GENETICALLY MODIFIED ORGANISMS

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Some of us joined this Academy when Carlos Chagas was president. Upon meeting him for the first time, we knew that we were in the presence of a person of great vision, enormous integrity, and unquestioned dedication to science. His dedication to science had two foundations. One was his inherent fascination with the natural world. The second was his conviction that science could advance human welfare. Ever since last summer I have been thinking of how interested he would have been in the extraordinary scientific news coming from his beloved Brazil.

On July 13, 2000, the cover of Nature Magazine displayed an insect, a leaf hopper, sitting on an orange or grapefruit. Inside, was a paper reporting the entire genome sequence, more than 2 million 600 base pairs (2,679,305), of the bacterium *Xylella fastidiosa*.[1] The many authors were from 34 different laboratories and a bioinformatics center in the State of Sao Paulo, Brazil. For part of its life cycle, *Xylella fastidiosa* lives in the leaf hopper's gut. From there, it is delivered into the xylem of a plant by the feeding leaf hopper where it multiplies and causes chlorosis, the loss of chlorophyll by citrus trees. The tree produces useless fruit prematurely with consequent loss of the crop. Relatives of this bacterium cause diseases in coffee, nuts, fruits including grapes, and other important plants. Xylella is a major problem for Brazil which produces a third of the world's oranges and half of the world's orange juice concentrate. Remarkably, at least 83 Xylella genes are derived from bacteriophage genomes... the viruses that infect bacteria. Among these are genes associated with virulence in other bacteria infecting other plants. Thus, the bacteriophage have been the agents of gene transfer between species.

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[1] A.J.G. Simpson *et al.*, *Nature*, 406, pp. 151-157, 2000.

The consortium of laboratories in Sao Paulo started this project with resources of $13 million as a matter of deliberate policy by a state research agency (FAPESP). Handsome support is continuing for projects to sequence the genomes of additional pests of Brazilian agricultural plants. Laboratories in Sao Paulo are now well equipped both to pursue the sequencing and the biology experiments necessary to exploit this work for the benefit of the state and its people.

The investigators are reportedly working to identify all the genes involved in pathogenicity. Some suspects have already been noted. Once identified, knowledge of these genes can be used in several ways to help control *Xylella* infections and the loss of crops. It can facilitate breeding of new varieties of plants by traditional methods. It can also be used to direct genetic modifications by modern molecular gene transfer techniques. Presumably the first approach would be acceptable in Brazil. Ironically, the second method, which is likely to be faster and more precise, is not now possible.

The report of the *Xylella* genome sequence, the first public sequence of a free-living plant pathogen, made international celebrities of the scientists in Sao Paulo. The event stimulated the federal government of Brazil to provide more funds for research, nation-wide. But, as the Nature editorial lauding this great achievement said, the challenge to Brazil is to "persuade the Brazilian public that transgenic plants can play an important economic role and at the same time take firm steps to avoid untoward social and environmental consequences".[2] At present, Brazil does not allow the planting of transgenic crops although the scientific director of FAPESP, José Fernando Perez, was a member of a panel set up by 7 National Academies which recently endorsed the use of genetically modified plants to help meet the food needs of the world's poor.

Xylella was only identified in 1993 and its residence in the leaf hopper not until 1996. In less than a decade, the science moved so far that the genes responsible for pathogenicity are now being identified. The history of the last 50 years has been like this for biologists. Startling insights and new information have accumulated at a dizzying pace, constantly challenging us to change ideas and fundamental concepts. Like most scientists, Carlos Chagas had little trouble adjusting to such revolutionary changes.

Revolutionary change does not go down so easily outside the scientific community. Change is often resisted, sometimes because it's discomforting,

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[2] *Nature*, 406, p. 109, 2000.

even scary, sometimes because it challenges philosophical or religious notions, sometimes because it conflicts with economic interests... although economic interests can also be a powerful catalyst for change.

Paul R. Ehrlich, the distinguished environmentalist, put it this way in a recent article.[3] "A major contemporary human problem, for instance, is that the rate of cultural evolution in science and technology has been extraordinarily high in contrast with the snail's pace of change in the social attitudes and political institutions that might channel the uses of technology in more beneficial directions".

On their part, scientists are often just as surprised and distressed at public reactions to new science as the public is to the science itself. In our exuberance over the new discoveries, scientists may not provide understandable explanations of what is going on, or listen carefully to the public concerns.

For much of the 19th century, a lot of what we now call biology was called "natural history". Tramping around in the countryside looking for new species of beetles or fossils or plants was seen as a charming and harmless pursuit of the wealthy, leisured class. Then, around the middle of that century, three great discoveries signaled a new kind of biology. One was the formulation, by Schleiden, Schwann, and Virchow of the cell theory – the concept that all organisms are composed of one or more living cells. One was Mendel's elaboration of the laws of inheritance. The third was Darwin's concept of evolution and the origin of the species. By the end of the 20th century, these three paths had converged into one biology, a science that is extraordinarily sophisticated and productive if less charming and acceptable to some.

Mendel was, among other things, a plant breeder. This ancient skill, in modernized form, is as relevant today as it was in his time, even for making transgenic plants.

One of the most important facts recognized by Mendel was that any particular gene, for example the gene responsible for the color of a pea, could occur in different forms. Depending on the two forms present in an individual plant, the peas would be green or yellow. These different versions of genes are responsible for variation within a species... including the variation you see if you look around this room at all the different faces.

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[3] P.R. Ehrlich, 'The tangled skeins of nature and nurture in human evolution', *Chronicle of Higher Education*, 22 September 2000. Online at http://chronicle.com/free/v47/i04/04b00701.htm.

Mendel had read Darwin a few years before 1866 when he reported the characteristics of inheritance in the peas he bred in his monastery garden. The 1863 edition of the German translation of Darwin's The Origin of the Species, with Mendel's notes in the margins, is still in the monastery library in Brno. But Darwin apparently never knew of Mendel. If he had he might have realized, as 20th century scientists did, that Mendel's work could explain the source of variations in nature upon which natural selection operates to produce new species. The idea of natural selection had its origins in the selection techniques practiced by plant and animal breeders and farmers for at least the last 10,000 years.

The earliest of plant and animal breeders made use of these variations, though they were ignorant of the underlying causes. They observed new, rare forms in fields and when the new property was advantageous, they bred it into their standard varieties. Wild potatoes, for example, have high levels of alkaloid toxins. At least 4000 years ago, Central Andean populations, probably around Lake Titicaca, began selecting and breeding potatoes, perhaps with alleles that reduce the poison. It's useful when thinking about the current debate over genetically modified plants to recall that when potatoes were brought to Europe in the middle of the 16th century, the French, suspicious of new foods, refused them and kept on refusing for 200 years while the rest of Europe enjoyed them. Poison was not the issue. The word in France was that potatoes caused leprosy. Similarly, tomatoes, another 16th century new world contribution to worldwide diets, suffered a similar fate. At first, only the Italians were bold enough to challenge the widespread notion that tomatoes were poisonous... as indeed some of its relatives and foliage are.[4]

Today, we know that genes are made of segments of DNA. Different forms of genes differ from one another in the sequence of the four DNA bases, or by lacking portions of the sequence, or by containing extra DNA sequences, or by changes not in the coding sequence itself, but in the surrounding DNA sequences that regulate the level at which the gene operates, or even whether it operates at all, under particular conditions. All of these naturally occurring changes in DNA structure can be mimicked by genetic engineering techniques.

A change in the regulation of gene activity... or what biologists call gene expression, underlies one of the five genetic differences between modern

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[4] H. McGee, *On Food and Cooking*, MacMillan, New York, 1984.

maize and teosinte, a wild relative of the same species (*Zea mays*) that is indigenous to central Mexico. Very few wild plants are closely related to maize and none of them look much like the maize we know. Nevertheless, teosinte, is the likely ancestor of maize on the basis of archeological, anthropological, and biological considerations. The two plants interbreed efficiently. Still, for more than a century they were assigned to different species and genus. It's easy to understand why. Teosinte is a bushy plant, with many tassels, the organ that produces pollen, and also many seed bearing stalks. The stalks are about an inch or 2 long and have two rows of tiny seeds, each of which is covered in a very hard case. Unlike maize, these seed stalks have no green, encasing husk. The seeds eventually fall to the ground, sowing next year's plants and providing food for birds which also disperse the seeds. Early inhabitants of middle America likely made food of teosinte by grinding the seeds, or popping them. Sometime more than 4000 years ago, they began to domesticate maize-like variants. Maize could never have arisen by natural processes and cannot propagate itself without human intervention. The seeds (or kernels) are tightly attached to the cob and unable to disperse because of the husks. Starting about 5000 years ago, smart middle American plant breeders selected and grew teosinte variants because they were advantageous. One of these variants resulted in growth as a single, straight stalk rather than a bush-like teosinte. The change is not in the coding segment of the gene, but in the regulation of gene activity.[5] The wealth of the ancient middle American empires depended on breeding for unusual mutations in teosinte. Their achievement now feeds the world. Yet today, such modifications made by molecular techniques would be rejected by many.

Plant breeders before the era of genetic engineering even combined different species and still do, using special techniques. Grapefruit, for example, is the result of an 18th century breeder's crossing of oranges and pummelo. What neither breeders nor anyone else knew until recently, was that DNA sequences have been transferred between organisms since evolution began, as is apparent in the genome of *Xylella* and as we have recently learned from the sequence of the human genome. Thus, besides different alleles, organisms have evolved through the acquisition of foreign DNA sequences.

Altogether, our modern diets are composed almost entirely of genetically modified organisms. If the history was better understood, the

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[5] J. Doebley, A. Stec, and L. Hubbard. 1997. Nature 386 485-488.

current public debates about genetically modified organisms, GMOs, might have greater clarity and depth. Few people understand the continuum that exists between ancient and modern methods. The general public is now at the mercy of the imprecise, even misleading statements made both by those who are opposed to the use of GMO's and those who are promoting them.

The new molecular techniques emerged about 30 years ago, when biologists developed the ability to make precise, conscious manipulations of genes through the techniques variously called recombinant DNA or DNA cloning. These techniques allow directed changes in DNA structure, changes that accomplish a predetermined purpose. These same capabilities have advanced basic biological understanding. The methods being used in plants are essentially the same as those being used to understand and develop treatments for a significant number of human diseases. All these methods generally involve changes in only a small number – from one to several thousands – of the billions of base pairs in the organism's genome.

Traditional interspecific breeding joins many genes from the two species. A lot of the subsequent breeding required over many years to achieve the desirable plant, involves breeding out those genes that were not wanted in the first place. The results are unpredictable and the successes are rare among the many failures to produce safe, hardy plants. There is a significant probability that undesirable traits – undesirable with respect to agriculture, the environment or food safety, will remain. In contrast, the new techniques permit introducing a single change in a single gene in a precise and verifiable manner. There is still a possibility that undesirable properties will occur, but the probability is much less.

What kinds of genes are introduced? Genes from varieties of the same species. Genes from related species. And genes from totally unrelated species, including from bacteria and animals. This is of course very different from what can be done with traditional breeding methods. And the apparent strangeness of the idea of using, for example, a fish gene to protect strawberry plants from frost, has attracted a great deal of discussion.

It is important then to consider exactly what is meant when we say we are putting a bacterial or a fish gene into a plant. The appropriate gene, a segment of DNA, is identified and isolated free of the rest of the DNA of the source organism by techniques known as cloning. Usually this means allowing a bacteria to reproduce the DNA segment. Once a bacteria is isolated that carries only the single, desired new gene, in addition to its own DNA, the bacterial population is expanded so that a sufficient amount of the DNA segment can be isolated... say a few micrograms. Sometimes that DNA can be introduced directly into a plant. Often, however, it will be modified to make it more suitable for its new location. For example, DNA code words might be changed to permit more efficient gene activity in its new plant host. This entails multiple cycles of expansion in bacteria. Then it is introduced into a plant, sometimes by shooting it in and sometimes by having it carried in on the DNA from a special bacteria which in nature, transfers its own DNA into plants. The original gene may have come from a fish, but it's been around and about in many different bacterial cells before it is finally inserted in the plant's genome-and it has been altered. At that point, it is a pure, definite chemical structure, a piece of DNA. Is it still a fish gene? That is a philosophical question, not a scientific one.

Some recent polls suggest that the descriptions of GMOs in the media have lead a substantial number of people to believe that only modified organisms contain DNA. Of course, the DNA itself is not an issue. The issues center on the particular proteins that the new gene encodes.

As with all complicated problems, there is no simple yes or no answer to the question of whether genetically modified plants will be safe for human health and the environment and views are sure to differ. The issues are not different from those posed by new plant varieties produced by traditional breeding. The questions do not arise from the process used to produce the plants, but rather the nature of the modified plant.

Each type of modified plant needs to be assessed on its own in relation to its use and the environment in which it is to be grown. Several different classes of concerns should be evaluated. For example, for food, we are interested in the safety of the engineered plants for human and animal consumption. With all modified plants, environmental effects, both positive and negative, need to be addressed. In addressing these questions, hypotheses will be made about possible problems.

For each plant, we need to consider the probability of the reality of the hypothetical concerns. This is essential if intelligent decisions are to be made about how to use limited resources to perform experimental evaluations of possible harm. If a hypothetical problem proves to be real, we need to consider the plant in the light of expected benefits. Equally important, the alternatives to using a particular engineered plant need to be considered. For example, maize and cotton have been engineered to resist certain insect pests by introducing a bacterial gene for an insecticidal protein, so-called Bt cotton and maize. Maize and cotton have also been bred for insect resistance by traditional breeding methods using naturally occurring insect-resistant plants as the source of resistance genes. Insects are also controlled by chemical spraying of fields. On balance, which method or combination of methods is safer for human use and for the environment as well as economically feasible?

For genetically engineered, or traditionally bred food plants, we need to ask whether the newly introduced changes yield a protein that is allergenic or toxic to humans or animals. Is the quantity of some toxic component found in the normal plant increased? If an antibiotic resistance marker gene was used for convenient manipulation when the DNA changes were made, we might be concerned if it compromised use of an important drug. But if the resistance gene is already ubiquitous and the antibiotic therapeutically useless, or the marker has only a very small possibility of being transferred into human pathogens, such a concern could be set aside. Demands for absolute assurance of the absence of any problem cannot be answered by science. Scientific data do not give absolute certainty. This of course is one of the challenges to making sensible public policy.

Five years ago, US farmers began planting Bt maize and cotton. The Bt gene yields a protein that is toxic to a major maize pest, the European maize borer and other pests that destroy cotton. The gene was copied from a bacteria called *Bacillus thuringensis*, or Bt for short. In summer of 1999, more than 30 percent of the maize and 48 percent of the cotton planted in the US was Bt – a total of 30 million acres. A lot of that maize gets fed to animals or goes into maize oil. Most people in the US have eaten those animals or that oil. There is no sign whatsoever that it is harmful to us or animals. The goal for these plants is to protect the 30-40% of potential food estimated to be lost to pests of various kinds, worldwide. Actually, organic farmers have used the bacteria themselves, by the ton, for more than 40 years, to control insect pests, so there was good reason to think that the Bt toxin would be harmless.

With respect to health, there are no indications of untoward effects from eating food from any of the currently harvested GM plants. Excepting for the problem of allergies, which all corporate and academic researchers and government regulators are aware of and attentive to, there are no obvious reasons to worry about the health effects of foods and fibers in the pipeline.

What about the balance between undesirable and desirable effects on the environment, including biodiversity, by insect-resistant GMO's? Crops of these plants require much less chemical insecticide than do unmodified crops. This means less pollution of air, water, and soil by noxious chemicals, a decrease in the substantial number of pesticide poisonings in farm communities, and a cost saving to farmers. For cotton alone, between 1996 and 1998, there was, according to USDA, a reduction of more than 1 million gallons in chemical pesticide use.[6] Spraying chemicals indiscriminately eliminates all the insects in a field – billions of them, including species that are vital for pollination and biological control. Thus insect biodiversity can be positively affected by GMOs.

However, two years ago, two scientific reports showed that milkweed leaves dusted with heavy concentrations of Bt maize pollen are toxic to Monarch butterfly larvae in laboratory experiments.[7,8] This was not surprising because it was known that the Bt toxins are toxic to lepidoptera in general. Nevertheless, these findings garnered enormous public attention although the authors pointed out that it remained to be seen what happens under field conditions. Concern was amplified by the well known fact that there has been an unexplained drop of about 70% in the population size of Monarchs wintering in Mexico since 1996. Is there a relation between the use of Bt maize and the decline in Monarchs? Perhaps, but it is likely that the effect of Bt maize will be at most slight compared to the known effects of habitat destruction in Mexico and the use of chemical insecticides in both Mexico and the US. More recent experiments, some in the field, indicate that the lethal effect of Bt maize depends on the particular variety of Bt maize and the level of the Bt toxin produced as well as the amount of pollen that spreads, and how far.[9]

Wise policy making will need to take into account the relative effects on Monarch mortality of chemical insecticide, the spraying of tons of the *Bacillus thuringensis* bacteria, and the use of genetically modified plants, as well as the crop yields, costs per acre, and the local conditions (such as the abundance of Monarchs, and the timing of larval feeding compared to pollen production).

Another environmental concern is that pest-resistant plants can spread, through seed dispersal or transfer of pollen to wild relatives of crop plants. This could lead to insect resistant weeds. A paper published in Nature this

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[6] Biotech Knowledge Center. 1999. Reference No. 1653, Monsanto company, July 7 On line at http://biotechknowledge.com/showlibsp.php3?uid=1653.

[7] J.E. Losey, L.S. Rayor, and M.E. Carter. *Nature* (London) 399, p. 214, 1999.

[8] L.C. Hansen and J.H. Obrycki. 'Field deposition of Bt transgenic maize pollen: lethal effects on the monarch butterfly', *Oecologia*, 19 August 2000. Online at http://link.springer-ny.com/link/service/journals/00442/contents/tfirst.htm

[9] D.S. Pimentel and P.H. Raven. 97 pp. 8198-8199, 2000.

month reported that several crop plants (e.g., rape, maize) made resistant to the herbicide glufosinate or containing Bt genes, did not survive beyond two years in natural habitats.[10]

Another concern is that the insect (and other) pests may develop resistance to the agent in the GMO. Such resistance is already a problem with respect to chemical insecticides and to the use of naturally occurring resistance genes introduced into crops by traditional plant breeding. It has also been observed in Hawiian organic water cress as a consequence of heavy doses of the Bt bacteria, a situation unrelated to the use of GMOs.[11]

The development of resistance to all insecticides is a fact of life for farmers just as resistance to antibiotics is a medical problem. That's one reason farmers constantly look for new ways to control pests, including Bt maize and cotton.

Many of these environmental concerns can be mitigated by the nearby planting of unmodified crops. Since January of last year, farmers in the US have been required, by the EPA, to plant as much as 20 to 50 percent of their acreage in conventional maize to decrease the probablility of these sorts of concerns.[12] There are ongoing discussions about whether this is sufficient, but the general principle is embedded in US regulatory structure.

These are complex matters. We should not be acting on 'hunches' or preliminary findings, or irrational concerns but on thoughtful, informed analysis. In the US, we do have mechanisms for such analysis and regulation. It is important that the regulatory process be monitored so that it is rigorous, open, transparent, and well-enforced so that the public can judge for itself whether or not its interests are being served.

Thus far I have been describing those aspects of the use of GMO's that can be addressed by science. There are other issues being raised for which science can provide at best limited useful information. For many, food is a personal and cultural issue, not a scientific one, as the stories about potatoes and tomatoes demonstrate. Surely we all need to recognize that it is reasonable for people to have choices about what they themselves eat. This is an argument for labeling foods, if scientifically valid and informative labels can be devised. However, this argument is sometimes carried to extremes. One example is the new 'golden rice', which has been

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[10] M.J. Crawley, S.L. Brown, R.S. Hails, DD. Kon and M. Rees, *Nature*, 409, pp. 682-683, 2001.

[11] F. Gould. *Private communication.*

[12] Rick Weiss, *Washington Post*, p. A2, 16 January 2000.

engineered to produce significant amounts of beta-carotene, the precursor to vitamin A. The hope is that widespread use of golden rice can ameliorate the blindness suffered by many in Asia and Africa because of dietary deficiency in vitamin A. Yet, some argue that golden rice cannot succeed because it will not be palatable to people accustomed to white rice. That is a choice that affected populations will make for themselves. Personally, I find it hard to imagine that people anywhere would be willing to see their children go blind rather than change their habits.

One set of arguments in opposition to the use of GMO's is especially difficult for scientists. These are the arguments that derive from a sense that such plants are not 'natural'. What, after all, is natural? Certainly not our standard diets, derived as they are from millennia of careful, directed breeding. All species tend to alter the natural world starting with the earliest photosynthetic organisms that increased the meager 'natural' levels of oxygen in the air. Yes, surely we need to protect our planet and all the organisms that share it with us. We need to adopt from the new technologies, those elements that can help us do that. One conundrum illustrates for me the difficult choices that need to be made. Some experts believe that the older breeding methods have achieved just about as much as they can in terms of the productivity of current farm land and water. In many parts of the world, the response to this is to clear more and more forest and cultivate more and more land to feed increasing populations. Yet, most people agree that preserving forests is essential for the balance on the planet and the preservation of biological diversity. The new genetic engineering techniques appear to offer potential for improving the productivity of current agricultural land and water and saving forests. How do we choose?

Novelty engenders suspicion. In time, familiarity and particularly obvious utility, tend to dissipate those suspicions that were ill-founded to begin with. When benefits become clear, especially if they are directly to individuals and not just to farmers, the public view may become less suspicious. Twenty years ago a debate raged over the production of useful therapeutic agents through genetic engineering. Like the engineered plants today, people argued that the methods were dangerous, unnatural, even immoral. Today, few people object to human insulin, or growth hormone, materials that are made by recombinant DNA techniques.

There are other aspects of the vocal opposition to genetically modified (GM) plants that elude scientific consideration. One is antagonism to the practices of large agricultural industries. Another is that the commercialization of the plants means they will be unavailable in developing countries, where they may be most important to alleviate starvation. This is a legitimate concern because an estimated 80 percent of the new plants have been developed by companies. We should surely strive to avoid injustices like those associated with the limited distribution of drugs to fight AIDs.

Yet another aspect of the opposition comes from the organic food industry which can hope to advance itself through this campaign. The industry lobbied hard to include, in the official U.S. definition of organic, the absence of GMOs, although organic farming techniques could benefit greatly from the use of certain GMOs. At least parts of the opposition to GMO's are also violent and disrespectful of law and private property. In Europe, the willful destruction of greenhouses, laboratories, and experimental fields has been going on for years and similar acts are now occurring in the U.S.

None of this is to say that the promoters of GMO's are blameless. Several large corporations invested heavily in the development and production of seeds of genetically modified plants. They have been aggressive in promoting the sale of these seeds. The concerned public is suspicious of their promotional emphasis on the value and harmlessness of the plants. Suspicion is fed by the fact that the corporations have not tried hard to develop a labelling system that will be informative and scientifically sound. Can the 6 billion people on earth now and increasing numbers in the future be adequately and economically fed without the investments and products of the large companies? Some think so. But even in the U.S., billions of dollars of food is lost to insect and nematode pests each year.

There is a moral imperative to feed and improve the health of all the world's people while preserving our planet. The public needs to decide whether to support the development of GMO's that can bring, on balance, real advantages to agriculture, health and the environment. With careful attention, we can avoid situations that result in harm and reap a good harvest.