requirement will be to allow protection of plant varieties through the PVP system.

The impacts of IPRs are more substantial for modern biotechnologies and products with multiple patents, such as GM plants, than for new plant varieties obtained through breeding or for products that are derived from other biotechnologies, such as micropropagation or tissue culture. GM technology may increase the dominance of corporations in the area of food production, particularly if strict intellectual property regimes are permitted globally. Plant breeders' rights, rather than patents, should be favoured in less-developed countries in order to protect the interests of poor farmers. Poor countries should therefore be wary of any provisions in trade deals that try to impose stronger intellectual-property standards than TRIPS requires. Rich countries should accept that considerations of how intellectual-property rights affect poor countries are not just a concern of overseas-aid agencies, but also play a part in broader trade and economic relations.

5.3.5 Regional Example: China

China was the first country to begin growing a GM crop commercially with a virus-resistant tobacco in 1988, following a public–commercial biotech collaboration between the Beijing University and the government tobacco companies. Since then, China has tested over a hundred GM crop varieties and is making major investments through its institutions such as the Chinese Academy of Agricultural Sciences and the Chinese Academy of Sciences. China has dramatically accelerated innovation and commercialisation in plant biotech research. Nearly all scientists are employed in the public sector, therefore it is easier to undertake research on crop technologies. By making good use of the complementary benefits of biotechnology and traditional crop breeding, the Chinese public research programme is making progress on many fronts, from sequencing the rice genome to developing hybrids for wheat, soybean, rapeseed and other crops. The broad spectrum of traits that is addressed by Chinese researchers include yield increases, disease resistances, abiotic stress responses, enhancement of the nutritional value of crops and reduction of the use of inputs that are causing environmental and health concerns. China's biggest genetic effort focuses on rice, the worlds most consumed grain. The China National Rice Research Institute in Hangzhou is performing leading research on engineered rice varieties with better yields, nutrition and taste, and improved drought and insect resistance. Although only an eighth of China's land is suitable for cultivation, it is among the worlds largest producers of rice, barley, sorghum, potato, peanuts, tea, fruits and vegetables. Analysts therefore predict that further progress in biotechnology could turn China into a global competitor, having a major commercial influence in agro-biotechnology. In non-food use of GM crops, insect resistant cotton tops the list of field releases.

Amidst all this activity, Chinese regulators have, since 2000, been reluctant to approve the commercial planting of transgenic food crops, although candidate crops continue to move into field trials. Before this intervention there was no government control over when GM crops graduated from the research to the commercial arena, nor were there labelling requirements when GM foods were sold in the market. China's new GMO regulations of May 2001 require labelling and safety certification of all GM products, and also cover GMO research, testing, production, processing, import/export activities and liability when handling GMOs. While the government claims to be worried about whether Europe will accept exports of transgenic food, it is also assumed that the Chinese government is exploiting the biosafety issue to frustrate the commercial ambitions of Western agribiotech firms, because it realises that its own research programme needs more time to catch up.

5.3.6 Product Example: Golden Rice

An observed correlation between progressive and serious eye damage in children and increased child mortality rates in Indonesia prompted researchers to supply vitamin A capsules. The startling result of the significant decline in child mortality rates, common in developing countries, was confirmed with similar experiments in Africa and Asia. While vitamin A is primarily essential for the general health of the eye, it has many secondary roles, such as maintenance of the immune system. Vitamin A deficiency is prevalent among the poor in Asia, because their diets are very much dependent on rice, which does not contain beta-carotene, a vitamin A precursor. While individuals may be able to obtain sufficient vitamin A by consuming larger amounts of dark-green leafy vegetables and fruits, vitamin A-deficient populations live in marginalised areas and have poor diets (see also Sect. 5.1.2.5.3).

It is now widely accepted by the international nutrition community that the distribution of vitamin A is a priority for government intervention. Nutritionists in developing countries have been able to demonstrate that many children and young women suffer more from a lack of essential vitamins and minerals in their diets than from a lack of calories. Poor dietary quality has therefore been dubbed "hidden hunger" and stimulated further research related to other micronutrient deficiencies, in particular iron and iodine deficiencies.

Golden Rice was developed to provide a new, alternative intervention to combat vitamin A deficiency. Peter Beyer was studying the regulation of the terpenoid pathway in daffodil and isolated the relevant genes of the beta-carotene synthetic pathway. Researchers in the laboratory of Ingo Protrykus at the Swiss Federal Institute of Technology succeeded, against all odds, in the introduction of the genes and the co-ordinated function of the four identified enzymes in rice. The endosperm of the grains of the GM rice was coloured yellow, and was shown to contain beta-carotene and other carotenoids, which the human body uses to convert into vitamin A. The dream of the inventors is that golden rice, once adapted to fields in developing countries, would be able to deliver the vitamin A precursors in a preferred food product, avoiding the complicated institutional infrastructure of vitamin A supplementation and fortification.

The inventors, however, realised that further development and marketing of the GM rice would be impossible without the help of a commercial partner. They signed an agreement with Syngenta to provide the necessary technology and support, for free, to the needy people in developing countries. In return, the company would able to explore commercial opportunities for the sale of golden rice into the expanding market for healthy foods in more developed countries. Syngenta would also be providing regulatory, advisory and research expertise to assist in making golden rice readily available among developing nations.

There is a range of challenges and further developments that will need to be addressed in the next few years. Since the major rice varieties for consumption are of the indica type and golden rice is a japonicum, breeding efforts are underway to obtain varieties that will deliver similar or better yields. Secondly, the amount of carotenes delivered in the grains needs to be raised in order for golden rice to have sufficient impact. Since wheat consumption is rising throughout Asia, it may also be necessary to fortify wheat varieties. Then there are still important questions to be answered in relation to food safety, consumer acceptability, and biodigestibility. Several governments have indicated their financial support for making future golden rice varieties available to farmers, but the implementation of these plans depends on reaching global agreements on GM technology, favourable regulatory regimes and consumer acceptance.

It appears that golden rice has the potential to be a low-cost, wide-coverage intervention to mitigate the effects of vitamin A deficiency. While it may significantly contribute in this battle under certain scenarios, it is unlikely to meet all requirements and to form a stand-alone strategy. Therefore, further research is needed as well as exploring other possibilities such as expressing genes to raise iron and vitamin E levels or the development of a high-quality protein rice with enhanced levels of selected amino acids. Ingo Protrykus has expressed the opinion that the golden rice project has been an excellent example of a public–private partnership that has real benefits for the poor and that public sentiment can only be improved if more such projects were developed in public institutions, using public funding and addressing an urgent need that cannot be solved with traditional techniques.

5.3.7 Conclusions

Biotechnology offers tools that allow plant breeders to generate superior plant varieties, or select these much faster than they could when restricted to using conventional plant breeding techniques. While consumers in developed countries have the right and luxury to debate the pros and cons of products from GM techniques, it would be wrong to slow down basic research to study whether such technologies are safe, sustainable, and suitable for developing countries. The debate whether application of GM technology will help to feed the earth's growing population currently rests in the hands of the experts in developed countries. Most of the people that will need to be fed, however, live in developing nations. It is ironic to note that modern agricultural practices and technologies have resulted in the most abundant, healthiest, and cheapest supply of food in the history of the human race. Therefore, any government should be allowed the right to make their own decisions on biotechnology, which they cannot do if access to such technology is denied to them or trade issues prevent such developments.

Unlike the techniques of the green revolution, GM technology was largely developed by private companies. In the minds of some people the mingling of development and profit makes the technology suspect. However, the profit motive is a strong incentive to produce a healthy product. At the same time, there is no sustained and coherent effort to make this technology accessible and usable by people who cannot afford such technologies and products. Moreover, if only large multinational companies gain control over the food chain then the production technology may become driven by the economic logic of delivering higher returns and not by concerns over the environmental health or sustainability of the planet.

Food quality and food security should be an essential human right. Therefore plant biotechnology must be adequately supervised, its technologies accessible to all involved in agriculture, and inventions as well as indigenous genetic resources should be protected. In view of these points it must be concluded that there is still a great deal to be accomplished by politicians as well as scientists in public research institutes.

5.3.8
Organisations and Sources

Below is a far-from-complete list of national and international organisations involved in different aspects of technology transfer of agro-biotechnology between developed and developing countries. While the number of research co-operations and other initiatives is much more extensive, such a list is deceptive. The total investment in agricultural research in many countries is in crisis and funding levels are insufficient to generate a steady flow of technology.

5.3.9
Not-for-Profit Organisations

- AfricaBio
  The International Service for the Acquisition of Agri-biotech Applications, and other stakeholder organisations. http://www.africabio.com
- APEC
  The Asia-Pacific Economic Cooperation has a task force that deals with issues related to biotechnology, such as biodiversity protection and the safety of GM food.
- BIO_EARN
  The East African Regional Programme and Research Network for Biotechnology, Biosafety and Biotechnology Policy Development is co-ordinated by the Stockholm Environment Institute (SEI) to build national capacity and competence in biotechnology, biosafety and biotechnology policy involving more than 70 researchers and more than 100 policy makers in the region. Selected institutes in Ethiopia, Kenya, Tanzania and Uganda receive support through a regional network. www.bio-earn.org
- CAMBIA
  Centre for the Application of Molecular Biology to International Agriculture is a not-for-profit research institute in Canberra, Australia, which was set up in 1991 to develop and package the novelty generation and selection tools that biotechnology is making possible so that farmers and local researchers can use them. www.cambia.org
- CAST
  The US Council for Agricultural Science and Technology is an international consortium of 38 scientific and professional societies. Its mission is to identify food and fiber, environmental, and other agricultural issues and to interpret related scientific research information for legislators, regulators and the media for use in public policy decision making. www.cast-science.org
- CGIAR
  The Consultative Group on International Agricultural Research is an alliance of 24 developing and 22 industrialised countries, four private foundations, and 16 international agricultural research centres known as The Future Harvest Centers, among which IRRI, CIMMYT, IITA and IPGRI. The CGIAR is best known for starting the green revolution of rice and wheat in Asia. www.cgiar.org

- CIAT
  The Centro Internacional de Agricultura Tropical conducts international research on beans, cassava, and forages has a global reach, while that on rice and tropical fruits targets Latin America and the Caribbean. www.ciat.cgiar.org
- CIMMYT
  Using traditional breeding methods, scientists from the International Maize and Wheat Improvement Association, a Future Harvest Center, and their South African counterparts set out to develop corn that could increase the food and income of poor southern African farmers who grow food in drought-prone, nutrient-depleted soils. www.cimmyt.org
- CIRAD
  Centre de Coopération Internationale en Recherche Agronomique pour le Développement is a French scientific organisation, with researchers posted in 50 countries, specialising in agricultural research for the tropics and subtropics of the world, focusing on crops like rice, cotton, coffee and rubber. http://www.cirad.fr/en/index.php
- FBAE
  The Foundation for Biotechnology Awareness and Education, based in Bangalore, India, supports sustainable development through biotechnology by promoting biotechnology awareness and education. www.fbae.org
- IITA
  The International Institute of Tropical Agriculture, based in Nigeria, is one of the CGIAR research centres. By linking advanced research institutions around the world to six Benchmark Areas in countries in Africa, it will be able to make use of the shared benefits of biotechnology. www.iita.org
- IPGRI
  The International Plant Genetic Resources Institute, a Future Harvest Center, is based in Rome www.ipgri.cgiar.org/One of its programs is the International Network for the Improvement of Banana and Plantain (INIBAP). www.inibap.org
- IRRI
  The International Rice Research Institute, a Future Harvest Center, aims to ensure that rice farmers and consumers get the best deal and the best options offered by science and the private sector, while helping companies find ways to get the returns they need to support the further development of their activities and the rice industry. www.irri.org/default.asp
- ISAAA
  The International Service for the Acquisition of Agri-biotech Applications has established the Global Knowledge Center on Crop Biotechnology to share crop biotechnology information with as many people as possible. When fully operational, the Knowledge Center will consist of at least 20 country nodes, and will facilitate information sharing between and across these countries. www.isaaa.org
- ISAS
  The International Society of African Scientists is a non-profit organisation founded in 1982 to promote the advancement of science and technology among

people of African descent, and to solve technical and development problems facing Africa and the Caribbean. www.dca.net/isas/

- ITDG
  The Intermediate Technology Group is an international non-governmental organisation specialising in technology transfer for Practical Answers to Poverty. ITDG works in Latin America, East Africa, Southern Africa and South Asia, with particular concentration on Peru, Kenya, Sudan, Zimbabwe, Sri Lanka, Bangladesh and Nepal.http://www.itdg.org
- MARDI
  The Malaysian Agricultural Research and Development Institute was established in 1969 to produce and promote appropriate and efficient technologies that could improve production and income from agriculture. www.mardi.my
- REDBIO
  The Technical Cooperation Network on Plant Biotechnology focuses on bringing biotechnology to the service of sustainable development of the Latin America and Caribbean forestry and agricultural sectors. www.redbio.org
- TWN
  The mission of the Third World Network, established in 1984, is to conduct research on economic, social and environmental issues pertaining to the South, to publish books and magazines, to organise and participate in seminars and to provide a platform representing broadly southern interests and perspectives at international fora such as the UN conferences and processes. www.twnside.org.sg
- UNFPA
  The United Nations Population Fund helps developing countries collect and analyse population data and to integrate population and development strategies into national, regional and global planning. www.unfpa.org

5.3.10
Information Sources

OECD (2003) Accessing agricultural biotechnology in emerging economies. OECD, Paris. http://www.oecd.org/pdf/M00041000/M00041637.pdf

ICSU (2003) New genetics, food and agriculture: genetic discoveries – societal dilemmas. ICSU, Paris. http://cbac-cccb.ca/epic/internet/incbac-cccb.nsf/en/ah00335e.html

ESTO/JRC (2003) Review of GMOs under research and development and in the pipeline in Europe. JRC, Brussels. http://www.jrc.es/gmoreview.pdf

Nuffield Council on Ethics (2003) The use of genetically modified crops in developing countries. Draft report, October 2003. Nuffield Council on Ethics, London. http://www.nuffield-bioethics.org/filelibrary/pdf/gm_draft_paper.pdf