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World Scientists' Statement

Calling for a Moratorium on GM Crops and Ban on Patents

We the undersigned scientists call upon our Governments to:

- **Impose an immediate moratorium on further environmental releases of transgenic crops, food and animal-feed products for at least 5 years.**
- **Ban patents on living organisms, cell lines and genes.**
- **Support a comprehensive, independent public enquiry into the future of agriculture and food security for all, taking account of the full range of scientific findings as well as socioeconomic and ethical implications.**

1. We are extremely concerned over the continued release and commercialization of transgenic crops, food and animal-feed products in the face of growing scientific evidence of hazards to biodiversity, food safety, human and animal health, while neither the need nor the benefits of genetic engineering agriculture are yet proven.

1.1 New scientific evidence has convinced us of the need for an immediate moratorium on releases.

1.1.1. Herbicide resistant transgenes have spread to wild relatives by cross-pollination in both oilseed rape and sugar beet,[1] creating many species of potential superweeds. One study shows that transgenes may be up to 30 times more likely to escape than the plant's own genes.[2]

1.1.2. Bt-toxins engineered into a wide range of transgenic plants already released into the environment may build up in the soil and have devastating impacts on pollinators and other beneficial insects.[3]

1.1.3. Serious doubts over the safety of transgenic foods are raised by new revelations on the results of animal feeding experiments. Potatoes engineered with snowdrop lectin fed to rats caused highly significant reduction in weight of many organs, impairment of immunological responsiveness and signs suggestive of viral infection.[4]

1.1.4. Research from the Netherlands show that antibiotic resistant marker genes from genetically engineered bacteria can be transferred horizontally to indigenous in an artificial gut.[5]

1.1.5. Researchers in the US found widespread horizontal transfer of a yeast genetic parasite to the mitochondrial genome of higher plants,[6] raising serious concerns over the uncontrollable horizontal spread of transgenes and marker genes from transgenic plants released into the environment.

2. The patenting of living organisms, cell lines and genes under the Trade Related Intellectual Property Rights agreement is sanctioning acts of piracy of intellectual and genetic resources from Third World nations,[7] and at the same time, increasing corporate monopoly on food production and

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[1] Brookes, M. (1998). Running wild, *New Scientist* 31 October; Snow, A. and Jorgensen, R. (1998). Costs of transgenic glufosinate resistance introgressed from Brassica napus into weedly Brassica rapa. *Abstract, Ecological Society of America,* Baltimore, Aug. 6, 1998

[2]Bergelson, J., Purrington,c.B. and Wichmann, G. (1998). Promiscuity in transgenic plants. *Nature* 395, 25.

[3]Crecchio, C. and Stotzky, G. (1998). Insecticidal activity and biodegradation of the toxin from Bacillus thuringiensis subsp. kurstaki bound to humic acids from soil," *Soil Biology and Biochemistry* 30, 463-70, and references therein.

[4]Leake, C. and Fraser, L. (1999). Scientst in Frankenstein food alert is proved right. UK Mail on Sunday, 31 Jan. ; Goodwin, B.C. (1999). Report on SOAEFD Flexible Fund Project RO818, Jan. 23, 1999.

[5]MacKenzie, D. (1999). Gut reaction. *New Scientist* 30 Jan., p.4.

[6] Cho, Y., Qiu, Y.-L., Kuhlman, P. and Palmer, J.D. (1998). Explosive invasion of plant mitochondria by a group I intron. *Proc. Natl. Acad. Sci. USA* 95, 14244-9.

[7]See Shiva, V. (1998). *Biopiracy The Plunder of Nature and Knowledge*, Green Books, London; also Latin American Declaration on Transgenic Organisms, Quito, 22 Jan. 1999.

distribution. Small farmers all over the world are being marginalized, threatening long term food security for all.[8]

3. The Governments of industrialized nations, by voting for patents on organisms, cell lines and genes, including human genes, are in danger of allowing corporations unrestricted exploitation of their citizens and natural resources through the treaties being negotiated in the WTO and the MAI. Environmental standards, food safety standards and even basic human rights will be sacrificed to corporate financial imperatives.[9]

4. Governmental advisory committees lack sufficient representation from independent scientists not linked to the industry. The result is that an untried, inadequately researched technology has been rushed prematurely to the market, while existing scientific evidence of hazards are being downplayed, ignored, and even suppressed,[10] and little independent research on risks is being carried out.

5. The technology is driven by an outmoded, genetic determinist science that supposes organisms are determined simply by constant, unchanging genes that can be arbitrarily manipulated to serve our needs; whereas scientific findings accumulated over the past twenty years have invalidated every assumption of genetic determinism.[11] The new genetics is compelling us to an ecological, holistic perspective, especially where genes are concerned. The genes are not constant and unchanging, but fluid and dynamic, responding to the physiology of the organism and the external environment, *and require a stable, balanced ecology to maintain stability*.

In summary, we call upon our Governments to:

- **Impose an immediate moratorium on further environmental releases of transgenic crops, food and animal-feed products for at least 5 years.**
- **Ban patents on living organisms, cell lines and genes.**
- **Support a comprehensive, independent public enquiry into the future of agriculture and food security for all, taking account of the full range of scientific findings as well as socioeconomic and ethical implications.**

World Scientists Statement - supplement
Supplementary Information on the Hazards of Genetic Engineering Biotechnology

1. Genetic engineering is a new departure from conventional breeding and introduces significant differences.

1.1. Conventional breeding involves crossing related species, and plants with the desired characteristics are selected from among the progeny for reproducing, and the selection is repeated over many generations. Genetic engineering bypasses reproduction altogether. It transfers genes *horizontally* from one individual to another (as opposed to *vertically*, from parent to offspring), often making use of infectious agents as *vectors* or carriers of genes so that genes can be transferred between distant species that would never interbreed in nature. For example, human genes are transferred into pig, sheep, fish and bacteria. Toad genes are transferred into potatoes. Completely new, exotic genes, are being introduced into food crops.

1.2. Natural infectious agents exist which can transfer genes horizontally between individuals. These are viruses and other pieces of parasitic genetic material, called *plasmids* and *transposons*, which are able to get into cells and then make use of the cell's resources to multiply many copies of themselves or to jump into (as well as out of) the cell's genome. While the natural agents are limited by species barriers, genetic engineers make artificial vectors by combining parts of the most infectious natural agents, and design them to overcome species barriers, so the same vector may now transfer, say, human genes, which are spliced into the vector, into the cells of all other

[8]The Corner House (1998), Food? Health? Hope? Genetic Engineering and World Hunger, Briefing 10.

[9]See Mander, J. and Goldsmith, E. eds. (1996). *The Case against the Global Economy and for a Turn toward the Local*, Sierra Club Books, San Francisco.

[10] See note 4.

[11]See Ho, M.W. (1998, 1999). *Genetic Engineering Dream or Nightmare? The Brave New World of Bad Science and Big Business*, Gateways Books and Third World Network, Bath and Penang.

mammals, or cells of plants. Once inside the cell, the artificial vector carrying the foreign gene(s) can then insert into the cell's genome, and give rise to a genetically engineered organism.
1.3. Typically, foreign genes are introduced with strong genetic signals - called *promoters* or *enhancers*, most often from viruses - to boost the expression of the genes to well above the normal level that most of the cell's own genes are expressed. Such viral promoters are used even in cases of so-called "vectorless" transfers, where gene expression "cassettes" are introduced by injection, biolistic bombardment and other physical means. There will also be selectable "marker genes" introduced along with the gene(s) of interest, so that those cells that have successfully integrated the foreign genes into their genome can be selected. The most commonly used marker genes are antibiotic resistant genes, which enable the cells to be selected with antibiotics. These marker genes often remain in the genetically engineered organisms.

2. Genetic engineering introduces new dangers and problems to health and biodiversity.
There are four main sources of hazards and problems: those due to the new genes and gene products introduced; unintended effects inherent to the technology; interactions between foreign genes and host genes; and those arising from the spread of the introduced genes by ordinary cross-pollination as well as by horizontal gene transfer.

3. Hazards may come from new genes and gene products.
New genes and gene products are introduced into our food, often from bacteria and viruses and other non-food species that we have never eaten before, and certainly not in the quantities produced in the genetically engineered crops, where they are typically expressed at high levels. The long term impacts of these genes and gene products on human health will be impossible to predict, particularly as the products are not segregated and there is no post-market monitoring.
3.1. Bt-toxins may have major impacts on biodiversity.
There is evidence that one class of gene products most commonly introduced, the bt-toxins, from the soil bacterium, *Bacillus thuringiensis*, targetted against insect pests, are harmful to beneficial species such as bees.[12] That is because they are often introduced in a truncated, preactivated, non-selective form. Harmful effects can even go up the food-chain. Lacewings fed on pests that have eaten genetically engineered bt-maize took longer to develop and were two to three times more likely to die.[13] Purified bt-toxins, similar to ones found in some lines of transgenic bt-crops, do not disappear when added to soil but instead become rapidly bound to clay and humic acid soil particles. The bound bt-toxins, unlike free toxins, are not degraded by soil microbes, nor do they lose their capacity to kill soil insects.[14] Unlike suspensions of the bacteria which have been used as sprays by organic farmers, in which the toxins are inactivated by uv light, the engineered toxins are released directly into the soil, thereby escaping degradation.The buildup of bt-toxins in the soil will have devastating impacts on pollinators and other beneficial insects. At the same time, it will accelerate the evolution of bt-resistance among pest, rendering the toxin ineffective as a pesticide. Bt-resistance is already a major problem only years after the first release, and scientists are recommending 20 to 40% of non-transgenic crop to be simultaneously planted as "refugia" to slow down the evolution of resistance.[15]
3.2. Transgenic snow-drop lectin is harmful to beneficial insects.
Yet another transgenic plant has been shown to harm beneficial insects up the food-chain. Ladybirds fed on aphids that have eaten transgenic potato with snow-drop lectin lived half as long, laid 38% fewer eggs that were 4 times more likely to be unfertilized and 3 times less likely to

[12] See Ho, M.W. (1998,1999). *Genetic Engineering Dream or Nightmare? The Brave New World of Bad Science and Big Business*, Gateway Books, Bath; Ho, M.W., Meyer, H. and Cummins, J. (1998). The biotechnology bubble. *The Ecologist* 28(3), 146-153, and references therein.
[13]Hilbeck, A., Baumgartner, M., Fried, P.M. and Bigler, F. (1998). Effects of transgenic *Bacillus thuringiensis*-corn-fed prey on mortality and development time of immature Chrysoperla carnea (Neuroptera: Chrysopidae). *Environmental Entomology* 27, 480-7.
[14] Crecchio, C. and Stotzky, G. (1998). Insecticidal activity and biodegradation of the toxin from Bacillus thuringiensis subsp. kurstaki bound to humic acids from soil," *Soil Biology and Biochemistry* 30, 463-70, and references therein.
[15]See *Union of Concerned Scientists Newsletter* Fall-Winter, 31 Jan. 1999; also, Griffiths, M. (1998). Nature fights back as technology tries to outsmart it. *Farming News*, October 23.

hatch.[16] This transgenic potato has now been revealed to be highly toxic to rats (see below), and is most probably harmful to small mammals in the wild.

3.3 Hazards arise from transgenic plants engineered to be resistant to broad-spectrum herbicides.

By far the major category of transgenic plants are engineered to be resistant to broad-spectrum herbicides such as glyphosate.

3.3.1.The toxicity of glyphosate is well-documented.[17] Acute toxicity of some glyphosate products include eye and skin irritation, cardiac depression and vomiting. In California, glyphosate is found to be the third most commonly-reported cause of pesticide-related illness among agricultural workers. The toxicities are often associated with supposedly inert solvents and detergents in some formulations which greatly increase the harmful effects of glyphosate. These synergistic interactions are now widely recognized.[18] Chronic toxicity of glyphosate include testicular cancer, reduced sperm counts and other negative reproductive impacts in rats.[19] There are also indications that at least some glyphosate formulations cause mutations in genes.[20]

3.3.2. Broad-spectrum herbicides will have major impacts on biodiversity.[21] They kill all other plants indiscriminately. This will destroy wild plants as well as insects, birds, mammals and other animals that depend on the plants for food and shelter. In addition, Roundup (Monsanto's formulation of glyphosate) can be highly toxic to fish. Glyphosate also harms earthworms and many beneficial mycorrhizal fungi and other microorganisms that are involved in nutrient recycling in the soil. It is so generally toxic that researchers are even investigating its potential as an antimicrobial.[22]

3.3.3. Herbicide resistant transgenic plants may lead to increased use of herbicides, contrary to what is being claimed. The transgenic plants themselves are already turning up as volunteer plants after the harvest, and have to be controlled by additional sprays of other herbicides.[23] The use of glyphosate with genetically engineered resistant plants will encourage the evolution of glyphosate resistance in weeds and other species, even without cross-pollination. A ryegrass highly resistant to glyphosate has already been found in Australia.[24] Resistance evolves extremely rapidly because *all* cells have the capability of mutating their genes at high rates to resistance if they are exposed continuously to sub-lethal levels of toxic substances including herbicides, pesticides and antibiotics. This is inherent to the "fluidity" of genes and genomes that has been documented within the past 20 years.[25] It will render resistant plants useless after several generations, as the herbicide is widely applied. At the same time, resistant weeds and pathogens may become increasingly abundant. Additional herbicides will then have to be used to control the resistant weeds.

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[16] Birch, A.N.E., Geoghegan, I.I., Majerus, M.E.N., Hackett, C. and Allen, J. (1997). Interaction between plant resistance genes, pest aphid-population and beneficial aphid predators. *Soft Fruit and Pernial Crops*. October, 68-79.

[17]Cox, C. (1995). Glyphosate, Part 2: Human exposure and ecological effects. *Journal of Pesticide Reform* 15 (4).

[18]Howard, V. (1998). Synergistic effects of chemical mixtures. Can we rely on traditional toxicology: *The Ecologist* 27(4) 193-5.

[19]FAO/WHO (1986) Pesticide residues in food. Evaluations Part I and Part II, Rome 29.09 - 8. 10, 1985; Ohnesorge, F.K. (1994). Toxikologische Aspekte. In Nutzpflanzen mit künstlicher Herbizidresistenz: Verbessert sich die Rückstandssituation? Verfahren zurTechnikfolgenabschatzung des Anbaus von Kulturpflanzen mit gentechnisch erzerugter Herbizidresistenz. van den Daele W. Pühler A, Sukopp H (Hrsg.) WZB Berlin.

[20] Kale, P.G., Petty, B.T. Jr., Walker, S., Ford, J.B., Dehkordi, N., Tarasia, S., Tasie, B.O., Kale, R. and Sohni, Y.R. (1995). Mutagenicity testing of nine herbicides and pesticides currently used in agriculture. *Environ Mol Mutagen* 25, 148-53

[21] See Greenpeace Report, 1998, and references therein.

[22] Roberts, F., Roberts, C.W., Johson, J.J., Kyle, D.E., Drell, T., Coggins, J.R., Coombs, G.H., Milhous, W.K., Tzipori, S., Ferguson, D.J.P., Chakrabarti, D. and McLeod, R. (1998). Evidence for the shikimate pathway in apicomplexan parasites. *Nature* 393, 801-5.

[23]See "Disappointing Biotech Crops" <www.btinternet.com/~nlpwessex>.

[24]New Scientist, 6 July, 1996.

[25]See Dover, G.A. and Flavell, R.B. (1982). *Genome Evolution*, Academic Press; also Ho, M.W. 1998, 1999. *Genetic Engineering Dream or Nightmare? The Brave New World of Bad Science and Big Busness*, Gateways Books and Third World Network, Bath and Penang.

3.3.4 Herbicide resistant transgenic crops are incompatible with sustainable agriculture. Many studies within the past 10 to 15 years have shown that sustainable organic agriculture can improve yields and regenerate agricultural land degraded by the intensive agriculture of the green revolution.[26] Sustainable organic agriculture depends on maintaining natural soil fertility as well as on mixed cropping and crop rotation. This has been reversing the destructive effects of intensive agriculture that have led to falling productivity since that 1980s. Glyphosate resistant plants requires application of glyphosate which not only kills other species of plants but harms mycorrhizal fungi symbiotically associated with the roots of plants, which are now found to be crucial for maintaining both species diversity and productivity of ecosystems.[27] The depletion of mycorrhizal fungi in intensive agriculture could therefore decrease both plant biodiversity and ecosystem productivity, while increasing ecosystem instability. "The present reduction in biodiversity on Earth and its potential threat to ecosystem stability and sustainability can only be reversed or stopped if whole ecosystems, including ecosystem components other than plants are protected and conserved."[28]

4. Problems due to unintended effects inherent to the technology.

Genetic engineering organisms is hit or miss, and not at all precise, contrary to misleading accounts intended for the public, as it depends on the *random* insertion of the artificial vector carrying the foreign genes into the genome. This random insertion is well-known to have many unexpected and unintended effects including cancer, in the case of mammalian cells.[29] Furthermore, the effects can spread very far into the host genome from the site of insertion.[30]

4.1. This is attested to by the high failure rates in making transgenic animals, and gross deformities among the "successes",[31] which are unacceptable in terms of animal welfare.

4.2. There have also been many failures among crops that have been commercialized and widely planted.[32] The Flavr Savr tomato was a commercial disaster and has disappeared. Monsanto's bt-cotton failed to perform in the field in both US and Australia in 1996, and suffered excessive damages from bt-resistant pests. Monsanto's 1997 Roundup resistant cotton crops fared no better. The cotton balls drop off when sprayed with Roundup and farmers in seven states in the US have sought compensation for losses. The transgenic "Innovator" herbicide tolerant canola failed to perform consistently in Canada. This has led the Saskachewan Canola Growers Association to call for an official seed vigor test.

4.3. There is widespread instability of transgenic lines, they generally do not breed true.[33] One of the main problems is gene silencing - cellular processes that prevent foreign genes from being expressed.[34] The instability of transgenic lines are inherent to the hit or miss technology, untried technology[35] which may ruin our agricultural base and severely compromise world food security.

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[26] See Pretty, J. (1995). *Regenerating Agriculture: Policies and Practice for Sustainability and Self-Reliance*, Earthscan, London; also Ho (1998,1999), note 11.

[27]van der Heijden, M.G.A., Klironomos, J.N., Ursic, M., Moutoglis, P., Streitwolf-Engel, R., Boller, T., Wiemken, A. and Sanders I.R. (1998). Mycorrhizal fungal diversity determines plant variability and productiviy. *Nature* 396, 69-72.

[28]van der Heijden, *et al*, 1998, p.71. (note 16).

[29] Walden, R., Hayashi, H. and Schell, J. (1991). T-DNA as a gene tag. *The Plant Journal* 1, 281-288; Wahl, G.M., de Saint Vincent, B.R. & DeRose, M.L. (1984). Effect of chromosomal position on amplification of transfected genes in animal cells. *Nature* 307: 516-520; see also entries in Kendrew, J., ed. (1995). *The Encyclopedia of Molecular Biology*, Blackwell Science, Oxford.

[30]Recently reviewed by Doerfler, W., Schubbert, R., Heller, H., Kämmer, C., Hilger-Eversheim, D., Knoblauch, M. and Remus, R. (1997). Integration of foreign DNA and its consequences in mammalian systems. *Tibtech* 15, 297-301.

[31]See Ho *et al*, 1998 (note 1) and references therein.

[32]See Ho *et al*, 1998 (note 1) and references therein.

[33]See Ho, M.W. and Steinbrecher, R. (1998). Fatal Flaws in Food Safety Assessment: Critique of The Joint FAO/WHO Biotechnology and Food Safety Report, *Environmental and Nutritional Interactions* 2, 51-84; and references therein.

[34] Finnegan H. & McELroy (1994). Transgene inactivation plants fight back! *Bio/Techology* 12: 883-888.

[35]See Ho *et al*, 1998 (note 1).

5. Unexpected and unintended effects will also arise from interactions between foreign genes and genes of the host organism.

No gene functions in isolation. Among the unintended effects relevant to food safety are new toxins and allergens, or changes in concentrations of existing toxins and allergens.

5.1. In 1989, a genetically engineered batch of tryptophan killed 37 and made 1500 ill, some seriously to this day, the suspected culprit was a trace contaminant which may have arisen from the genetic engineering.[36]

5.2. A Brazil nut allergen was identified in soya bean genetically engineered with a brazil nut gene which was not thought to be allergenic.[37]

5.3. Soya beans are known to have at least 16 proteins that can cause allergic reactions, which differ for different ethnic groups. A major allergen, trypsin-inhibitor which also has antinutritional effects, was found to be 26.7% higher in Monsanto's transgenic soya beans approved for market on the basis of "substantial equivalence",[38] and hence safe for human consumption.[39] The same transgenic soya reduced growth rate of male rats and increased milk fat in cows.[40] It is also suspected that the transgenic soya may have higher levels of phytoestrogens linked to reproductive abnormalities in mice, rats and ewes as well as humans.[41] Women with oestrogen-induced breast cancer, pregnant women and children may be particularly susceptible to phytoestrogens.[42]

5.4. Serious doubts have been raised over the safety of transgenic foods by recent revelations on the results of animal feeding experiments. Potatoes engineered with snowdrop lectin fed to rats caused highly significant reduction in both dry and wet weights of many essential organs: small intestine, liver, spleen, thymus, pancreas and brain. In addition, it resulted in impairment of immunological responsiveness and signs suggestive of viral infection.[43] The two transgenic lines were substantially different from each other and from the unengineered (unmodified) parent with respect to potato-lectin content, protease inhibitor, gross composition and amino acid content, yet the official audit concludes that they were “substantially equivalent”.

6. Hazards arise from the uncontrollable spread of transgenes and antibiotic resistance marker genes.

Genetic pollution, as opposed to chemical pollution cannot be recalled. Genes, once released, have the potential to multiply and recombine out of control.

6.1. Transgenes and marker genes have spread to wild relatives by cross-pollination, creating superweeds.

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[36]Mayeno, A.N. and Gleich, G.J. (1994). Eosinophilia-myalgia syndrome and tryptophan production: a cautionary tale. *Tibtech* 12, 346-352.

[37]Nordlee, J.A., Taylor, S.L., Townsend, JA., Thomas, L.A. & Bush, R.K. (1996). Identification of a brazil-nut allergen in transgenic soybeans. *The New England Journal of Medicine* March 14, 688-728.

[38]Padgette, S.R., Taylor, N.B., Nida, D.L., Bailey, M.R., MacDonald, J., Holden, L.R., and Fuchs R.L. (1996). The composition of glyphosate-tolerant soybean seeds is equivalent to that of conventional soybeans. *Journal of Nutrition* 126, 702-16.

[39] See Ho, M.W. and Steinbrecher, R. (1998). *Fatal Flaws in Food Safety Assessment: Critique of The Joint FAO/WHO Biotechnology and Food Safety Report*, *Environmental and Nutritional Interactions* 2, 51-84.

[40]Hammond, B.G., Vicini, J.L. Hartnell, G.F., Naylor, M.W., Knight, C.D., Robinson, E.H., Fuchs, R.L. and Padgette, S.R. (1996). The feeding value of soybeans fed to rats, chickens, catfish and dairy cattle is not altered by genetic incorporation of glyphosate tolerance. *Journal of Nutrition* 1126(3) 717-26.

[41] See Oekoinstitut Freiburg: Reply to the Statement made by the Bundesministerium fur Gesundheit (Ministry of Health of the German Federal Republic) on 5 December 1996, in respect of the importation of genetically engineered glyphosate-tolerant soybeans from the company Monsanto, 1997.

[42]Dibb, S. (1995). Swimming in a sea of oestrogens - chemical hormone disrupter. *The Ecologist* 25, 27-31.

[43]Leake, C. and Fraser, L. (1999). Scientst in Frankenstein food alert is proved right. UK Mail on Sunday, 31 Jan. ; Goodwin, B.C. (1999). Report on SOAEFD Flesible Fund Project RO818, Jan. 23, 1999.

This has occurred in oilseed rape[44] and sugar beet,[45] creating potential superweeds. Spread of genes by cross-pollination is to be expected, whether the plants are transgenic or not. However, a recent report suggests that transgenes may be up to 30 times more likely to escape than the plant's own genes.[46] This raises the question as to whether other mechanisms for the spread of the transgenes (and marker genes) are present in transgenic plants, the most obvious being horizontal gene transfer to unrelated species.

6.2. Transgenes and marker genes may also spread by horizontal gene transfer. The same cellular mechanisms that enable the artificial vector carrying the foreign genes to insert into the genome can also mobilize the vector to jump out again to reinsert at another site or to infect other cells. For example, the enzyme, integrase, which catalyzes the integration of viral DNA into the host genome, also functions as a *dis*integrase catalyzing the reverse reaction. These integrases belong to a superfamily of similar enzymes present in all genomes from viruses and bacteria to higher organisms.[47]

6.2.1 Secondary horizontal tranfer of transgenes and antibiotic resistant marker genes from genetically engineered crop plants into soil bacteria and fungi have been documented in the laboratory.[48] Despite the misleading title in one of the publications,[49] a high "optimal" gene transfer frequency of 6.2×10^{-2} was found in the laboratory, from which the authors "calculated" a frequency of 2.0×10^{-17} under extrapolated "natural conditions". The natural conditions, are of course, largely unknown.

6.2.2 Plants engineered with genes from viruses to resist virus attack actually showed increased propensity to generate new, often super-infectious viruses by horizontal gene transfer and recombination with infecting viruses.[50]

6.2.3 A genetic parasite belonging to yeast, a *group I intron*, was found to have jumped into many unrelated species of higher plants recently.[51] Until 1995, this parasite was thought to be largely confined to yeast and only one genus of higher plants out of the 25 surveyed had the parasite. But in a new survey of species from 335 genera of higher plants, 48 were found to have the parasite. These 48 genera were in five different families: Asterids, Rosids, Monocots, Piperales, and Magnoliales. Sequence analyses indicate that the same group I intron is present in all the higher

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[44]See Ho, M.W. and Tappeser, B. (1997). Potential contributions of horizontal gene transfer to the transboundary movement of living modified organisms resulting from modern biotechnology. *Proceedings of Workshop on Transboundary Movement of Living Modified Organisms resulting from Modern biotechnology : Issues and Opportunities for Policy-makers* (K.J. Mulongoy, ed.), pp. 171-193, International Academy of the Environment, Geneva.

[45] Brookes, M. (1998). Running wild, *New Scientist* 31 October.

[46]Bergelson, J., Purrington,c.B. and Wichmann, G. (1998). Promiscuity in transgenic plants. *Nature* 395, 25.

[47]Asante-Appiah E. and Skalka, A.M. (1997). Molecular mechanisms in retrovirus DNA integration. *Antiviral Researh* 36, 139-56.

[48] Hoffman, T., Golz, C. & Schieder, O. (1994). Foreign DNA sequences are received by a wild-type strain of *Aspergillus niger* after co-culture with transgenic higher plants. *Current Genetics* 27: 70-76; Schluter, K., Futterer, J. & Potrykus, I. (1995). Horizontal gene-transfer from a transgenic potato line to a bacterial pathogen (*Erwinia-chrysanthem*) occurs, if at all, at an extremely low-frequency. *Bio/Techology* 13: 1094-1098; Gebhard, F. and Smalla, K. (1998). Transformation of *Acinetobacter* sp. strain BD413 by transgenic sugar beet DNA. *Appl. Environ. Microbiol*. 64, 1550-4.

[49]Schlutter *et al*, 1995 (see note 37).

[50] Vaden V.S. and Melcher, U. (1990). Recombination sites in cauliflower mosaic virus DNAs: implications for mechanisms of recombination. *Virology* 177, 717-26; Lommel, S.A. and Xiong, Z. (1991). Recombination of a functional red clover necrotic mosaic virus by recombination rescue of the cell-to-cell movement gene expressed in a transgenic plant. *J. Cell Biochem*. 15A, 151; Greene, A.E. and Allison, R.F. (1994). Recombination between viral RNA and transgenic plant transcripts. *Science* 263, 1423-5; Wintermantel, W.M. and Schoelz, J.E. (1996). Isolation of recombinant viruses between cauliflower mosaic virus and a viral gene in transgenic plants under conditions of moderate selection pressure. *Virology* 223, 156-64.

[51] Cho, Y., Qiu, Y.-L., Kuhlman, P. and Palmer, J.D. (1998). Explosive invasion of plant mitochondria by a group I intron. *Proc. Natl. Acad. Sci. USA* 95, 14244-9; Gray, M.W. (1998). Mass migration of a group I intron: Promiscuity on a grand scale. *Proc. Natl. Acad. Sci. USA* 95, 14003-5.

plants and that almost all of them represent independent horizontal gene transfer events. The researchers themselves raise serious concerns about releasing transgenic crops into the environment, given that horizontal gene transfer is now found to be so widespread.

6.2.4. Thus, genetically engineered crops, many of which still carry antibiotic resistant marker genes may spread these genes to pathogenic bacteria in the environment, as there is now evidence that DNA released from dead and live cells are not readily broken down, but are rapidly adsorbed onto clay, sand and humic acid particles where they retain the ability to infect (transform) other organisms. They may also contribute to generating new viral pathogens. This is particularly relevant in the light of the current world health crisis in drug and antibiotic resistant infectious diseases, and evidence indicating that horizontal gene transfer has been responsible for spreading drug and antibiotic resistance genes as well as creating new pathogens.[52]

6.2.5. There is also evidence that DNA is not broken down rapidly in the gut as previously supposed. Thus, transgenes and antibiotic resistance marker genes may spread to bacteria in the gut.[53] New research shows that antibiotic resistant marker genes from genetically engineered bacteria can be transferred to indigenous bacteria at a substantial frequency of 10^{-7} in an artificial gut.[54]

6.2.6. Viral and plasmid DNA fed to mice has been found to resist digestion in the gut. Large fragments passed into the bloodstream and into white blood cells, spleen and liver cells. In some instances, the viral was found attached to mouse DNA and *E. coli* DNA.[55] When fed to pregnant mice, large fragments of the DNA are found in the nucleus of cells of the foetus and the newborn.[56] Viral DNA is now known to be more infectious than the intact virus, which has a protein coat wrapped around the DNA. For example, intact human polyoma virus injected into rabbits had no effect, whereas, injection of the naked viral DNA gave a full-blown infection.[57] Many kinds of artificially constructed vectors are found to infect mammalian cells.[58] Thus, the foreign DNA introduced by artificial vectors into genetically engineered plants and animals may constitute a health hazard by itself. As mentioned above, integration of foreign DNA into cells are well-known to have many adverse effects including cancer.

7. Existing scientific evidence indicates that genetic engineering agriculture is an dangerous diversion.

Genetic engineering agriculture not only obstructs the implementation of real solutions to the problems of food security for all, but also poses unprecedented risks to health and biodiversity. Far from feeding the world, it will intensify corporate control on food production and distribution which created poverty and hunger in the first place. It will also reinforce existing social structures and intensive agricultural practices that have led to widespread environmental destruction and falling yields since the 1980s.[59]

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[52] See Ho, M.W., Traavik, T., Olsvik, R., Tappeser, B., Howard, V., von Weizsacker, C. and McGavin, G. (1998). Gene Technology and Gene Ecology of Infectious Diseases. *Microbial Ecology in Health and Disease* 10, 33-59.

[53]See Ho *et al*, 1998 (note 41) and refs. therein.

[54]MacKenzie, D. (1999). Gut reaction. *New Scientist* 30 Jan., p.4.

[55] Schubbert, R., Lettmann, C. & Doerfler, W. (1994). Ingested foreign (phage M13) DNA survives transiently in the gastrointestinal tract and enters the bloodstream of mice. *Mol. Gen. Genet.* 242: 495-504; Schubbert, R., Renz, D., Schmitz, B. and Doerfler, W. (1997). Foreign (M13) DNA ingested by mice reaches peripheral leukocytes, spleen and liver via the intestinal wall mucosa and can be covalently linked to mouse DNA. *Proc. Natl. Acad. Sci. USA* 94, 961-6.

[56] Doerfler, W., Schubbert, R., Heller, H., Hertz, J., Remus, R., Schrier. J., Kämmer, C., Hilger-Eversheim, K., Gerhardt, U., Schmitz, B., Renz, D., Schell, G. (1998)*APMIS* Suppl. 84, 62-8.

[57]See Traavik, T. (1995). *Too Early May Be Too Late. Ecological Risks Associated with the Use of Naked DNA as a Biological Tool for Research, Production and Therapy* (Norwegian), Report for the Directorate for Nature Research Tungasletta 2, 7005 Trondheim. English translation, 1999; Ho *et al*, 1998 (see note41); also Ho, 1998,1999 Chapter 10 (see note 1).

[58] See Ho *et al*, 1998 (see note41); also Ho, 1998, 1999 Chapter 10 (see note 1).

[59]See Brown, L. R. (1998). Struggling to raise cropland productivity. In *State of the World 1998* (L.R. Brown, C. Flavin and H. French, eds.) pp. 79-95, Worldwatch Institute Report, Earthscan Publications, London; Ho, 1998,1999, (note 1), Chapter 9; GeneWatch (1998). Genetically Engineered Food: The Case for a Moratorium.

(The letter below was drafted for the World Trade Organisation Conference in Seattle, November 30-2 Dec. 1999, based on the World Scientists Statement, and then updated to April, 2001)

Open Letter from World Scientists to All Governments Concerning Genetically Modified Organisms (GMOs)

- The scientists are extremely concerned about the hazards of GMOs to biodiversity, food safety, human and animal health, and demand a moratorium on environmental releases in accordance with the precautionary principle.
- They are opposed to GM crops that will intensify corporate monopoly, exacerbate inequality and prevent the essential shift to sustainable agriculture that can provide food security and health around the world.
- They call for a ban on patents of life-forms and living processes which threaten food security, sanction biopiracy of indigenous knowledge and genetic resources and violate basic human rights and dignity.
- They want more support on research and development of non-corporate, sustainable agriculture that can benefit family farmers and consumers.

Previous versions of this letter were submitted to: **World Trade Organization Conference** in Seattle (November 30 – Dec. 2, 1999), **UN Biosafety Protocol Meeting** in Montreal (24 – 28, Jan. 2000), **UN Commission on Sustainable Development Conference** on Sustainable Agriculture in New York (April 24-May 5, 2000), **UN Convention on Biological Diversity Conference** in Nairobi (May 16-24, 2000) **United States Congress** (29 June, 2000); and **US National Academy of Sciences** (14 April 2001)

Signed by 456 scientists from 56 countries, including:

Dr. David Bellamy, Biologist and Broadcaster, London, UK
Prof. Liebe Cavalieri, Mathematical Ecologist, Univ. Minnesota, USA
Dr. Thomas S. Cox, Geneticist, US Dept. of Agriculture (retired), India
Dr. Tewolde Egziabher, Spokesperson for African Region, Ethiopia
Dr. David Ehrenfeld, Biologist/Ecologist, Rutgers University, USA
Dr. Samuel Epstein, School of Public Health, Univ. Illinois, USA
Dr. Brian Hursey, ex FAO Senior Officer for Vector Borne Diseases, UK
Prof. Ruth Hubbard, Geneticist, Harvard University, USA
Prof. Jonathan King, Molecular Biologist, MIT, Cambridge, USA
Prof. Gilles-Eric Seralini, Laboratoire de Biochimie & Moleculaire, Univ. Caen, France
Dr. David Suzuki, Geneticist, David Suzuki Foundation, Univ. British Columbia, Canada
Dr. Vandana Shiva, Theoretical Physicist and Ecologist, India
Dr. George Woodwell, Director, Woods Hole Research Center, USA
Prof. Oscar B. Zamora, Agronomist, U. Philippines, Los Banos, Philippines

See complete list on www.i-sis.org.uk

We, the undersigned scientists, call for the immediate suspension of all environmental releases of GM crops and products, both commercially and in open field trials, for at least 5 years; for patents on living processes, organisms, seeds, cell lines and genes to be revoked and banned; and for a comprehensive public enquiry into the future of agriculture and food security for all.[60]

1 Patents on life-forms and living processes should be banned because they threaten food security, sanction biopiracy of indigenous knowledge and genetic resources, violate basic human rights and dignity, compromise healthcare, impede medical and scientific research and are against the welfare of animals.[61] Life-forms such as organisms, seeds, cell lines and genes are discoveries and hence not patentable. Current GM techniques which exploit living processes are unreliable, uncontrollable and unpredictable, and do not qualify as inventions. Furthermore, those techniques are inherently unsafe, as are many GM organisms and products.

[60] See World Scientists' Statement, Institute of Science in Society website <www.i-sis.dircon.co.uk>

[61] See Ho, M.W. and Traavik, T. (1999). *Why Patents on Life Forms and Living Processes Should be Rejected from TRIPS – Scientific Briefing on TRIPS Article 27.3(b*). TWN Report, Penang. See also ISIS News #3 and #4 <www.i-sis.org>

2. It is becoming increasingly clear that current GM crops are neither needed nor beneficial. They are a dangerous diversion preventing the essential shift to sustainable agricultural practices that can provide food security and health around the world.

3. Two simple characteristics account for the nearly 40 million hectares of GM crops planted in 1999.[62] The majority (71%) are tolerant to broad-spectrum herbicides, with companies engineering plants to be tolerant to their own brand of herbicide, while most of the rest are engineered with bt-toxins to kill insect pests. A university-based survey of 8200 field trials of the most widely grown GM crops, herbicide-tolerant soya beans – revealed that they yield 6.7% *less* and required two to five times *more* herbicides than non-GM varieties.[63] This has been confirmed by a more recent study in the University of Nebraska.[64] Yet other problems have been identified: erratic performance, disease susceptibility,[65] fruit abortion[66] and poor economic returns to farmers.[67]

4. According to the UN food programme, there is enough food to feed the world one and a half times over. While world population has grown 90% in the past 40 years, the amount of food per capita has increased by 25%, yet one billion are hungry.[68] A new FAO Report confirms that there will be enough or more than enough food to meet global demands without taking into account any yield improvements that might result from GM crops well into 2030.[69] It is on account of increasing corporate monopoly operating under the globalised economy that the poor are getting poorer and hungrier.[70] Family farmers around the world have been driven to destitution and suicide, and for the same reasons. Between 1993 and 1997 the number of mid-sized farms in the US dropped by 74,440,[71] and farmers are now receiving below the average cost of production for their produce.[72] The farming population in France and Germany fell by 50% since 1978.[73] In the UK, 20 000 farming jobs were lost in the past year alone, and the Prime Minister has announced a £200m aid package.[74] Four corporations control 85% of the world trade in cereals at the end of 1999.[75] Mergers and acquisitions are continuing.

5. The new patents on seeds intensify corporate monopoly by preventing farmers from saving and replanting seeds, which is what most farmers still do in the Third World. In order to protect their patents, corporations are continuing to develop terminator technologies that genetic engineer harvested seeds not to germinate, despite worldwide opposition from farmers and civil society at large.[76]

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[62] James, C. (1998,1999). *Global Status of Transgenic Crops,* ISAAA Briefs, New York.

[63] Benbrook, C. (1999). *Evidence of the Magnitude and Consequences of the Roundup Ready Soybean Yield Drag from University-Based Varietal Trials in 1998*, Ag BioTech InfoNet Technical Paper No. 1, Idaho.

[64] "Research Shows Roundup Ready Soybeans Yield Less". News Release from IARN News Service, University of Nebraska <IANRNEWS@unlnotes01.unl.edu>

[65] "Splitting Headache" Andy Coghlan. *NewScientist*, News, November 20, 1999.

[66] "Metabolic Disturbances in GM cotton leading to fruit abortion and other problems"<bikwessex@bigfoot.com>

[67] "Genetically Altered Crops – Will We Answer the Questions?"Dan McGuire, American Corn Growers Association Annual Convention, Las Vegas Nevade, Feb.4, 2000; see also "Biotech News" Richard Wolfson, *Canad. J. Health & Nutrition*, April, 2000.

[68] See Watkins, K. (1999). Free trade and farm fallacies. *Third World Resurgence* 100/101, 33-37; see also El Feki, S. (2000). Growing pains, *The Economist*, 25 March, 2000.

[69] *Agriculture: Towards 2015/30*, FAO Global Perspectives Studies Unit, July 2000 http://www.fao.org/es/ESD/at2015/toc-e.htm

[70] This is now admitted in an astonishing series of articles by Shereen El Feki in *The Economist* (March 25, 2000), hitherto generally considered as a pro-business right-wing magazine.

[71] Farm and Land in Farms, Final Estimates 1993-1997, USDA National Agricultural Statistics Service.

[72] See Griffin, D. (1999). Agricultural globalization. A threat to food security? Third World Resurgence 100/101, 38-40.

[73] El Feki, S. (2000). Trust or bust, *The Economist*, 25 March, 2000.

[74] Meikle, J. (2000). Farmers welcome £200m deal. The Guardian, 31 March, 2000.

[75] Farm Aid fact sheet: The Farm Crisis Deepens, Cambridge, Mass, 1999.

[76] US Department of Agriculture now holds two new patents on terminator technology jointly with Delta and Pine. These patents were issued in 1999. AstraZeneca are patenting similar techniques. Rafi communique, March, 2000; "Terminator on Trial" Rafi News Release 12 May 2000.

6. Christian Aid, a major charity working with the Third World, concluded that GM crops will cause unemployment, exacerbate Third World debt, threaten sustainable farming systems and damage the environment. It predicts famine for the poorest countries.[77] African Governments condemned Monsanto's claim that GMOs are needed to feed the hungry of the world: "We..strongly object that the image of the poor and hungry from our countries is being used by giant multinational corporations to push a technology that is neither safe, environmentally friendly, nor economically beneficial to us… we believe it will destroy the diversity, the local knowledge and the sustainable agricultural systems that our farmers have developed for millennia and …undermine our capacity to feed ourselves."[78] A message from the Peasant movement of the Philippines to the Organization for Economic Cooperation and Development (OECD) of the industrialized countries stated, "The entry of GMOs will certainly intensify landlessness, hunger and injustice."[79]

7. A coalition of family farming groups in the US have issued a comprehensive list of demands, including ban on ownership of all life-forms; suspension of sales, environmental releases and further approvals of all GM crops and products pending an independent, comprehensive assessment of the social, environmental, health and economic impacts; and for corporations to be made liable for all damages arising from GM crops and products to livestock, human beings and the environment.[80] They also demand a moratorium on all corporate mergers and acquisitions, on farm closures, and an end to policies that serve big agribusiness interests at the expense of family farmers, taxpayers and the environment.[81] They have mounted a lawsuit against Monsanto and nine other corporations for monopolistic practices and for foisting GM crops on farmers without adequate safety and environmental impact assessments.[82]

8. Some of the hazards of GM crops are openly acknowledged by the UK and US Governments. UK Ministry of Agriculture, Fisheries and Food (MAFF) has admitted that the transfer of GM crops and pollen beyond the planted fields is unavoidable,[83] and this has already resulted in herbicide-tolerant weeds.[84] An interim report on UK Government-sponsored field trials confirmed hybridisation between adjacent plots of different herbicide tolerant GM oilseed rape varieties, which gave rise to hybrids tolerant to multiple herbicides. In addition, GM oilseed rape and their hybrids were found as volunteers in subsequent wheat and barley crops, which had to be controlled by standard herbicides.[85] Bt-resistant insect pests have evolved in response to the continuous presence of the toxins in GM plants throughout the growing season, and the US Environment Protection Agency is recommending farmers to plant up to 40% non-GM crops in order to create refugia for non-resistant insect pests.[86]

9. The threats to biodiversity from major GM crops already commercialized are becoming increasingly clear. The broad-spectrum herbicides used with herbicide-tolerant GM crops decimate wild plant species indiscriminately, they are also toxic to animals. Glufosinate causes birth defects

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[77]Simms, A. (1999). *Selling Suicide, farming, false promises and genetic engineering in developing countries*, Christian Aid, London.

[78] "Let Nature's Harvest Continue" Statement from all the African delegates (except South Africa) to FAO negotiations on the International Undertaking for Plant Genetic Resources June, 1998.

[79] Letter from Kilusang Mgbubukid ng Pilipinas to OECD, 14 Feb. 2000 <www.geocities.com/kmp.ph>

[80] Farmer's Declaration on Genetic Engineering in Agriculture, National Family Farm Coalition, USA, <nffc@nffc.net>

[81]Farmer's rally on Capitol Hill, September 12, 1999.

[82] McGuire, D. (2000). Genetically altered crops: will we answer the questions? American Corn Growers Association Annual Convention, Las Vegas, Feb. 4, 2000.

[83]MAFF Fact Sheet: Genetic modification of crops and food, June, 1999.

[84] See Ho, M.W. and Tappeser, B. (1997). Potential contributions of horizontal gene transfer to the transboundary movement of living modified organisms resulting from modern biotechnology. *Proceedings of Workshop on Transboundary Movement of Living Modified Organisms resulting from Modern biotechnology : Issues and Opportunities for Policy-makers* (K.J. Mulongoy, ed.), pp. 171-193, International Academy of the Environment, Geneva.

[85] "The BRIGHT Project: Botanical and Rotational Implications of Genetically Modified Herbicide Tolerance: Progress Report, March 2000, sponsored by MAFF, SERAD, HGCA, BBRO, Aventis, Crop Care, Cyanamid, Monsanto

[86]Mellon, M. and Rissler, J. (1998). *Now or Never. Serious New Plans to Save a Natural Pest Control*, Union of Conerned Scientists, Cambridge, Mass.

in mammals,[87] and glyphosate is linked to non-Hodgkin lymphoma.[88] GM crops with bt-toxins kill beneficial insects such as bees[89] and lacewings,[90] and pollen from bt-corn is found to be lethal to monarch butterflies[91] as well as swallowtails.[92] Bt-toxin is exuded from roots of bt-plants in the rhizosphere, where it rapidly binds to soil particles and become protected from degradation. As the toxin is present in an activated, non-selective form, both target and non-target species in the soil will be affected,[93] with knock on effects on species above ground.

10. Products resulting from genetically modified organisms can also be hazardous. For example, a batch of tryptophan produced by GM microorganisms was associated with at least 37 deaths and 1500 serious illnesses.[94] Genetically modified Bovine Growth Hormone, injected into cows in order to increase milk yield, not only causes excessive suffering and illnesses for the cows but increases IGF-1 in the milk, which is linked to breast and prostate cancers in humans.[95] It is vital for the public to be protected from all GM products, and not only those containing transgenic DNA or protein. That is because the *process* of genetic modification itself, at least in the form currently practised, is inherently unsafe.

11. Secret memoranda of US Food and Drug Administration revealed that it ignored the warnings of its own scientists that genetic engineering is a new departure and introduces new risks. Furthermore, the first GM crop to be commercialized – the Flavr Savr tomato – did not pass the required toxicological tests.[96] Since then, no comprehensive scientific safety testing had been done until Dr. Arpad Pusztai and his collaborators in the UK raised serious concerns over the safety of the GM potatoes they were testing. They conclude that a significant part of the toxic effect may be due to the "[gene] construct or the genetic transformation (or both)" used in making the GM plants.[97]

12. The safety of GM foods was openly disputed by Professor Bevan Moseley, molecular geneticist and current Chair of the Working Group on Novel Foods in the European Union's Scientific Committee on Food.[98] He drew attention to unforseen effects inherent to the technology, emphasizing that the next generation of GM foods - the so-called 'neutraceuticals' or 'functional

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[87]Garcia,A.,Benavides,F.,Fletcher,T. and Orts,E. (1998). Paternal exposure to pesticides and congenital malformations. *Scand J Work Environ Health* 24, 473-80.

[88] Hardell, H. & Eriksson, M. (1999). A Case-Control Study of Non-Hodgkin Lymphoma and Exposure to Pesticides. *Cancer*85, 1355-1360.

[89]"Cotton used in medicine poses threat: genetically-altered cotton may not be safe" *Bangkok Post*, November 17, 1997.

[90]Hilbeck, A., Baumgartner, M., Fried, P.M. and Bigler, F. (1998). Effects of transgenic *Bacillus thuringiensis*-corn-fed prey on mortality and development time of immature Chrysoperla carnea (Neuroptera: Chrysopidae). *Environmental Entomology* 27, 480-96.

[91]Losey, J.E., Rayor, L.D. and Carter, M.E. (1999). Transgenic pollen harms monarch larvae. *Nature* 399, 214.

[92] See Wraight, C.L., Zangerl, R.A., Carroll, M.J. and Berenbaum, M.R. (2000). Absence of toxicity of *Bacillus thuringiensis* pollen to black swallowtails under field conditions. PNAS Early Edition www.pnas.org; despite the claim in the title, the paper reports toxicity of bt-pollen from a high-expressing line to swallowtail larvae in the laboratory. The issue of bt-crops is reviewed in "Swallowing the tale of the swallowtail" and "To Bt or Not to Bt", ISIS News #5 www.i-sis.org

[93] Deepak Saxena, Saul Flores, G, Stotzky (1999) Transgenic plants: Insecticidal toxin in root exudates from Bt corn *Nature* 402, 480.

[94] Mayeno, A.N. and Gleich, G.J. (1994). Eosinophilia-myalgia syndrome and tryptophan production : a cautionary tale. *Tibtech* 12, 346-352.

[95] Epstein, E. (1998). Bovine growth hormone and prostate cancer; Bovine growth hormone and breast cancer. *The Ecologist* 28(5), 268, 269.

[96] The secret memoranda came to light as the result of a civil lawsuit spearheaded by lawyer Steven Druker against the US FDA, May 1998. For details see Biointegrity website: <www.biointegrity.com>

[97] Ewen, S.W.B. and Pusztai, A. (1999). Effects of diets containing genetially modified potatoes expressing Galanthus nivalis lectin on rat small intestine. The Lancet 354, 1353-1354; see also http://plab.ku.dk/tcbh/PusztaiPusztai.htm

[98] Pat Phibbs, P. (2000). Genetically modified food sales 'dead' In EU Until safety certain, says consultant , The Bureau of National Affairs, Inc., Washington D.C. March 23, 2000.

foods', such as vitamin A 'enriched' rice - will pose even greater health risks because of the increased complexity of the gene constructs.

13. Genetic engineering introduces new genes and new combinations of genetic material constructed in the laboratory into crops, livestock and microorganisms.[99] The artificial constructs are derived from the genetic material of pathogenic viruses and other genetic parasites, as well as bacteria and other organisms, and include genes coding for antibiotic resistance. The constructs are designed to break down species barriers and to overcome mechanisms that prevent foreign genetic material from inserting into genomes. Most of them have never existed in nature in the course of billions of years of evolution.

14. These constructs are introduced into cells by invasive methods that lead to random insertion of the foreign genes into the genomes (the totality of all the genetic material of a cell or organism). This gives rise to unpredictable, random effects, including gross abnormalities in animals and unexpected toxins and allergens in food crops.

15. One construct common to practically all GM crops already commercialized or undergoing field trials involves a gene-switch (promoter) from the cauliflower mosaic virus (CaMV) spliced next to the foreign gene (transgene) to make it over-express continuously.[100] This CaMV promoter is active in all plants, in yeast, algae and *E. coli*. We recently discovered that it is even active in amphibian egg[101] and human cell extract.[102] It has a modular structure, and is interchangeable, in part, or in whole with promoters of other viruses to give infectious viruses. It also has a 'recombination hotspot' where it is prone to break and join up with other genetic material.[103]

16. For these and other reasons, transgenic DNA – the totality of artificial constructs transferred into the GMO - may be more unstable and prone to transfer again to unrelated species; potentially to all species interacting with the GMO.[104]

17. The instability of transgenic DNA in GM plants is well-known.[105] GM genes are often silenced, but loss of part or all of the transgenic DNA also occurs, even during later generations of propagation.[106] We are aware of no published evidence for the long term stability of GM inserts in terms of structure or location in the plant genome in any of the GM lines already commercialized or undergoing field trials.

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[99] See Ho, M.W. (1998,1999). *Genetic Engineering Dream or Nightmare? The Brave New World of Bad Science and Big Business*, Gateway, Gill & Macmillan, Dublin.

[100] See Ho, M.W., Ryan, A., Cummins, J. (1999). The cauliflower mosaic viral promoter – a recipe for disaster? Microbial Ecology in Health and Disease 11, 194-197; Ho, M.W., Ryan, A., Cummins, J. (2000). Hazards of transgenic crops with the cauliflower mosaic viral promoter. *Microbial Ecology in Health and Disease* (in press); Cummins, J., Ho, M.W. and Ryan, A. (2000). Hazards of CaMV promoter. *Nature Biotechnology* 18, 363.

[101] N Ballas, S Broido, H Soreq, A Loyter (1989) Efficient functioning of plant promoters and poly(A) sites in Xenopus oocytes *Nucl Acids Res* 17, 7891-903.

[102] Burke, C, Yu X.B., Marchitelli, L.., Davis, E.A., Ackerman, S. (1990). Transcription factor IIA of wheat and human function similarly with plant and animal viral promoters. *Nucleic Acids Res* 18, 3611-20.

[103] See Kohli, A., Griffiths, S., Palacios, N., Twyman, R.M., Vain, P., Laurie, D.A. and Christou, P. (1999). Molecular characterization of transforming plasmid rearrangements in transgenic rice reveals a recombination hotspot in the CaMV 35S promoter and confirms the predominance of microhomology mediated recombination. Plant J. 17, 591-601; Kumpatla, S.P. and Hall, T.C. (1999). Organizational complexity of a rice transgenic locus susceptible to methylation-based silencing. *IUBMB Life* 48, 459-467.

[104]Reviewed in Ho, 1998,1999 (note 37); Ho, M.W., Traavik, T., Olsvik, R., Tappeser, B., Howard, V., von Weizsacker, C. and McGavin, G. (1998b). Gene Technology and Gene Ecology of Infectious Diseases. *Microbial Ecology in Health and Disease* 10, 33-59; Traavik, T. (1999a). *Too early may be too late, Ecological risks associated with the use of naked DNA as a biological tool for research, production and therapy*, Research report for Directorate for Nature Management, Norway.

[105] Kumpatla, S.P., Chandrasekharan, M.B., Iuer, L.M., Li, G. and Hall, T.c. (1998). Genome intruder scanning and modulation systems and transgene silencing. *Trends in Plant Sciences* 3, 96-104.

[106] See Pawlowski, W.P. and Somers, D.A. (1996). Transgene inheritance in plants. *Molecular Biotechnology* 6, 17-30.

18. The potential hazards of horizontal transfer of GM genes include the spread of antibiotic resistance genes to pathogens, the generation of new viruses and bacteria that cause disease and mutations due to the random insertion of foreign DNA, some of which may lead to cancer in mammalian cells.[107] The ability of the CaMV promoter to function in all species including human beings is particularly relevant to the potential hazards of horizontal gene transfer.

19. The possibility for naked or free DNA to be taken up by mammalian cells is explicitly mentioned in the US Food and Drug Administration (FDA) draft guidance to industry on antibiotic resistance marker genes.[108] In commenting on the FDA's document, the UK MAFF pointed out that transgenic DNA may be transferred not just by ingestion, but by contact with plant dust and air-borne pollen during farm work and food processing.[109] This warning is all the more significant with the recent report from Jena University in Germany that field experiments indicated GM genes may have transferred via GM pollen to the bacteria and yeasts in the gut of bee larvae.[110]

20. Plant DNA is not readily degraded during most commercial food processing.[111] Procedures such as grinding and milling left grain DNA largely intact, as did heat-treatment at 90^{O}C. Plants placed in silage showed little degradation of DNA, and a special UK MAFF report advises against using GM plants or plant waste in animal feed.

21. The human mouth contains bacteria that have been shown to take up and express naked DNA containing antibiotic resistance genes, and similar transformable bacteria are present in the respiratory tracts.[112]

22. Antibiotic resistance marker genes from GM plants have been found to transfer horizontally to soil bacteria and fungi in the laboratory.[113] Field monitoring revealed that GM sugar beet DNA persisted in the soil for up to two years after the GM crop was planted. And there is evidence suggesting that parts of the transgenic DNA have transferred horizontally to bacteria in the soil.[114]

23. Recent research in gene therapy and nucleic acid (both DNA and RNA) vaccines leaves little doubt that naked/free nucleic acids can be taken up, and in some cases, incorporated into the genome of all mammalian cells including those of human beings. Adverse effects already observed include acute toxic shock, delayed immunological reactions and autoimmune reactions.[115]

24. The British Medical Association, in their interim report (published May, 1999), called for an indefinite moratorium on the releases of GMOs pending further research on new allergies, the spread of antibiotic resistance genes and the effects of transgenic DNA.

25. In the Cartegena Biosafety Protocol successfully negotiated in Montreal in January, 2000, more than 130 governments have agreed to implement the precautionary principle, and to ensure that

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[107]Reviewed by Doerfler, W., Schubbert, R., Heller, H., Kämmer, C., Hilger-Eversheim, D., Knoblauch, M. and Remus, R. (1997). Integration of foreign DNA and its consequences in mammalian systems. *Tibtech* 15, 297-301.

[108]Draft Guidance for Industry: Use of Antibiotic Resistance Marker Genes in Transgenic Plants, US FDA, September 4, 1998.

[109]See Letter from N. Tomlinson, Joint Food Safety and Standards Group, MAFF, to US FDA, 4 December, 1998.

[110] See Barnett, A. (2000). GM genes 'jump species barrier'. The Observer, May 28.

[111]Forbes, J.M., Blair, D.E., Chiter, A., and Perks, S. (1998). *Effect of Feed Processing Conditions on DNA Fragmentation Section 5 - Scientific Report*, MAFF; see also Ryan, A. and Ho, M.W. (1999). Transgenic DNA in animal feed. ISIS Report, November 1999 <www.i-sis.org>

[112]Mercer, D.K., Scott, K.P., Bruce-Johnson, W.A. Glover, L.A. and Flint, H.J. (1999). Fate of free DNA and transformation of the oral bacterium Streptococcus gordonii DL1 by plasmid DNA in human saliva. *Applied and Environmental Microbiology* 65, 6-10.

[113] Reviewed in Ho, 1998,1999 (note 37).

[114] Gebbard, F. and Smalla, K. (1999). Monitoring field releases of genetically modified sugar beets for persistence of transgenic plant DNA and horizontal gene transfer. *FEMS Microbiology Ecology* 28, 261-272; reviewed in ISIS News #5.

[115] See Ho, M.W., Ryan, A., Cummins, J. and Traavik, T. (2000). *Unregulated Hazards, 'Naked' and 'Free' Nucleic Acids*, ISIS Report for Third World Network, Jan. 2000, London and Penang <www.i-sis.org>

biosafety legislations at the national and international levels take precedence over trade and financial agreements at the WTO. Similarly, delegates to the Codex Alimentarius Commission Conference in Chiba Japan, March 2000, have agreed to prepare stringent regulatory procedures for GM foods that include pre-market evaluation, long-term monitoring for health impacts, tests for genetic stability, toxins, allergens and other unintended effects.[116] The Cartegena Biosafety Protocol has now been signed by 68 Governments in Nairobi in May, 2000.

26. We urge all Governments to take proper account of the now substantial scientific evidence of actual and suspected hazards arising from GM technology and many of its products, and to impose an immediate moratorium on further environmental releases, including open field trials, in accordance with the precautionary principle as well as sound science.

27. Successive studies have documented the productivity and sustainability of family farming in the Third World as well as in the North.[117] Evidence from both North and South indicates that small farms are more productive, more efficient and contribute more to economic development than large farms. Small farmers also tend to make better stewards of natural resources, conserving biodiversity and safeguarding the sustainability of agricultural production.[118] Cuba responded to the economic crisis precipitated by the break up of the Soviet Bloc in 1989 by converting from conventional large scale, high input monoculture to small organic and semi-organic farming, thereby doubling food production with half the previous input.[119]

28. Agroecological approaches hold great promise for sustainable agriculture in developing countries, in combining local farming knowledge and techniques adjusted to local conditions with contemporary western scientific knowledge.[120] The yields have doubled and tripled and are still increasing. An estimated 12.5 million hectares worldwide are already successfully farmed in this way.[121] It is environmentally sound and affordable for small farmers. It recovers farming land marginalized by conventional intensive agriculture. It offers the only practical way of restoring agricultural land degraded by conventional agronomic practices. Most of all, it empowers small family farmers to combat poverty and hunger.

29. We urge all Governments to reject GM crops on grounds that they are both hazardous and contrary to ecologically sustainable use of resources. Instead they should support research and development of sustainable agricultural methods that can truly benefit family farmers the world over.

(A much shortened version of this letter was published in *Nature*, 1999)

Defence of substantial equivalence unscientific

Sir - Trewavas and Leaver [1] and Burke [2] betray precisely the unscientific approach to the regulation of GM foods - a charge they are attempting to refute - by claiming that hundreds of millions of people in the United States and Europe have eaten GM foods for years with no untoward effects. Has there been post-release health monitoring? What could such monitoring tell us when there has been no product segregation nor labelling? Where are the 'unexposed controls'?

Kearns and Mayers [3] cite the FAO/WHO Biotechnology and Food Safety Report [4] as evidence that the principle of substantial equivalence works for safety assessment. A detailed critique of that report and the case studies on how the principle has been applied [5] concluded that the principle of substantial equivalence is "unscientific and arbitrary", that it encapsulates a "dangerously permissive attitude" towards the industry and "offers less than minimalist protection

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[116] Viewpoint, Henry Miller, *Financial Times*, March 22, 2000

[117] See Pretty, J. (1995). Sustainable Agriculture, Earthscan, London; also Pretty, J. (1998). *The Living Land - Agriculture, Food and Community Regeneration in Rural Europe*, Earthscan, London; see also *Alternative Agriculture: Report of the National Academy of Sciences*, Washington D.C., 1989.

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[121] Peter Rosset, Food First Institute.

for consumers and biodiversity because it is designed to be as flexible, malleable and open to interpretation as possible".[6]

A scientific approach to establishing substantial equivalence would require a comparison of the GM to the nonGM variety *from which the GM variety was derived*, both grown for a number of generations in same environment, with the GM variety receiving any specific treatment that it would in the field. For example, GM soya tolerant to Roundup herbicide would have to be treated with Roundup, a requirement Monsanto failed to satisfy when the GM soya was granted market approval.

In practice, the company is allowed to compare the GM variety to any variety within the species, and even to an abstract entity with selected characteristics from all varieties. It could have the worst characteristics of all the varieties and still pass as substantially equivalent. The GM product could even be compared to products from an unrelated species or an arbitrary collection of species, as was done for a GM canola oil containing lauric acid normally found in coconut oil. There are no defined tests that products have to go through to establish substantial equivalence. The tests are so undiscriminating that unintended changes, such as new toxins and allergens, could easily escape detection. A GM potato, grossly altered, with deformed tubers, was nevertheless tested and passed as substantially equivalent.

The principle, as applied, will lead one to conclude that a person who plays football like Pele and does theoretical physics like Einstein is substantially equivalent to another who plays football like Einstein and does theoretical physics like Pele.

One reason for the unsatisfactory state of GM food regulation is the erroneous, *a priori* assumption, stated in the FAO/WHO Biotechnology and Food Safety Report and adopted by our regulators, that genetic engineering does not differ from conventional selective breeding (an assumption which goes contrary to the claim of novelty in patent applications). Hence, Trewavas and Leaver insist, GM food should not be subject to more rigorous testing than novel nonGM food.

In reality, genetic engineering enables exotic genes from viruses and bacteria and other non-food species to be introduced into our food crops. These genes are combined in novel constructs that have never existed, often with viral promoters to make genes over-express continuously. The constructs are inserted into genomes by transformation techniques that cannot control where the genes go, resulting in a range of unpredictable positional effects and rearrangements [7]. Furthermore, the exotic genes and gene constructs may have increased propensity to spread horizontally to unrelated species [8].

The work of Pusztai and his collaborators [9] draws attention to the inadequacy of the regulatory process as much as it casts doubt on the safety of GM foods. Part of the toxicity of the GM potatoes is indeed attributed to the "construct or the genetic transformation (or both)" common to other GM crops. More than 130 scientists around the world are questioning the safety of GM crops and demanding an immediate moratorium on all environmental releases [10]. It's time scientists engage in the real scientific debate.

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(A slightly different version of this article was published in *Sovereign* Issue 27, 46-8, 1999)

Head to Head Debate

Mae-Wan Ho

Genetically Modified (GM) crops are neither needed nor beneficial. They are a dangerous diversion from the real task of providing food and health around the world.

The promises to genetic engineer crops to fix nitrogen, resist drought, improve yield and to 'feed the world' have been around for at least 30 years. Such promises have built up a multibillion-dollar industry now controlled by a mere handful of corporate giants.

But the miracle crops have not materialised. So far, two simple characteristics account for all the GM crops in the world. More than 70% are tolerant to broad-spectrum herbicides, with companies engineering plants to be tolerant to their own brand of herbicide, while the rest are engineered with bt-toxins to kill insect pests. A total of 65 million acres were planted in 1998 within the US, Argentina and Canada. The latest surveys on GM crops in the US, the largest grower by far, showed no significant benefit. On the contrary, the most widely grown GM crops - herbicide-tolerant soya beans - yielded on average 6.7% *less* and required two to five times *more* herbicides than non-GM varieties.

The same GM crops have already given rise to herbicide-tolerant weeds and bt-resistant insect pests. Worse still, the broad-spectrum herbicides not only decimate wild species indiscriminately, but are toxic to animals. One of them, glufosinate, causes birth defects in mammals, while another, glyphosate, is now linked to non-Hodgkin's lymphoma. GM crops with bt-toxins kill beneficial insects such as bees and lacewings, and pollen from bt-maize is lethal to monarch butterflies.

According to the UN food programme, there is enough food to feed the world one and a half times over. World cereal yields have consistently outstripped population growth since 1980, but one billion are hungry. It is on account of corporate monopolies operating under the globalised economy that the poor are getting poorer and hungrier. Corporations already control 75% of the world trade in cereals. The new patents on seeds will intensify corporate monopoly by preventing farmers from saving and replanting seeds, which is what 85% of the farmers still do in the Third World. Christian Aid, a major charity working with the Third World, concludes that GM crops will cause unemployment, exacerbate Third World debt, threaten sustainable farming systems and damage the environment. It predicts famine for the poorest countries.

What about GM crops with enhanced nutritional value, such as putting soya protein into rice, or incorporating genes to increase iron content? The major cause of malnutrition worldwide is the substitution of industrial monocultures for the varied diet provided by traditional farming/foraging systems. Moreover, intensive agricultural practices deplete and leach nutrients from the soil, thereby changing the nutritional values of all food crops for the worse within the past 40 years. No amount of genetic engineering can reverse this trend, which can be achieved only by re-introducing sustainable farming methods and recovering agricultural biodiversity.

It is clear that GM crops offer no benefits and cannot feed the world. There are also enormous risks. The most immediate are random and unpredictable. Dr. Arpad Pusztai, an eminent scientist in the Rowett Institute of Scotland, lost his job when he released findings that showed two GM potato lines were toxic to rats.

A more insidious danger is horizontal gene transfer - the transfer of genetic material directly to unrelated species. It is inherent to the way GM organisms are constructed that the foreign genes introduced (transgenic DNA) may be more likely to transfer again to unrelated species. Such horizontal gene transfer can give rise to new viruses and bacteria that cause diseases and spread antibiotic and drug resistances among the pathogens.

It was because of these concerns that the pioneers of genetic engineering called for a moratorium in the '70s. Unfortunately, commercial pressures cut the moratorium short. Since then, drug and antibiotic resistant infectious diseases have returned with a vengeance. New viruses are appearing at alarming frequencies, while life-threatening bacteria are rapidly becoming resistant to all antibiotics and are hence untreatable. New evidence also indicates that transgenic DNA from dust and pollen in GM crops can spread to organisms in all environments, including the human body.

Another hazard is that the transgenic DNA can jump into the genomes of cells, resulting in harmful effects that include cancer. In its interim report (May 1999), the British Medical Association called for an indefinite moratorium on the release of GM crops pending further studies on new allergies, on the spread of antibiotic resistances and on the effects of transgenic DNA. These concerns are shared by at least 100 scientists from 20 countries who have signed a World Scientists' Statement calling for a 5 year moratorium and a ban on patents of life-forms (see www.i-sis.org.uk).

While the 'benefits' from GM crops remain illusory and hypothetical, the successes of sustainable, organic farming are well-documented, in the Third World, as well as in Europe and North America. There is also an enormous 'health bonus' in phasing out agrochemicals which are linked to many forms of cancer, to reproductive abnormalities and degenerative diseases.

The current obsession with gene manipulation may be entirely misplaced. Indeed, genes and genomes can remain relatively stable and constant only within a stable, balanced ecosystem. Organic agriculture is predicated on such a balanced ecosystem. The requirements for genetic health, similarly, are no different from those for physiological health: unpolluted environment; wholesome organic foods free from agrochemicals; sanitary and socially satisfying living conditions. Those are the real choices for civil society.

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ISIS News 3, December 1999, ISSN: 1474-1547 (print), ISSN: 1474-1814 (online)

Viral Gene Switch – A Recipe for Disaster?

This story highlights the hazardous nature of the genetic engineering process as well as the new gene constructs created and released into the environment.

A scientific paper on the cauliflower mosaic viral promoter (CaMV promoter) has attracted at least nine attacks, including one from Monsanto, before it is actually published. The attacks and rebuttals have been ricocheting around the web, but what is it all about? (Please visit ISIS website for the paper, Ho, M.W., Ryan, A. and Cummins, J. (1999). The cauliflower mosaic viral promoter – a recipe for disaster? *Microbial Ecology in Health and Disease* (in press), and the official author's reply to critiques.)

Prof. Joe Cummins of the University of Western Ontario was the first scientist to question the safety of the cauliflower mosaic viral (CaMV) promoter, which is in practically all GM crops currently grown commercially or undergoing field trials. He pointed out that the promoter could recombine with other viruses to generate new disease-causing viruses. In our joint paper, we review some recent findings which give further grounds for concern, and recommend the immediate withdrawal of all crops and products containing the CaMV promoter, which effectively means all commercial and field tested GM crops, and products with incompletely degraded DNA.

The story begins with the 'promoter'. A 'promoter' is a stretch of genetic material that acts as a switch for turning genes on. Every gene needs a promoter in order to work, or to become expressed. But the promoter is not a simple switch like that for an electric light, for example, which has only two positions, either fully on or fully off. Instead, the gene promoter has many different parts or modules that act as sensors, to enable it to respond, in ways we do not yet fully understand, to signals from other genes and from the environment. These signals tell it when and where to switch on, by how much and for how long. And under certain circumstances, the promoter may be silenced, so that it is off all the time.

The role of the promoter of a normal gene in an organism is to enable the gene to work appropriately in the extremely complex regulatory circuits of the organism as a whole. The promoter associated with each of the organism's own genes is adapted to its gene, while the totality of all the genes of the organism have been adapted to stay and work together for millions, if not hundreds of millions of years. The genome of each organism is organized in a particular way that is more or less constant across the species, so individuals within a species can freely interbreed. Each species protects its integrity and remains genetically stable because there are biological barriers that prevent distant species from interbreeding or otherwise exchanging genetic material. Foreign DNA is generally broken down or put out of action. Genetic engineering attempts to overcome these biological barriers so genes can be arbitrarily transferred between species that would never interbreed in nature. In order to do so, special tricks are needed.

When genetic engineers transfer foreign genes into an organism to make a GMO, they also have to put a promoter in front of each of the genes transferred, otherwise it would not work. The promoter plus the gene it switches on make up a 'gene-expression cassette'. Many of the genes are from bacteria and viruses, and the most commonly used promoter is from the caulifower mosaic virus. Several gene-expression cassettes are usually stacked, or linked in series, one or more of them will be genes that code for antibiotic resistance, which will enable those cells that have taken up the foreign genes to be selected with antibiotics. The stacked cassettes are then spliced in turn into an artificial gene carrier or 'vector'. The vector itself is generally made by joining together parts of viruses and other infectious genetic parasites (plasmids and transposons) that cause diseases or spread antibiotic and drug resistance genes. In the case of plants, the most

widely used vector is the 'T-DNA' which is part of the tumour-inducing plasmid ('Ti plasmid') of *Agrobacterium*, a soil bacterium that infects plants and give rise to plant tumours or galls.

The role of the vector is to smuggle genes into cells that would otherwise exclude them. And more importantly, the vector can jump into the cell's genome and so enable the gene-expression cassettes it carries to become incorporated into the genetic material of the cell. The genetic engineer cannot control where and in what form the vector jumps into the genetic material of the cell, however. And this is where the first unpredictable effects can arise. Each transgenic line or GMO is unique, and gives rise to different unintended effects. In the case of food, this can mean unexpected toxins and allergens (see GM Soya & Increased Soya Allergy in Science Notes, this issue).

The foreign genetic material in the GMO – referred to as the 'transgenic DNA' or the 'construct' – is quite complicated. It consists of new genes and new combinations of genes - from diverse species and their genetic parasites - that have never existed in nature. Such chimaeric constructs are already known to be structurally unstable, that is, they have a tendency to break and join up and rearrange. It is to be expected that such structural instability can only increase when the construct is introduced, by a hit or miss process, into a new genome. The instability of GMOs is a big problem for the industry. GMOs often do not breed true (Terminator in New Guises, this issue).

Why use a promoter from a virus such as the CaMV? Like all viruses, CaMV is a genetic parasite that has the capability to infect cells and hi-jack the cell to make many copies of itself in a short period of time. Its promoter is therefore very aggressive, and is also found to be active in *all* plants, monocots, dicots, algae, and the *E. coli* bacteria that live in the gut of all mammals. Hence, the CaMV promoter is very popular with genetic engineers. It effectively makes the gene placed next to it turn on full blast in any plant genome, at perhaps a thousand times the volume of any of the organism's own gene.

Having it in the genome is rather like having the loudest phrase of a heavy-metal piece, played with the most powerful amplifier, over and over again, throughout a live performance of a Mozart concerto. What the CaMVpromoter does is to place the foreign gene outside the normal regulatory circuits of the host organism, subjecting the host organism to unremitting metabolic stress. This will multiply the unintended, unpredictable effects in the GMO. It may also be another reason why GMOs are notoriously unstable (Finnegan, J. & McElroy, D. 1994, Bio/Technology 12, 883). The organism generally reacts to the presence of foreign genetic material by breaking it down or putting it out of action in other ways. Even after the genetic material is incorporated into the genome, it can silence the foreign genes so they are no longer expressed (see Terminator in New Guises, this issue).

The key recent finding, which provoked us to write our paper, was the report by Kohli *et al*, (1999) *The Plant Journal* 17, 591, that the CaMV promoter contains a 'recombination hotspot' – a site where the DNA tends to break and join up with other DNA, thus changing the combination and arrangement of genes. Around the hotspot are several short stretches, or modules, for binding various enzymes, all of which are also involved in recombination , ie, breaking and joining DNA. Furthermore, the CaMV promoter recombination hotspot strongly resembles the borders of the T-DNA vector carrying the transgenes, which are also known to be prone to recombination. It is that which enables the vector to invade the cell's genome in the first place.

The aim of our original paper, restated explicitly in our official rebuttal, was to review the relevant findings and, in particular, to point out the *implications* which the researchers themselves are unwilling or unable to draw. The findings that transgenic DNA has the tendency to break and join in several places imply that parts or all of it may be more likely than the plant's own DNA to jump out of the genome and successfully transfer horizontally to unrelated species. Horizontal gene transfer, in this context, means the transfer of the genetic material directly by infection to the genetic material of unrelated species, in principle to all species interacting with the GMO: bacteria, fungi, earthworms, nematodes, protozoa, insects, small mammals and human beings. This process is uncontrollable and cannot be recalled. Transgenic DNA has been designed to be invasive and to overcome species barriers; once released, it will invade different organisms especially bacteria which are in all environments, where it will multiply, mutate and recombine.

There are additional findings that suggest an increased potential for transgenic DNA to spread horizontally. For example, the enzymes in the cell that insert the transgenic DNA into the genome can also make it jump out again. DNA released from both dead or live cells can survive without being degraded in all environments, including the mouth and gut of mammals. DNA can be readily taken up into cells. And *all* cells can take up naked or free DNA. A recent finding suggests that integrated viral sequences are preferentially taken up and incorporated into the cell's genome

(see Reusable DNA Alert, this issue). The instability of transgenic DNA may also be enhanced as the result of the metabolic stress inflicted on the organism by the CaMV promoter, which gives rise to continuous over-expression of transgenes.

The major consequences of the horizontal transfer of transgenic DNA are the spread of antibiotic resistance marker genes among bacteria and the generation of new bacteria and new viruses that cause diseases from the many bacterial and viral genes used. The generation of new viruses could occur by recombination with live or dormant viruses that we now know to be present in all genomes, plants and animals included. Recombination with defective, dormant animal viral promoters may also occur, as we know that there are modules that are interchangeable between plant and animal promoters. Recombination of CaMV promoter modules with defective promoters of animal viruses may result in recombinant promoters that are active in animal cells. This may reactivate the virus, generate new viruses or give functional viral promoters causing over-expression of one or another of dozens of cellular genes that are now believed to be associated with cancer.

In conclusion, there is sufficient scientific evidence to support well-founded suspicion of serious, irreversible harm to justify the immediate withdrawal of all GM crops and products containing the CaMV promoter from environmental release. This is fully in accord with the precautionary principle.

ISIS News 4, March 2000, ISSN: 1474-1547 (print), ISSN: 1474-1814 (online)

The CaMV Promoter Saga Continues..

Nature Biotechnology makes a habit of losing e-mails and submissions

To recapitulate on the story so far, a scientific paper, “Cauliflower mosaic viral promoter – A recipe for disaster?”, co-authored by Mae-Wan Ho, Angela Ryan and Joe Cummins was submitted to the Journal, *Microbial Ecology in Health and Disease* last October (now published: vol.11, 194-197, 1999). The Journal’s Editor, promptly posted it on the Journal’s website before publication and put out a press release. Within two days, someone managed to solicit at least nine critiques, including one from Monsanto, which were posted on a website funded by the biotech industry and widely circulated on the internet. The critiques varied in tone from moderately polite to outright rude. We wrote a detailed rebuttal, which was likewise circulated and posted to the same website, and have not received any replies from our critics since. In January, *Nature Biotechnology* published a distorted, one-sided and offensive account of our paper, concentrating on the criticisms and ignoring our rebuttal completely.

Our paper reviews and synthesizes existing scientific findings on the cauliflower mosaic viral (CaMV) promoter that is in practically all GM crops already commercialized or undergoing field trials. The findings suggest to us that artificial gene-constructs containing the CaMV promoter may be especially prone to breaking and joining up with other genetic material, thereby increasing the chance that it can be transferred horizontally to unrelated species. The potential hazards are harmful mutations, cancers, reactivation of dormant viruses and generation of new viruses. These considerations are especially relevant in the light of recent findings by Arpad Pusztai and his collaborator Stanley Ewen (*The Lancet* 354, p.1353, 1999), that transgenic potatoes - containing the CaMV 35S promoter - may be unsafe for young rats, part of the effects being attributed to the construct or the genetic engineering process, and hence common to all GM crops.

Secret documents belonging to the US Food and Drug Administration, which came to light as the result of a civil lawsuit against the agency (see Special House of Commons Briefings, this issue, and www.biointegrity.org) reveal that the first GM crop to be commercialized, the Flavr Savr tomato – which also had the CaMV promoter - actually failed to pass the standard safety tests. Since then, no comprehensive safety testing has been done on any GM foods. In line with the precautionary principle, we recommend the immediate withdrawal of all GM crops and products containing the CaMV promoter, until and unless they can be proven safe.

Nature Biotechnology had agreed in principle to our right to reply. But their editorial office has somehow managed to lose our e-mails and submission more than once over the past three months, and each time after a long delay. We have finally got an acknowledgement from them that they have received our corrected galleys. It is now posted on our website.

Meanwhile, we have written a more detailed reply for *Microbial Ecology in Health and Disease*, Hazards of Transgenic Plants with Cauliflower Mosaic Viral Promoter, with new references and arguments. This shall be posted on our website when it is accepted for publication.

Postcript: The paper was published. All three papers are available on pdf files on ISIS website www.i-sis.org.uk

Hazards of CaMV Promoter

(This letter appeared in *Nature Biotechnology* April 2000, as rebuttal to an article in Nature Biotechnology (Jan. 2000) attacking an earlier article, now published (Ho, M.W., Ryan, A., Cummins, J. (1999) The cauliflower mosaic viral promoter – a recipe for disaster? *Microbial Ecology in Health and Disease* 11, 194-197. The attack was most probably libellous, and *Nature Biotechnology* only agreed reluctantly to a right of reply from us, when MWH pointed that out to the Editor.)

In your account (Jan. 2000) (1) of our pre-publication manuscript, you quote the criticisms but ignore completely our full rebuttal, which was posted on the web last November. We shall outline the main points made in reply to the criticisms. The full details and references are available on our website (2).

Our manuscript (3) reviews and synthesizes the scientific literature on the 35S promoter of the cauliflower mosaic virus (CaMV) used to give constitutive over-expression of transgenes in practically all GM crops already commercialized or undergoing field trials. The promoter functions efficiently in all plants, as well as green algae, yeast and *E. coli*. It has a modular structure, with parts common to, and interchangeable with promoters of other plant and animal viruses. It also has a recombination hotspot, flanked by multiple motifs involved in recombination, similar to other recombination hotspots including the borders of the *Agrobacterium* T DNA vector most frequently used in making transgenic plants. The suspected mechanism of recombination – double-stranded DNA break-repair - requires little or no DNA sequence homologies. Finally, recombination between viral transgenes and infecting viruses has been demonstrated in the laboratory (4).

The findings suggest that transgenic constructs with the CaMV 35S promoter may be structurally unstable and prone to horizontal gene transfer and recombination. The potential hazards are mutagenesis, carcinogenesis, reactivation of dormant viruses and generation of new viruses. These considerations are especially relevant in the light of recent findings that certain transgenic potatoes - containing the CaMV 35S promoter - may be unsafe for young rats, and that a significant part of the effects may be due to “the construct or the genetic transformation (or both)” (5).

Our critics believe the CaMV 35S promoter is not harmful because people have been eating the virus in infected cabbages and cauliflower for many years. What we have been consuming is predominantly intact virus and not naked viral genomes. Naked viral genomes have been found to give full-blown infections in non-host species that are not susceptible to the intact virus (6). Moreover, the 35S promoter in the CaMV is a stable, integral part of the virus, and cannot be compared to the 35S promoter in artificial transgenic constructs. Artificial constructs are well-known to be structurally unstable (7). We know that the 35S promoter in the virus does not transfer into genomes because pararetroviruses, such as CaMV, do not integrate into host genomes to complete their lifecycle; and viral replication takes place in the cytoplasm (8). But that says nothing about the 35S promoter in transgenic constructs that are integrated into host genomes.

Proviral sequences are present in all genomes, and as all viral promoters are modular, and have at least one module – the TATA box - in common, if not more, it is not inconceivable that the 35S promoter in transgenic constructs can reactivate dormant viruses or generate new viruses by recombination. The CaMV 35S promoter has been joined artificially to the cDNAs of a wide range of viral genomes, and infectious viruses produced in the laboratory (9). There is also evidence that proviral sequence in the genome can be reactivated (10).

The fact that plants are “loaded” with potentially mobile elements can only make things worse. Most, if not all of the elements will have been ‘tamed’ in the course of evolution and hence no longer mobile. But integration of transgenic constructs containing the 35S promoter may mobilize the elements. The elements may in turn provide helper-functions to destabilize the transgenic DNA, and may also serve as substrates for recombination to generate more exotic invasive elements.

In signing on to the International Biosafety Protocol in Montreal in January, more than 150 governments agreed to implement the precautionary principle. The available evidence clearly indicates that there are serious potential hazards associated with the use of the CaMV promoter. All GM crops and products containing the CaMV promoter should therefore be withdrawn both from commercial use and from field trials unless and until they can be shown to be safe.

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Signed:
Joe Cummins, Mae-Wan Ho Angela Ryan

(This letter was submitted to *Nature* in response to an attack on MWH, but *Nature* rejected it)

Natural versus artificial genetic engineering

Sir – Trewavas and Leaver (1) claim that genetic engineering is no different from the natural processes that have been occurring in evolution. What is more, they argue that this is actually supported by what I wrote in my book (2).

Perhaps they have not read the whole of the book, for I explain that while artificial genetic engineering is uncontrollable, random and unpredictable, natural genetic engineering is quite precise and repeatable because it is regulated by the organism as a whole (3). This regulatory system has evolved over hundreds of millions of years. Under normal, steady state conditions, proof-reading, DNA-repair and other mechanisms ensure that the DNA remains constant and stable. Moreover, predictable rearrangements, amplifications, deletions and mutations may also take place during normal development and in response to certain environmental conditions.

In contrast, DNA polymerase reactions in the test-tube are prone to error, and artificial transformation processes give completely unpredictable, unrepeatable results. Moreover, the transgenic lines obtained are often unstable. Trewavas and Leaver assume that lethal insertions are selected out, while potentially innocuous insertions are detected by 'substantial equivalence'. But, unless current risk assessment is tightened up to address the unpredictability of the process, to insist that each transgenic line is clearly and separately identified and to ensure that it is genotypically as well as phenotypically stable in successive generations of growth, there is essentially no protection for the consumer or the farmer (4).

One main reason for both the unpredictability and instability of artificial genetic engineering is that foreign DNA is broken down and inactivated by restriction mechanisms in the host cells. Another reason is the structural instability of the transgenic constructs themselves, which are very complicated and made up of DNA originating from many different sources (5).

Several expression-cassettes are usually stacked in series, each cassette consisting of a gene with a promoter. The promoter is often taken from a virus in order to make the gene over-express. The stacked cassettes are, in turn, spliced into a vector, the most widely used being the T-DNA of *Agrobacterium*; and it is this whole construct which is intended for integration. But restriction mechanisms and structural instability work together to give uncontrollable deletions, rearrangements and repeats in the actual insert. Transgenic instability often persists after the insertion event (6). The constitutive over-expression of transgenes placed under viral promoters may be one cause of gene-silencing (7). Structural instability is also expected on account of the multiple recombination hotspots present in the transgenic DNA.

For example, the borders of the T-DNA vector are recombination hotspots, as is the 3' end of the 35S promoter from the cauliflower mosaic virus (CaMV) (8), which is used in practically all present-generation transgenic plants. Recombination hotspots are expected to increase the likelihood of secondary mobility and horizontal gene transfer (9). Secondary mobility within the host genome may cause rearrangements and other effects that could drastically alter the agronomic and other properties of the transgenic line.

That plant genomes, like animal genomes, harbour retrotransposons, relict retroviruses and pararetroviruses (10) is no reason for complacency. These sequences have existed for millions of years in the genome, and are probably no longer harmful, either to the plant itself or to other organisms interacting with it. However, in the presence of the transgenic DNA, relict/dormant viral sequences may recombine with the CaMV promoter (or modules thereof) to generate live viruses, and the transgenic DNA may also be mobilized by the relict elements. Horizontal gene transfer will spread transgenic DNA to unrelated species, in principle, to all species that interact with the transgenic plant, including bacteria and viruses in all environments, and animals which feed on the

plant. Chief among the potential dangers are the creation of new viruses and bacteria that cause diseases, the spread of antibiotic resistant marker genes and insertion mutagenesis, including cancer in mammalian cells.

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OECD Agenda: "There is no evidence that GM-food is harmful"

Pusztai on OECD Meeting on GMOs Feb. 29 – March 2, 2000

Dr. Arpad Pusztai *was the only scientist sceptical of GM food safety to be invited to the much publicized OECD's intergovernmental Conference on GMOs. Here is his personal account, slightly edited.*

After the meeting was opened by a number of politicians, Prof. Charles Arntzen from the Boyce Institute, USA, kicked off with the virtues of edible vaccines in potatoes. He made no comment on whether they would be tested rigorously; nor on the fact that they have to be eaten raw as heating would destroy the vaccine. Next, Dr Suman Sahai from Gene Campaign, India, argued convincingly that GMOs offer no benefit for developing countries. Instead, it was a means of exploitation, of robbing the poor to enrich the rich in the First World. Then came the darling of the Conference, Professor Zhangliang Chen (Vice President of Beijing University, China) who said China is slowly replacing everything with GM-counterparts and they have also tested their health effects on rats. However, no details on design or methodology or publications in peer-reviewed journals were given. This did not stop him from giving a glowing certificate of health and worth to all the GM-crops he tested. I was attacked for publishing our results in worthless rags such as *The Lancet* and *The Journal of Nutrition* when we should have done like Professor Chen and not published anything at all. I have a feeling that I was expected to ask for the forgiveness of the new God of GM-biotechnology.

After coffee came Professor Gordon Conway (President of Rockefeller Foundation) who gave his totally 'unbiased' views on the benefits, risks and ownership of GM-crop biotechnology. The 'balance' was redressed by the panellist who had 5 min each: both Benedikt Haerlin (Greenpiece International) and Mrs Marilena Lazzarini from the Institute for Consumer Defence, Brazil spoke well but made no great stir in the GM-biotechnology-dominated audience. In contrast a Novartis employee, Dr Andreas Seiter, did go through the biotech industry routine and was acclaimed by the audience.

The afternoon session on GM Food and Human Health should have been very short, as we have no data on this topic at all but that did not deter the Organisers. The first speaker, Prof. Ambroise Martin (University Lyon) had 20 min but did not say much. The next speaker was in Geriatric Medicine at Cornell University. He talked a lot about medical aspects of the old and at the end he waxed eloquently about the work of Arntzen who is a genius and is going to solve all the problems of the old by making them eat potatoes, bananas, etc with edible vaccines in them. The last speaker of the session before coffee was Prof. Hans Gunter (Darmstadt Technical University) who gave all the possible health risks of GM-food. There is obviously a subtle change in the air on GM-food in Germany – he sounded a warning note of caution. He advocated post-market monitoring of the effects of GM-food although he did not specify how to do this.

After coffee there was a presentation on Food Allergy and GMOs by Prof. Carsten Bindslev-Jensen (Denmark) who said that they tested all GM-food they could lay their hands on for allergy (skin-

prick test with human subjects) and found that none of them was any worse than the non-GM counterparts. My problem with this is that I do not believe in these tests for a start so I am not so sure whether his message was a good one or not or just simply means that he used a technique, which is severely limited and found no problem.

Then came the panel discussion. As a special favour granted by Sir John Krebs, I was given 10 min to give my slides on my protocol (now on my homepage) which was cut to 8 min by the Chairman. It would not have made much difference if I had been given 1 h, the effect would have been the same. Nobody made the slightest reference to it then or later. As Prof. Chen from China had such a "poor" opportunity previously to give his views he was allowed another bite of the same cherry. The message was still the same and the audience loved it. Prof. Alan McHughen (University of Saskatchewan), another GM enthusiast, said that we must introduce all his GM-crops but must also be vigilant. He could not say how, in 5 mins. Finally, Dr James Maryanski of FDA told us of all the great safety tests the FDA had done and also how generously they were with public hearings, and made 44,000 pages of their files available to the public. If course, this is not really needed because GM-food is the best and most rigorously tested food in the history of mankind.

He was refuted by US Lawyer Steven Druker from the Alliance of Biointegrity. The FDA had not revealed those 44,000 pages out of the goodness of their hearts -they were made to do so by a Court Action. The files revealed how the FDA had completely ignored the advise of their own scientists about safety, especially, that there was no substantial equivalence between GM and nonGM crops. You can find Steven's contribution on the biointegrity website <www.biointegrity.org>.

I would like to say something about the personal attacks on me from the floor. I had some exchanges with Phil Dale from the John Innes Centre in Norwich. He said (remember that we ought to have discussed my slides!) that I am a particularly unfair person because I never discussed the results of our nutritional work with the SCRI and Durham scientists, although they were involved in the research. Actually, as I have coordinated the whole programme, I made sure that we had 3-6 monthly workshops with written minutes of the events. The next bits of exchange was with Monsanto and other biotech people who got upset about my remark that when we started in 1995 there was not a single paper published in peer-reviewed journals on the nutritional/physiological testing of any GM-food. They kept jumping up, one after another. to say that there were lots of papers; the Monsanto guy, Fox, said that he himself must have produced them by the dozen. I kept challenging them as to where these were published but they were not forthcoming in their replies. Eventually a number of people like Joan Ruddock tried to defend me from the floor. In fact, she later confronted the Monsanto guy in private when, as always, he admits that they must have misunderstood me. The truth is that they count anything, even their memos, as publications. It is no wonder that the Chinese scientists' talk went down so well with them.

On Tuesday the GM- propaganda machine got into a higher gear. Kuiper chaired the sessions throughout the whole day. Needless to say, he never allowed me to take part in the discussions. The first speaker was Prof. Bernard Chevassu-au-Louis (President of the French Health and Food safety Agency). He gave his lecture in French which even with the translation was a little difficult to follow. Generally, he did seem to be good. His most memorable contribution was that, on the basis of substantial equivalence one could not differentiate a mad cow with BSE from a healthy one, that has put the substantial equivalence principle in the proper context, no matter how much Dr Peter Kearns (OECD) tried to salvage it. He said we must use it as our guiding principle. This just showed up that these people do not understand (or do not want to) that science is quantitative. It is not much use to say that you are a little mad; one needs to know how little?

Dr Calestous Juma (Director, Science Technology, Development Programme, Harvard University) could not come, so we had a real treat, a Professor of Microbiology, who doubles up as the S. African regulatory authority stepped into his shoes. She was enthusing all the time and according to her, the greatest triumph of the GM technology is that one S. African woman farmer, by planting GM-cotton took 30,000 rands (£3,000) to the bank at the end of the season. We were all duly impressed and many biotechnologists during the rest of the meeting referred to her example. Unfortunately, even this was not documented but the believer of the new faith swallowed it nevertheless. Next was Dr Alan Randell (Codex Alimentarius, FAO) who gave a very good factual account of the work of the Codex people. Obviously, he was in favour of GM but he also recognised that we need to do our homework and carry out proper testing according to strictly agreed protocols. We shall see!

After coffee unquestionably the best talk of the session was given by Prof. John Durant (Head of Science Communication, Science Museum UK). He explained to all the blockheads of the GM-biotech industry representatives that it was no use to blame the GM fiasco on the press, on maverick scientists (I expect the likes of me), the gullibility of consumers, sinister green pressure groups, etc. The fault lies with the proponents. So from there on, the motto of the Conference was borrowed from him: "openness, transparency and inclusiveness". In the best example of hypocrisy, the Conference went on and referred constantly back to him The Consumer Perspective was then given very lucidly and forcibly by Mr Julian Edwards, which was good and to be expected.

The following panel and plenary discussion was quite something. I have never heard such extreme and sometimes disgraceful views expounded in public as was done by Dr Val Giddings (Vice-President for Food, Agriculture, Biotechnology Industry Organisation (BIO) US). To give you some of the flavour of what he said - the only way to solve allergenicity, once for all, was via GM-technology. It was pointed out that we only escaped by the skin of our teeth the brazil nut allergen transfer into soya. But he then used this as an example of how well the regulation worked. He went on - when he was in Brazil he was told by some of the politicians there that even if there were some deaths due to anaphylaxis it is a price well worth paying if they could at the same time feed the population with this GM-soya. To show up how impartial the Chair was, nobody had a chance to reply to this once the people regained their breath after Dr Giddings great intervention. Mr Martin van Zwannenberg (ex-Divisional Director of Food Technology, Marks & Spencer, UK) had the distinction to almost physically attack me for my views, which disgraced science, etc...

Just imagine what sort of crowd they assembled here in Edinburgh? Clearly the creme of the society and 'science'.. Dr Michael Hansen (Consumers Union, USA) pointed out that (what I said above) science is quantitative and the present woolly definition of substantial equivalence is only a cop-out for the biotech regulators because how small is small. In fact the best would be to totally abandon this stupid thing. Needless to say, 90% of the people at the Conference would not agree with him. There was one very gung-ho GM person, who was absolutely impervious to any argument that was to her dislike. She was flatly opposed even to the idea of labelling. So much so that her views got into the final draft rapporteurs' report as something we "all agreed about". In fact, she was probably the only one who totally opposed the idea of labelling and nobody else made a great deal of it, even those from the GM-biotech industry kept reasonably quiet.

Sir John Krebs chaired the Wednesday session and this was somewhat of an eye-opener for me. The only speaker of the morning was Dr Ismail Serageldin (Vice-President, World Bank). He referred a lot to the South African farmer woman with her GM-cotton. Professor Chen from Zimbabve also extolled the virtues of GM for the developing world and so on. Unfortunately, the Organisers forgot to invite people such as Tewolde Egziabher and others to counterbalance this open enthusing on the great value of the GM-technology. Obviously, the World Bank will be giving big loans to the poor Third World Countries to buy the technology or even more the seeds in order to increase their dependency on the First World multinational companies and increase their financial debt. After this Dr Peter Tindemans (The Netherlands) and Dr Ian Gillespie (UK) - the rapporteurs, introduced their draft report which was then discussed by the participants under the Chairmanship of Sir John Krebs. Half of this was taken up by personal attacks on myself and other sceptics. I must say that this was too much even for people like Kuiper, Tom Sanders and some other scientists and the remainder of the Consumer, green groups (most of them left by this time).

Needless to say, I was not given any chance to defend myself. But this is in the great British tradition. After all, I was gagged for seven months before so what's the difference now? I am not going to say anything about the draft report because it is supposed to be confidential. However, I have already made my protest about some of the points in the report. The most blatant of which stated that there was general agreement on the point that there is no evidence at all to show that GM-food has a harmful effect on health. I believe this was the main purpose of the Conference: to state this clearly so that the Government's hands will be untied, and they can go ahead to legalise the whole GM-business. I gave them a very strongly worded protest on this point because even if they disregard all of my work, how can they make such a sweeping statement when there has never been any experiments with humans to show whether GM-food is good, bad or indifferent. When the final report of Sir John is published, it will give me the opportunity to put my comments on my homepage. I know that it is regularly visited by people from all over the world and if there are many like me, then they will not be able to get away with this.

Science behind Closed Doors

Corporate science engineering 'consensus'

At the World Economic Forum in Davos early this year, Bruce Alberts, President of the US National Academy of Sciences (NAS), gathered behind the scenes with a group of a dozen other presidents of national science academies to create an International Academy Council (IAC) to provide "impartial scientific advice" to governments and international organizations on issues such as genetic engineering, threatened ecosystems, and biodiversity.

Bruce Alberts also chairs The National Research Council (NRC), which has a full-time staff of 1000 and a $200 million annual budget. Through the NRC, the NAS conducts studies and prepares about 200 reports annually, largely under contract to federal agencies. In flagrant violation of the rules of open government - the 1972 Federal Advisory Committee Act - which Alberts still vehemently opposes, NRC committees and panels meet secretly in closed sessions. They do not disclose their minutes or conflict of interest statements, and fail to require that their membership reflects balanced representation of divergent interests and viewpoints.

The NRC committee which issued the 1996 report on "Carcinogens and Anti-carcinogens in the Human Diet" dismissed concerns on cancer risks to infants and children from food contaminated with carcinogenic pesticides, alleging that these "occur at levels far too low to have any adverse effects on health." Dr. Sam Epstein, acting on behalf of an *ad hoc* coalition of about 100 leading independent experts in public health and cancer prevention, and representatives of a wide range of labor and citizen groups, warned Alberts that the committee was grossly unbalanced, being disproportionately weighted with industry consultants, and pointed out further that no pediatrician had been invited to serve on the Committee. Alberts responded by admitting "that some of the committee members have performed some consulting for industry," but dismissed the concerns on grounds that "the same members have also advised or consulted for regulatory agencies"!

A more blatant conflict of interest arose in the composition of the NRC biotechnology panel set up in March, 1999, with disproportionate representation of experts directly linked to industry. It transpired that the panel's executive director, Dr. Michael Phillips, was secretly negotiating for a senior position in the Biotechnology Industry Organization, and joined the industry some 3 months later.

As federal support is beginning to shrink, the NAS plans to increase funding from non-federal sources, which currently account for some 15% of its budget. The NAS is also planning to extend its influence to major national policy concerns. Alberts has refused to release a pending report recommending reorganization of NAS policies and procedures.

All this was revealed in a letter submitted to *Science* magazine, co-signed by Samuel S. Epstein, M.D., School of Public Health, University of Illinois at Chicago and Chairman of Cancer Prevention Coalition, Edward Goldsmith, Editor and Founder of *The Ecologist* and Dr. Mae-Wan Ho of ISIS. The letter was rejected, despite repeated requests for reconsideration from Sam Epstein.

This is not the first time that magazines such as *Science*, *Nature* and *New Scientist* have refused to give voice to scientists dissenting from the corporate view, and they may be plumbing new depths in the current debate in genetic engineering, when undue and apparently unlimited access to their pages is granted to pro-biotech scientists and other supporters of the industry.

Nature Biotechnology (Jan. 2000) published a long report that attempted to discredit a (now published) paper on the potential hazards of the cauliflower mosaic viral promoter in the worst style of gutter journalism; and only gave the authors a very grudging right to reply after a delay of three to four months (see ISIS News #4) when the same offending journalist was allowed to have yet another go (see *Nature Biotchnology* April, 2000). I have long cancelled my personal subscriptions to these magazines.

There is still no open public debate on the abundant scientific evidence of actual and potential hazards of genetic engineering, nor on how scientific evidence ought to be used in the context of the precautionary principle. Some scientists have had their lives and work ruined, not the least by having to read boring scientific papers and reports no one would ever have volunteered to read, if they didn't think it is so important for the public to be informed as to what corporate science has in store for us.

We can have no confidence in any group of scientific advisors who have not been through the open democratic process. The US National Academy of Science report on GM crops was released in April this year amidst fresh controversy. While the Biotechnology Industry Organization (BIO) – the industry's lobby - was delighted by the report, claiming in a press release that GM foods "are thoroughly tested and safe", critics have rejected the report. US Senator Dennis Kucinich called for the study to be scraped because the panel was "tainted by pervasive conflicts of interest". Many scientists in the US are among the critics, though *Science* magazine refers to us all as 'activists' (*Science*, 14 April, 2000). We have repeatedly invited and challenged those scientists

who are still claiming that GM crops pose no special risks to open debate and discussions *in terms that the public can understand*, instead of hiding behind jargon words that defeat even most other scientists. They have turned us down again and again. MWH

Corporate Science on the Offensive

ISIS targeted

Dr. C. S. Prakash, Director of the Center for Plant Biotechnology Research at Tuskegee University (USA), is the latest corporate recruit to counter the worldwide rejection of GM crops. I first came across him in a pro-GM 'documentary' I was tricked into taking part by Equinox, the science series of Channel 4 TV in the UK (see ISIS NEWs #4). I met Prakash again at the multi-stakeholders dialogue at the 8th session of the United Nation's Commission on Sustainable Development (April 24-May 4, New York), where he sat with, and spoke for the biotech industry. On June 1, I encountered him for the third time in a debate in London, organized by the US Embassy. I was told Prakash has been sent over by the US State Department. Unlike his predecessor Val Giddings, Prakash oozes charm and bonhomie. He said he has already been touring Europe "to prevent other Mae-Wan Hos from springing up" and London, UK, was his last stop.

The debate, held in The School of Oriental and African Studies, was on the motion, "Agricultural biotechnology is vital for the developing world", with Prakash and Matt Ridley, speaking for, and myself and John Vidal speaking against. Ridley and Vidal are both well-known journalists on opposite ends of the political spectrum. To my surprise and dismay, it was not an open debate as only 'stakeholders' were invited. Judging by comments from the floor, the majority were from industry or pro-biotech pressure groups. The Monsanto 'science outreach' representative came out smelling like roses compared to two molecular geneticists associated with Cropgen, a new pressure-group of scientists funded by industry, members of which have been very prominent in the media recently, and appearing to be targeting ISIS in particular.

A few days later, one of the Cropgen scientists, Conrad Lichtenstein, wrote a pompous article in *The Guardian* newspaper ("A misguided media swarm" June 6) where he dismissed all the scientific studies that cast any doubt on the safety of GM crops, especially those that have been given a lot of press coverage: Arpad Pusztai's work that GM potatoes adversely affecting young rats and John Losey's finding that GM pollen is lethal to Monarch butterflies. In anticipation of the as yet unpublished report from Jena University in Germany - that GM genes have transferred from GM pollen to the bacteria and yeasts of baby bees - he argued that, if so, it must be occurring all the time. (Not so long ago, these scientists have denied that such horizontal gene transfer can occur.) And, he claims, it doesn't matter, because neo-Darwinian natural selection will select them out: the organisms to which the foreign genes have transferred will die out either immediately or in the long run, by the principle of the survival of the fittest. He failed to notice that neo-Darwinian natural selection operating on human beings to whom GM genes and constructs have spread won't be very good for health. The article ended with an attack on me.

He was "alarmed to hear an anti-GM university biologist state that GM genes are more resistant to the natural processes by which enzymes break down other DNA and that GM genes, as they are designed to "invade" genomes, are also more unstable and can more easily move around, dangerously spreading". He claimed that when he asked for direct experimental evidence, he was given "the techno-babble which puts fear into the hearts of the scientifically uneducated".

I wrote a letter to *The Guardian* (June 8) answering his attacks, and inviting him yet again to visit the ISIS website where all the evidence has been presented with detailed citations of the scientific papers. *The Guardian* then published another attack from him in the same tone (June 12) , demanding actual references to the scientific literature. I again submitted my reply.

But *The Guardian* did not publish my letter the next day, nor the next after I made a polite enquiry. Finally, when I threatened to complain to the Independent Press Commission, they agreed to publish a much shorter version without the references because their spokesperson said they simply cannot engage in detailed scientific debates of that kind. Why did they allow Lichtenstein to demand the references knowing that they won't allow me to supply them?

Lichtenstein and others like him are the reason why the public continue to perceive scientists as "arrogant and dysfunctional", as UK Member of Parliament Dr. Ian Gibson wrote (See "Scientists, Don't Forget the Social context!", this issue). They are also guilty of abuse of scientific evidence (as well as abuse of scientists) and acting against the precautionary principle.

The text of my talk, "GM Crops – How Corporations Rule and Ruin the World" can be found on the ISIS website. My first reply to Lichtenstein was published in the letters section of *The Guardian* (8 June) with the last two sentences omitted. The second reply published (16 June) was much shorter than what I had originally submitted, but makes the key point that the best kept secret of the

biotech industry is that there is no evidence for the long term stability of the GM inserts in both structure and location in the plant genome for any GM line already commercialized or undergoing field trials.

Both original letters are reproduced at the end of this report. Lichtenstein's comments on horizontal gene transfer and natural selection are typical of GM proponents adhering to the discredited, reductionist neo-Darwinian paradigm (see "An End to Bad Science and Beginning with Life Again" www.i-sis.org on how the new genetics makes neo-Darwinian theory untenable).

MWH

Ho Replies to Lichtenstein 1

I am the "anti-GM university biologist" that Conrad Lichtenstein referred to in his article on the GM controversy (6 June). The debate he described was arranged by the US Embassy for biotechnologist, Dr. C.S. Prakash, sent by the US State Department to promote GM agriculture in Europe. I agreed to participate because I believe in promoting critical public understanding of science and to draw attention to well-known and relevant scientific knowledge that is being ignored.

Almost by definition, genetic engineering organisms involves designing GM-constructs which invade genomes and overcome natural processes that break down foreign genetic material. Due to their highly mixed origins, however, GM-constructs are more unstable than natural genetic material as well as more invasive; and may therefore be more likely to spread to unrelated species. Those points were not challenged by Prakash because these basic principles and observations of genetic engineering are covered in text books and are also areas of active research. I answered Lichtenstein's questions in full and referred him to our website <www.i-sis.org> where the relevant scientific papers are cited and where more than 300 scientists from 39 countries, including many molecular geneticists who share my concerns, are demanding a moratorium on releases of GM organisms.

There is genuine scientific dissent among scientists and the public are not served by those who continue to misrepresent the GM debate as science *versus* anti-science. In demanding a moratorium, we are not trying to stop research into molecular genetics. On the contrary, we are arguing for more basic research that can tell us how and if GM technology can be safely used. More than that, we need open, wide-ranging and inclusive debates on the kind of science and technology that can best serve society.

Ho replies to Lichtenstein 2

Conrad Lichtenstein (Letters, 12 June) demands references on the invasiveness and instability of GM constructs in genetic engineering. There are many; here are just a few.

For designing GM constructs to overcome being broken down, and to increase invasiveness and stability, read Kumpatla *et al*, *Trends in Plant Sciences* 3, 96, 1998.

A major class of GM constructs are artificial vectors for transferring genes, made from the most invasive natural viruses and genetic parasites; their instability is highlighted in a text book, *Principles of gene manipulation*, by Old and Primrose, Blackwell Science, 5th ed, 1994.

There are many articles on the instability of GM plants, a recognized problem area. The most actively investigated are mechanisms silencing integrated GM genes, but loss of part or all of the GM construct has also been observed, even during later generations of propagation (see for example, Register *et al*, *Plant Molecular Biology* 25, 951, 1994).

Finally, a GM gene in *Arabidopsis* was found to be up to 30 times more likely to spread than the same gene created by conventional induction of mutation (Bergelson *et al*, *Nature* 395, 25, 1998). But no investigations were done to determine if this was associated with instability of the GM construct.

The instability and invasiveness of GM constructs are supported by direct and indirect evidence, while no evidence exists for the long term stability of the GM inserts with regard to structure and location in the plant genome. On grounds of safety and efficacy, such evidence should have been provided before approvals for releases were granted.

(This letter was published in *Science and Public Affairs*, August 2000, 27-8)

Calling scientists to account

Sir,

At long last, someone of Dr. Ian Gibson's standing is challenging scientists to consider the social consequences of their research! Doctors, lawyers, even corporations have been called to account, so why not scientists? Ian Gibson rightly calls for full public debate and dialogue, not just on the human genome project but also on genetically modified food. "Without a proper discourse", he warns, "science will move backwards and fail to capture public support and scientists will continue to be portrayed as dysfunctional and arrogant."

Proponents of genetic engineering are indeed giving the whole of science a bad press, which is particularly irksome for the vast majority of scientists who are not genetic engineers. Although they pay lip-service to openness and transparency and dialogue with the public, the reality is something else. There has not even been proper dialogue within the scientific community. Witness how, in the same issue of your magazine, Prof. Walter Bodmer, a prominent member of the Royal Society's Committee of the Public Understanding of Science, and others like him, are still insisting that genetic engineering is just like conventional breeding – a view that very few practicing molecular geneticist would defend – and that "scientific evidence is overwhelmingly in favour of the benefits outweighing the risks", which is far from the case.

The 'benefits' are potential, as Bodmer makes clear in the next sentence; in fact they are little more than promises made some thirty years ago which have still to materialize. On the other hand, there are already clear indications of hazards to health and biodiversity in the scientific literature. That is why more than three hundred scientists from 39 countries, many of whom molecular geneticists, are calling for a moratorium on environmental releases of GMOs (see www.i-sis.org). These same scientists are demanding a ban on patents on the new biotech patents, from human gene sequences and cell lines which violate basic human rights and dignity, to genetically engineered seeds which intensity corporate monopoly on food. They are also demanding support for research and development of sustainable, organic agriculture.

A holistic approach that integrates indigenous with western science and adapted to local ecological and social conditions is proving to be particularly beneficial. Some 12.5 million hectares worldwide are successfully farmed in this way. Yields have doubled and tripled, and are continuing to increase, far in excess of anything that GM crops have to offer. At the multi-stakeholders dialogue preceding the 8th Session of the United Nations Commission of Sustainable Development (April 24 – May 5) in New York, there was a chorus of approval and call for support for this approach from all civil society groups - farmers, trade-unions, consumers, indigenous peoples and diverse public interest organizations - all with the exception of industry. Why? Because when farmers are free to re-sow their seeds, harvest and sell their own produce locally, there would be no way corporate monopolies could profiteer by holding the hungry to ransom.

My experience with the genetic engineering debate has taught me how dangerous it is for scientists not see their work in the larger global context, and how necessary it is for scientists to listen to the enormous store of wisdom of 'ordinary' people all over the world. I, for one, has benefited a great deal from having to really listen to the public by having been co-opted as scientific advisor to a non-Government organization, the Third World Network. It would not be a bad idea for all scientists to be seconded for periods of six months or up to a year, to work with a public interest organization of their choice. It would make them infinitely better scientists, both in terms of being creative and socially responsive and responsible.

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Genetic Civil Rights Alert

To prevent companies and governments from stealing genes, invading genetic privacy and undermining human rights and dignity, we urgently need a Genetic Bill of Rights and a Global Ethics Council, ***Mae-Wan Ho*** *warns of the fall-outs from the human genome project.*

A visit to your local hospital, or a routine medical check-up may result in your DNA being 'finger-printed' into a database owned by a private company or by the government. Your gene sequences and cells may be patented and sold on the open market without your ever knowing about it. Your genetic information can be correlated with your life-time habits and medical history. Using this kind of genetic information, mass screening can be done. If you happen to carry a gene or genes associated with a whole range of diseases, you may be refused unemployment and health insurance. Should you wish to have children, your health insurance provider may require prenatal screening of the foetus, or pre-implantation screening of embryos in order to eliminate the 'bad' gene(s). Not only that, if you are ever suspected of having committed a crime, this information can be used to track you down in no time at all. The UK Government is committing major public funds to creating a DNA database of some three million suspects, to be held by the police.

These are some of the fall-outs from the Human Genome Project (see Human Genome: The Biggest Sellout in Human History, this issue). And it has prompted the public interest

organization, the Council for Responsible Genetics in the US to draft a comprehensive Genetic Bill of Rights www.gene-watch.org to protect “human rights and integrity” and the “biological integrity of the earth”. This is a very timely document that should serve as an excellent basis for legislation notably missing or incomplete worldwide.

But even this Bill of Rights may be inadequate to cope with rapid developments further down the line, such as human cloning, cell and tissue replacement and embryonic stem cell techniques. These procedures are likely to lead to an increase in international trafficking of human cells, eggs and embryos. Already, according to a South African government official who spoke at the recent State of the World Forum (see ISIS Gagged in State of the World Forum, this issue), biotech companies have contracted hospitals in South Africa to ship frozen placentas of black people to Paris.

A Global Ethics Council consisting of independent scientists as well as a representative cross section of civil society should be established as a matter of urgency to deal with these gross violations of human rights, privacy and dignity.

ISIS News 9/10, July 2001, ISSN: 1474-1547 (print), ISSN: 1474-1814 (online)

Open Letter on UK Farmscale Field Trials

ISIS sent an open letter 14 May 2001 to the Scientific Steering Committee (SSC) that oversees the farmscale field trials in the UK. At the time, Michael Meacher had already called for the field trial near the Henry Double Day Foundation organic farms to be moved, but the SSC had refused. Overwhelming pressure from the concerned citizens eventually forced the move. The letter is a good summary of the key scientific findings against the field trials.

“We are writing to express our concern the UK farmscale field trials of Aventis Chardon LL GM maize and other GM crops should not continue.

1. Both the legality and safety of Chardon LL maize and other GM crops have been strongly contested by scientists and others during the Chardon LL hearing held in the UK last year. The hearing was adjourned subsequent to a press release issued by UK Ministry of Agriculture Fisheries and Food (MAFF), October 30, 2000, admitting that Chardon LL has not passed the test for Distinctness, Uniformity and Stability required for commercial approval. We have pointed out that none of the GM crops could have passed this test on account of well-known problems of transgenic instability (1).

2. The possibility of cross-pollination with non-GM and organic crops as well as wild relatives is now generally acknowledged. In Canada, volunteer oil seed rape tolerant to three different herbicides has arisen in just two years after the three independent herbicide tolerant lines have been planted in adjacent fields (2). An interim report on UK field trials, similarly, confirmed that hybridisation between adjacent plots of different herbicide tolerant GM oilseed rape varieties gave rise to hybrids tolerant to multiple herbicides. In addition, GM oilseed rape and their hybrids were found as volunteers in subsequent wheat and barley crops, which had to be controlled by standard herbicides (3). Contamination of non-GM and organic oilseed rape is bound to occur, just as, in the case of Chardon LL, cross-pollination with organic and non-GM sweet corn is inevitable. Maize pollen, generally carried by wind, can be transported over great distances depending on weather conditions. Pollen is also collected and eaten by bees and other insect pollinators. Bees are known to travel up to 10km or more in foraging for food (4). Maize flowers late in the season when few other plants are in flower, and so bees and other pollinators may have little choice but to visit maize plants to gather pollen. This puts at risk organic and non-GM crops, pollinators including bees, the honey produced, farm workers and the general public.

3. A MAFF sponsored study found pollen, transgenic DNA and protein in honey (5), indicating that local honey could readily be contaminated. This has been confirmed by other studies since (6). None of the GM crops field tested, including Chardon LL, has been approved for human consumption. Contamination of the human food chain is a serious matter, as judged by the repercussions from the contamination caused by Aventis' Starlink GM fodder maize, first discovered in the United States, and then worldwide. Apart from the health risks, the total contribution of bee keeping in the UK - for both honey production and pollination - is estimated at £12 billion (MAFF figures).

4. A German study (in press - (7)) found transgenic DNA in microorganisms in the gut of bee larvae that had been fed GM pollen. This indicates that transgenic DNA, which includes the antibiotic resistance gene, can move from GM pollen into bee colonies. Many GM crops have intact antibiotic resistance genes, which are either expressed in the plants themselves or can be expressed when transferred to bacteria. Even though the ampicillin resistance gene in Chardon LL has lost its promoter, the promoter can be regained by recombination, or, the ampicillin resistance

gene may insert into a special mobile element, an 'integron', which would provide the gene with a promoter (8,9). We first drew attention to this possibility in a report published in 1998 (10) and again in our submission of evidence to the Chardon LL hearing (1).

5. Widespread tetracycline antibiotic resistance has been reported by beekeepers across Canada, USA and Argentina where most of the GM crops have been planted. Tetracycline and ampicillin have been used for the past forty years to control fowl brood, a common disease in bees. Although further investigations are required, it is possible that transgenic crops with antibiotic resistance genes, or else those using the antibiotic tetracycline as gene control trigger, such as certain male-sterile terminator crops (11), may be responsible for the sudden appearance of tetracycline resistance in bees.

6. The transfer of antibiotic resistance genes to bacteria and yeast in the gut of bee larvae is an example of horizontal gene transfer (12). MAFF-funded research scientists have warned of the transfer of antibiotic resistance genes to bacteria that inhabit the mouth, and respiratory tract of human beings (13, 14) and farm animals (15) via transgenic pollen, dust and animal feed. We have reviewed several recent reports on horizontal gene transfer and spelt out the implications (16).

7. UK's Advisory Committee for Releases to the Environment (ACRE) reviewed a key scientific paper (17) which monitored, *for the first time*, the transfer of GM constructs from transgenic plant debris to soil bacteria after field release. ACRE concluded that "no construct specific sequences were detected in bacteria isolated from these soils" and that the study "therefore provided no evidence for horizontal gene transfer in the environment" (18). *We are astonished at ACRE's selective interpretation of the evidence. The researchers have found evidence suggesting that GM construct has transferred to soil bacteria, but they failed to isolate the specific strain of bacteria, which, as they point out, is not surprising, as less than 1% of soil bacteria can be isolated by current techniques.* We invite ACRE to consider our review of the same paper (19).

8. There are essentially two other reasons, offered by ACRE (18) and others promoting GM crops, for dismissing horizontal gene transfer. The first is that horizontal gene transfer occurs only under 'optimised' conditions. One of the optimum conditions for horizontal gene transfer is sequence homology (similarity), which can increase horizontal gene transfer a thousand to a million-fold. By this criterion, GM constructs are indeed optimised for horizontal gene transfer: they are routinely constructed by combining sequences from widely diverse sources of bacteria, viruses, plasmids and transposons and hence possess homologies to all those agents found in the environment. The second justification is that horizontal gene transfer is a natural process. Indeed it is, but GM constructs are anything but natural. They are new combinations of genes that have never existed in billions of years of evolution. The horizontal transfer of GM constructs cannot, therefore, be considered a natural process. *On account of the predominant bacterial and viral origins of the genetic material constituting GM constructs, they have the potential to generate new bacterial and viral pathogens by recombination* (see ref. 12 for detailed arguments).

9. There are other features of the GM construct in many transgenic plants that are both hazardous in themselves and/or enhance horizontal gene transfer. The hazards specific to terminator crops, such as Aventis' spring and winter male-sterile oil seed rape included in the field trials, have been spelt out in a recent report (11). In the case of Chardon LL, we highlighted the cauliflower mosaic virus (CaMV) 35S promoter, the 'origin of replication' of the pUC plasmid vector, and uncharacterized plasmid sequences (1).

10. The CaMV 35S promoter and 'origin of replication' are both 'recombination hotspots (20-22). *Recombination hotspots exacerbate the widespread problem of trangene instability, and increase the likelihood of horizontal gene transfer*. In addition, the origin of replication is a signal for making more copies of the plasmid (or the virus) and the genes it carries. Thus, any GM construct with an origin of replication has the potential to be multiplied independently as a plasmid when transferred to bacteria, thus further increasing the opportunities for horizontal gene transfer and recombination.

11. We have drawn attention to other potential hazards of the CaMV 35S promoter when it is subject to horizontal transfer: recombination with other viral sequences to generate new viruses, and reactivation of dormant proviruses that are now found in all genomes (23). Our critics dismissed the hazards by stating that humans have eaten CaMV-infected cabbage without apparent harm. In reply, we pointed out that the 35S promoter, removed from the virus and joined to new genes, is not the same as the whole virus (24, 25). Although the virus is specific for cruciferae, the isolated promoter is promiscuous across the entire living world. It is active not only in all plants, algae, bacteria and yeast, but, as we discovered in literature more than 10 years old,

also in animal and human cells (26). *Our critics have yet to address the new arguments, nor the additional evidence of transgenic instability we have provided recently* (27, 28).

12. There are risks associated with the use of broad-spectrum herbicides. Beneficial organisms such as earthworms and mycorrhizal fungi and other microorganisms involved in nutrient recycling in the soil are susceptible to glyphosate (the active ingredient in Roundup herbicide). Glyphosate is so generally toxic that it has been considered for use as an antimicrobial (29). It is also linked to non-Hodgkin lymphoma (30). Glufosinate is known cause birth defects (31-33) and to damage nerve cells (34-35). It is notable that the herbicide has not been authorised for commercial use in the UK.

13. Before approval for environmental release of any GM crop, full account must be taken of all the relevant scientific evidence; where the existing evidence is not sufficient, more research should be commissioned before approval is granted. Post-release health and environmental monitoring must also be carried out to ensure that any GM crop released could be promptly recalled if there is fresh evidence of hazard. Government scientists should be systematically monitoring the scientific literature so as to anticipate developments that could prove harmful to health and the environment and to recommend effective preventative action. Governments should also provide a scientific 'clearing house' where new scientific information is made promptly available to all ministries and agencies and to the general public."

Signed:

Dr. Mae-Wan Ho, Angela Ryan, Prof. Brian Goodwin, Prof. Joe Cummins , Prof. Peter Saunders. (Please visit ISIS website for the detailed notes and references www.i-sis.org)

(This letter was submitted to *Nature* August 24, 2001. It was rejected, and subsequently circulated to ISIS e-mail list)

Sir- Your report[1] states, "The scientists behind Britain's farm-scale field trials accept that they cannot answer all the questions surrounding the ecological effects of herbicide-tolerant GM crops – much less GM technology in general." Yet, like other previous reports in *Nature*, it persists in giving the impression that the battle is between "environmental group and organic farming movement" on one side and "science" on the other. There are at least two problems with GM technology that have been debated among scientists, genetic instability of GMOs, and their propensity for horizontal gene transfer due to the structural instability of GM constructs and their homologies with a wide range of bacteria and viruses.[2,3]

We have insisted that molecular data documenting genetic stability of transgenic lines must be provided *before* any environmental release.[4] Unless a transgenic line is stable, one might as well forget about studying its long term environmental or health impacts. Unfortunately, none of the GM crops undergoing farm-scale field trials, or indeed, in commercial release elsewhere in the world, has been documented to be stable. And no studies on horizontal gene transfer are included in UK field trials.

The instability of GMOs is now generally recognised. Even the top 'success', Roundup Ready soya, is showing every sign of breakdown: reduced yield, non-germination, diseases and infestation by new pests.[5] Molecular genetic characterisation, the first ever done on any commercially grown GM crop so far, has failed to confirm the structure of the insert originally reported. Instead, both the GM construct and the host genome have been scrambled (rearranged), and hundreds of basepairs of unknown DNA has got in as well.[6]

A risk assessment study funded by the European Commission (EC) concludes:[7]

"Biotechnology relies to a large extent on our ability to introduce foreign genes into cells. A major problem with present day technology is the non-predictability of the integration of such transgenes. DNA introduced into plant cells mostly integrates at random, i.e. at non-predetermined positions of the genome….DNA integrated at random frequently contains multiply copies and often copies are scrambled. Multiple copies also often induce gene silencing and hence instability in the expression of the introduced genes. In addition, the DNA integrates at loci of unknown stability and capacity for expression of randomly integrated copies may induce unpredictable and undesirable mutations in the host genome….we still lack the knowledge for precision engineering of plants' genes."

The EC also funded research evaluating horizontal gene transfer from GMOs to the microflora and in animal gut.[8] It notes that the risks of "horizontal gene transfer cannot be excluded", and, "Free DNA persists in some materials for weeks, and furthermore, some bacteria develop natural/chemical competence to take up DNA from the environment. In addition, in the gastrointestinal tract of man and husbandry animals, DNA may remain stable for some time, particularly in the colon."

Finally, the new European Directive 2001/18 /EC on deliberate release of GMOs has now been agreed. Apart from the stricter requirements for long term ecological and health impact assessments, it also stipulates molecular data documenting that the GMO is genetically and phenotypically stable. These criteria, if strictly implemented, will disqualify most, if not all current GMOs, for environmental release, including those undergoing UK farm-scale field trials.

1. Gura, T. *Nature* 412, 760-3 (2001).
2. Ho, M.W, *et al*. *Microbial Ecology in Health and Disease* 10, 33-59, 1998.
3. Ho, M.W., Ryan, A., Cummins, J. *Microbial Ecology in Health and Disease* 12, 6-11, 2000.
4. Ho, M.W., Steinbrecher, R. *Environmental and Nutritional Interactions* 2, 51-84, 1998.
5. "Bad news beans – A year of challenges confronts soybean growers" Duane Daily, Extension & Ag. Information, University of Missouri, July 27, 2001 DailyF@missouri.edu
6. Windels, P. *et al*. *Eur Food Res Technol* DOI 10.1007/ s002170100336, (2001).
7. http://europa.eu.int/comm/research/quality-of-life/gmo/01-plants/01-14-project.html
8. http://europa.eu.int/comm/research/quality-of-life/gmo/04-food/04-07-project.html

Signed: Mae-Wan Ho, Angela Ryan, Joseph Cummins

ISIS Submit Evidence to House of Lords on Stem Cells

*Dr. **Mae-Wan Ho**, Director of ISIS submitted the following to the House of Lords Select Committee, stating our position on stem cells research, human cloning and germline modifcation.*

"The Institute of Science in Society is a not-for-profit organisation promoting social responsibility and sustainable, ecological approaches in science.

Our position on the related issues of stem cells research, human cloning and germline modification is presented below.

1. We reject any form of reproductive human cloning or human germline modification on grounds that they are,

- Contrary to universally held principles of human ethics
- Harmful to the social and moral fabric of civil society
- Misguided by the flawed science of genetic determinism
- Based on flawed technologies that inflict unacceptable dangers on individuals and the human species.

2. We reject 'therapeutic' human cloning because it involves the deliberate creation of human embryos for the sole purpose of providing embryonic stem cells, the embryos being sacrificed in the process. This deliberate creation and destruction of human life makes it even more objectionable, in moral terms, than reproductive human cloning. It, too, is misguided by flawed and incomplete scientific knowledge and inflicts unacceptable dangers through flawed technologies.

3. We reject human embryonic stem cell research because embryonic stem cells are already known to be associated with many problems including malignant transformation. The recent disaster involving five Parkinson's patients receiving fetal cell transplants should serve as a grave warning of the dangers inherent to the technology (*The Guardian* March 13, 2001). Furthermore, adult stem cells are showing much greater promise in replacement therapy, and there is thus no need at all for embryonic stem cells for therapeutic purposes.

4. We oppose patents associated with human cell lines and genes, and call for publicly-funded research to focus on therapeutic methods that do not involve patented procedures cell lines or genes.

Our detailed arguments are contained in the following articles enclosed:

1. The unnecessary evil of 'therapeutic' human cloning. By Mae-Wan Ho and Joe Cummins, ISIS News 7/8, Feb. 2001 <www.i-sis.org>
2. Why clone at all? By Mae-Wan Ho ISIS Report April. 2001 <www.i-sis.org>
3. Human embryo research not needed. By Mae-Wan Ho, ISIS News 7/8, Feb. 2001 <www.i-sis.org>

First GM humans already created. By Joe Cummins and Mae-Wan Ho, ISIS Report, 2 May 2001 www.i-sis.org

Royal Society Soft Selling GM Animals

*The UK Royal Society Report on GM animals is supposed to consider scientific evidence. Instead, it takes a permissive, verging on partisan stance. It dismisses all evidence of hazards and argues for more public funds to support research repugnant to the vast majority of civil society, and not in the public interest. **Dr. Mae-Wan Ho** takes the Report apart.*

"Medical research needs more GM animals", the Royal Society says [1]. "Genetically modified animals are essential for medical research and will also play a crucial role in the battle against

diseases such as foot and mouth". These sweeping claims come from a Report produced by a working group chaired by highly respected animal behaviourist, Professor Patrick Bateson, Vice-President of the Royal Society. Bateson offended the pro fox-hunt lobby a few years back by stating what most people would think obvious: that the hunted animals do suffer. So, when Prof. Bateson comes out in support of GM animals, one sits up and listens.

The Report claims to be "primarily about the scientific issues". While it does not totally ignore the moral aspects or the wider issues, it is "the importance of informing such debate with sound scientific evidence" that the Society wishes to stress. But it is precisely on sound scientific evidence that the Report falls down so badly. For the most part, it reads like an apology, and worse, a soft sell for practically all the uses and abuses of GM animal technology.

The tone of the Report is set right at the beginning. The legal definition of a genetically modified organism, according to the Internationl Biosafety Protocol negotiated in Montreal Jan. 2000, is "an organism whose genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination of genes". The definition is the result of at least 6 years' deliberation and debate among the top international scientific and legal experts, and hence not to be treated lightly. But the Royal Society opines, "even though this definition seeks to draw a sharp distinction between artificial and natural processes, mutation of specific genes occurs spontaneously under natural conditions." (p.3)

The attempt to blur the distinction between GM and non GM continues two pages on: "Three common mutagenic techniques may be used to produce random genetic changes: exposure to radiation, chemicals or viruses." Nowhere is the reader told that viral transformation is one of the main techniques for making GM animals. In fact, the Report is very short on details as to how animals are genetically modified with viral and other vectors, and on the GM constructs delivered into animals. Nor does it make clear that there are major problems and serious safety concerns inherent to GM technology, for animals as for plants.

The Report hardly refers to problems such as the uncontrollable randomness of GM inserts, the instability of GM constructs and gene transfer vectors and the instability of transgenic lines, all of which make quality control of GMOs and their products well nigh impossible. Also dismissed and underplayed are the dangers of horizontal gene transfer and recombination in creating new viruses and in causing harmful mutations and cancers by random insertion into the genome of cells. Instead, it conveys the impression that GM animal technology is well tried and reliable. "The first GM animal, a mouse, was made in the early 1980s and this technology has been successfully applied to most animals, including cattle, pigs and sheep, poultry, fish and also *Drosophila* and other insects." (p.6) Only in the final paragraph of this Section is there any mention of the "relative inefficiency of the techniques" and "high death rates of fetuses during development".

Professor Bateson, interviewed in *The Guardian*, said that there are already herds of GM animals producing pharmaceutical proteins. For years, I have challenged the biotech companies and other scientists to produce molecular data documenting the genetic stability of transgenic lines, and no one has come up with any. Belgian government scientists have now taken this seriously, and have analysed Monsanto's GM Roundup Ready soya (see "Scrambled genome of RR soya", this issue). They found the GM construct scrambled up, the plant genome at the site of insertion also scrambled up, and a large fragment of unknown origin has got in as well. All this is very different from the original data submitted by Monsanto. They suggested, without evidence, that all the scrambling had occurred on insertion, in which case, Monsanto must have got it wrong. If not, then there must have been scrambling since.

In his interview, Bateson also dismissed the dangers of horizontal gene transfer on grounds that it is a natural process. Indeed it is, but the constructs used in genetic modification technology are anything but natural. They are optimised for horizontal gene transfer: they are made by combining sequences from widely diverse sources of bacteria, viruses, plasmids and transposons and hence possess homologies to all those agents found in the environment. Homology increases the frequency of recombination up 10 million times or more (see "More Horizontal Gene Transfer Happens", this issue). GM constructs are new combinations of genes, almost none of which has previously existed in billions of years of evolution. The transfer of GM constructs, whether horizontal or vertical, cannot therefore, be considered natural. And, on account of the predominantly bacterial and viral origins of the genetic material in GM constructs, they have the potential to generate new bacterial and viral pathogens by recombination.

The Report states, "Despite the daily consumption of non-GM DNA from food in the diet, no evidence exists for the transfer of intact animal genes into humans from the food chain." One reason for this lack of evidence is that no one has investigated the fate of DNA in human beings. Researchers have found that when mice were fed viral and plasmid DNA large gene-size

fragments passed out in the faeces. Fragments were found incorporated into blood cells, liver and spleen cells, and even cells of the foetus and the newborn. These results are well known in the GM debate [2], but the Society's Report did not cite them. "GM DNA is no more or no less a hazard to humans than any other form of dietary DNA and the probability of functional gene transfer to humans via the food from a GM animal is remote." (p.20). Is this 'sound science'? Does the Society not know that GM DNA is specifically designed to jump into genomes and to cross species barriers? That we don't need a functional gene transfer to wreak havoc in the cell's genome? A small motif in a promoter sequence may be all that is needed to dramatically alter the expression of host genes.

The Royal Society has not taken all evidence into account. A national enquiry into human gene therapy was sparked off in the United States by the death of a healthy teenager in a clinical trial in 1999. A report released recently by the National Institutes of Health documents the overwhelming failures as well as the dangers from the vectors used. These gene transfer vectors are very similar to those used in GM animals, and one main problem identified is the generation of new viruses by recombination. Another problem is cancer due to uncontrollable random gene insertion into the genome (See "Gene therapy oversold by scientists who disregard risks", this issue).

The Report goes through the list of applications, both actual and potential in some detail. By far the biggest use of GM animals is in medical research, "to create models of human disease and help elucidate disease pathways and allow assessment of new therapies." However, too many models do not give the same disease symptoms as in human beings. "While most mammals may share similar biochemical pathways, it is clear that many physiological processes are different. Thus, it is unlikely and indeed unrealistic to expect every animal model to capture completely all aspects of a human disease." Is that a reason for not using GM animals then? Not at all, according to the Royal Society, even bad models reveal previously unknown pathways.

According to Craig Venter, there are some 30 000 genes in the human genome. This gives at least 60 000 transgenic mice lines, one for 'knock-out' and the other one for 'knock-in', and that's not counting lines containing one of the hundreds of possible variants for every gene, and lines containing multiple gene variants to investigate gene interactions. In order to investigate the effect of different genetic backgrounds, transgenic mice lines containing the same human gene variants have to be created in different inbred mice. The possibilities are mind-boggling. Transgenic mice alone could proliferate until they take over entire animal facilities, and whole Departments not doing transgenic research would have to be closed down to make room for more. If you think I am exaggerating, the Society reports that the use of animals in biomedical research was down 1% from 1998 figures, but GM animals were up 14%, most of them transgenic mice. And it will continue to rise, the Society says, "as the benefits from genetic modification research cannot be realised unless genetic modification research grows." This is the abysmal science of the lack of imagination, let alone the lack of consideration of animal welfare.

Another use of GM animals is as bio-reactors, to produce "substances of benefit to humans" in their milk or other tissues. The Society is coy about the 'other tissues', which happens to be blood, urine and semen. Can this be acceptable in terms of animal welfare? The Society thinks so. Many proteins, such as blood-clotting factors and antibodies, can be formed only in the cells of complex animals. Would cell culture not do? No, proteins such as human albumin, are required on a scale that would not be feasible with cell cultures, and extracting material from human tissues is fraught with danger because of possible contamination with viruses. But the danger of viral contamination is equally great, if not greater, with animals. Benign viruses belonging to one species often become virulent in another. Similarly, endogenous viruses, dormant in their host species, often become infectious in other species, a phenomenon known as xenotropism, a danger already widely recognized in xenotransplantation. The Society is in favour of xeno-transplantation too, despite the fact that many scientists are calling for a ban for fear of viral pandemics [3].

The Society lists many potential benefits of GM animals in agriculture: disease resistance and "desirable alterations in growth rates or feed conversion efficiency, make leaner meat, and enhance anti-microbial properties of milk for newborn animals". Especially good for the Third World, but further research is needed. And it must involve public/private partnership to overcome restrictions of "patent and licensing agreements". "GM insects that carry human disease [sic]", "so that they are incapable of transmitting the disease"? Here, at least the Society has finally taken on board transgenic instability and the dangers of using broad host-range transposons as vectors. But it is still happy for further research and releases to go ahead.

It is only when it comes to GM fish that the Society holds back. Its sister organisation, the Royal Society of Canada, has concluded in their report that "if GM fish escaped, the consequences for wild stocks and the environment would be uncertain. The effectiveness of attempting to render GM fish sterile is also uncertain." Therefore, RS Canada recommended a moratorium on rearing GM fish in marine pens and suggested that approval for commercial production should be conditional on rearing in land-locked facilities. The Royal Society of London endorses all those recommendations, thank goodness.

After weighing up the potential benefits and costs, taking into account animal welfare and safety, "The Royal Society believes that some concerns about animal welfare and food safety aspects of food animal biotechnology are justified." More information and more research, especially on animal welfare are needed. Although, it sees "no qualitative distinction", in terms of welfare, "between genetic modification using modern genetic modification technology and modification produced by artificial selection, chemicals or radiation. Indeed, the targeted character of modern genetic technology may provide fewer welfare problems than the older techniques."

The Society concludes, on practically no evidence whatsoever, that "the development of GM animals has been hugely beneficial in many areas, not least into research on the causes and possible treatments of disease. It also has the potential to bring about other benefits, but serious concerns remain about welfare and health and safety issues that need to be addressed if these are to be realised."

But what the Report really wants to achieve is this: "Continued research on the welfare and uses of GM animals, *funded in part from public sources*, and with the results made openly available, is essential if these uncertainties are to be properly addressed and the risks understood."

In plain language, the Royal Society is going along with the corporate agenda for practically all the uses and abuses of GM animal. It is condoning the secrecy with which GM animal research, as indeed all GM research is conducted by the industry. It is condoning the privatisation of life and knowledge, and worse, using that as an excuse for squandering yet more public money to support research repugnant to the vast majority of civil society and not in the public interest. The Royal Society may be an independent organisation but it is acting more like a spokesperson for the industry [4].

Animal research in the destructive, mechanistic tradition has long outlived its usefulness [5] (see also "Animal Experiments Worse Than Useless" this issue). The Royal Society ought to be taking the lead in promoting novel, noninvasive, nondestructive techniques that are more humane and more informative as well [6].

1. Royal Society press release on GM animals , 21 May 2001, launching Royal Society Report, "The use of genetically modified animals", science.policy@royalsoc.ac.uk
2. See Ho, M.W. (2000) Horizontal gene transfer. Hidden hazards of genetic engineering. ISIS Report www.i-sis.org
3. See Ho, M.W. and Cummins, J. (2000). Xenotransplantation. How bad science and big business puts the world at risk from viral pandemics. ISIS Sustainable Science Audit 2, August 2000; also August 2000 www.i-sis.org; also Third World Resurgence 127/128,46-55.
4. "The new thought police. Suppression of scientific dissent" by Mae-Wan Ho and Jonathan Mathew, *ISIS News* 7/8, Feb. 2001 February 2001, ISSN: 1474-1547 (print) ISSN: 1474-1814 (online) www.i-sis.org
5. See Fox, M. *Beyond Evolution*, The Lyons Press, New York, 1999, ISBN 1-55821-901-3
6. See Ho, M.W. (1993,1998). *The Rainbow and the Worm, The Physics of Organisms*, World Scientific, Singapore.

The Human Genome Is A Big White Elephant

Dr. Mae-Wan Ho *argues that the massive divestment of public research funding into health genomics is aimed at bailing out an industry already in trouble over GM crops, and in danger of being driven to bankruptcy by the human genome. The real disaster, however, will fall on public health. It prevents scientists and civil society from addressing the real causes of ill health, which are overwhelmingly social and environmental, and will end up victimizing those most in need of care and treatment.*

The human genome may go down in history as the biggest white elephant for humanity. It cost a lot and is useless, it does not work, and is so expensive to maintain and grows so big so fast that it will bankrupt the industry as well as entire nations. The only clear message in the 'book of life' is "there is no one home, life is not to be found here".

I started my career in human biochemical genetics, studying genuine genetic diseases that could be attributed to mutations in single genes. These account for no more than 2% of all

human ailments. But diagnosing and curing rare single gene defects "did not fit the business model". So, 'genetic defects' and 'gene therapy' expanded in recent years to include the far more common and potentially highly profitable diseases such as cancer, heart disease, AIDS, Alzheimer's and Parkinson's. Francis Collins, head of the public human genome consortium, runs a laboratory in the US National Institutes of Health. He is now engaged in a "huge and very complicated" search for genes for adult-onset diabetes. Adult-onset diabetes, like asthma and cancer has reached epidemic proportions over the years, increasing from 4.9% in 1990 to 6.5% in 1998, in both sexes, across all ages, ethnic groups, education levels, and in nearly all states in the United States. That should have alerted all rational scientists to look for environmental causes instead of genes.

The public has paid out billions of dollars in the United States and hundreds of millions of pounds in the United Kingdom for what Jim Watson promised to be the blueprint for making a human being. Now, dozens of genome sequences later, the sequencers haven't a clue of how to make the smallest bacterium or the simplest worm, let alone a human being. The human genome may consist of up to 98.9% 'junk DNA' with no known function. Geneticists are baffled. "The genome isn't a code, and we can't read it."

Public investment was needed to keep the human genome in the public domain, we were told. But that had not prevented any human gene from being patented. On the contrary, scientists funded by the public have been busy patenting genes and starting up private companies, with little or no return to the public coffers. Now, the elephant attendants are saying the human genome needs more money before it can deliver the goods. The UK Government is obligingly giving away £2.5 billion over the next four years to 'health genomics', to identify all the genes that predispose the UK population to disease. The elephant is growing big fast.

Such massive divestments of public funds are designed to bail out the biotech industry already in trouble over GM crops, and now showing every sign of being driven bankrupt by the human genome. But the real disaster will fall on public health. It is narrowing the options for healthcare and foreclosing other promising approaches. Health genomics is a major diversion and obstruction, and is preventing us from addressing the overwhelming environmental and social causes of ill-health. It will also victimise those most in need of care and treatment. It is "a scientific and financial black hole", a colossal waste of scientific imagination and financial resources.

In many respects, health genomics epitomises the failures of reductionist medicine, which have reached crisis proportions. Drug and antibiotic resistant infectious diseases have come back with a vengeance within the past 25 years. Infectious diseases are responsible for one-quarter of the 53.9 million deaths in the world, second to cardiovascular disease. For poor countries and children under five, however, infectious diseases top the list, accounting respectively for 45% and 63% of deaths. Among the factors blamed are the overuse and abuse of antibiotics, destruction of the environment, poverty, mal-nutrition and increase in air travel, all of which serves to remind us that disease cannot be understood in reductionist terms. One likely contributing factor that has yet to be named by the scientific establishment is the rise of commercial genetic engineering within the same period. Genetic engineering, in agriculture as in medicine, uses the same tools and makes the same kinds of artificial constructs, all of which enhance horizontal gene transfer and recombination, precisely the processes that create new pathogens and spread drug and antibiotic resistance genes.

The other big killers are cardiovascular disease, which tops the list at 31%, and cancer at 13%, after infectious diseases. Both cardiovascular disease and cancer are predominantly illnesses of rich industrialized nations. Cancers are linked to ionizing radiation and to the hundreds of actual and potential carcinogens among the industrial and agricultural chemicals polluting our air, water and soil. Environmental influences clearly swamp out even large genetic differences.

Health genomics research will do nothing to identify or remove the causes of cancer. Instead, it will identify all the genes that supposedly 'predispose' the victims to cancers, to enable corporations that have made lots of money polluting the environment with carcinogens to make lots more money selling diagnostic tests and 'miracle cures'. Patients are bankable assets, and terminal cancer patients all the more so.

The disease statistics are bad enough. But the cures may be far worse. Successive studies have documented a rising epidemic of iatrogenic diseases, ie, diseases caused by medical treatments, interventions and drugs. Doctors are now the third leading cause of death in the US, responsible for some 250 000 every year, among which are 106 000 due to non-error negative effects of drugs. The problem is not confined to the US, it is endemic in all industrialised countries that adhere to the same reductionist model of health and disease: Canada, Australia, New Zealand and Britain. We can already see the tip of the iceberg in the new classes of iatrogenic diseases that

'health genomics' will bring. Clinical trials of 'gene therapy' have killed six and caused more than 650 adverse events. The 'miracle cure' for Parkinson's turned into an irredeemable nightmare because the cells from foetuses transplanted into five patients' brains grew uncontrollably. And watch out for viral pandemics if xenotransplantation is to go ahead.

A sweeping paradigm change is long overdue. The human genome, like the genome of any other organism, is fluid and dynamic. Genes function organically, in entangled networks that respond from moment to moment to the changing context of the whole organism in its ecosystem. They are not mechanical elements operating in fixed circuit boards. Let me give a few recent examples of how genes, genomes and organisms respond organically to their environment, demanding a radical rethink of the conventional approach.

Many bacteria are now found to change reversibly from a benign, non-proliferative phase to a pathogenic, proliferative phase, depending on ecological conditions. Some scientists are now rethinking the failed conventional model of killing pathogens with new, ever more deadly antibiotics as bacteria become resistant to the old ones. They are designing drugs that physiologically tame the bacteria, rather than kill them. A logical extension of that approach is to find how ecological balance could be achieved, so bacteria do not become virulent.

The dominant reductionist model of cancer says cancer is caused by mutations in specific cancer genes and cancer-suppressing genes. There is growing evidence that those gene mutations are neither necessary nor sufficient for cancer to develop. Every cancer has a different genetic signature. In fact, every cancerous growth in an individual differs in genetic signature. The cancerous state is a physiological response of the cell to its environment, which is ultimately the whole organism in its ecological context. Cancer is associated with gross genetic instability that gives rise to large genomic abnormalities. Cancer cures based on single molecular interventions offered by health genomics will therefore be largely irrelevant and ineffective. The emphasis must be prevention rather than cure. The phenomenon of spontaneous cancer remission should also be much more thoroughly investigated. Remissions can occur after various experiences that affect the whole body, such as fever, a change of diet or change of life-style.

There has been a large number of observations suggesting that genes in bacteria and other organisms can mutate in response to environmental challenges, so as to enable them to survive. There is evidence that defective genes in human beings can also regain function by mutation. Cells in the body of some individuals born with defective genes have been found to revert spontaneously to functional states. Thus, rather than persist in futile and dangerous attempts at 'gene therapy', substantial effort ought to be redirected towards elucidating the physiological and environmental conditions that can encourage the body to mend its own defective genes.

We have had decades, if not centuries, of reductionist, mechanistic science that has given us a surfeit of knowledge of the parts, not all of which has been put to good, sustainable use. Now is the time to complement this knowledge of the parts with investigations aimed at knowledge of the organic whole that can truly bring health and well being to the community. In particular, I propose that we target at least part of our research budget to the following areas which are currently either grossly under-funded, or not funded at all.

1. Ecology and Energy Use in Sustainable Systems

- To investigate the precise role of complexity and biodiversity
- To elucidate energy-relationships, energy use, renewable energies
- To identify biophysical indicators of ecosystem health
- To develop non-invasive, non-destructive technologies for monitoring and regulating environmental quality

2. Science of the Organism and Holistic Health

- To articulate a concept of an organic whole as the basis of health
- To identify biophysical and dynamical indicators of health
- To develop non-invasive, non-destructive technologies for monitoring health and for quality control of food and other agricultural produce
- To develop effective therapeutic methods based on minimum intervention.

3. Working Science Partnerships

- To enable scientists to work directly with local communities
- To revitalise and protect traditional agricultural and healthcare systems from biopiracy and globalisation
- To develop appropriate sciences and technologies

4. Science and Technology Monitor

- To monitor new developments for social/ecological account
- ability and safety
- To promote critical public understanding
- To promote science-public dialogue and public participation

(For complete version with references, see ISIS website www.i-sis.org)

Investing in Healthcare or the Health market?

Are we getting value for our tax money in biomedical research? ***Nick Papadimitriou*** *exposes how the UK Medical Research Council is squandering our tax money to help corporations cash in on the health market.*

The Medical Research Council (MRC) in the UK is responsible for dispensing tax payer's money to fund biomedical research, both in its own research facilities and in select university laboratories.

Back in 1998, a Biotechnology Exploitation Group (BEG) was established by the Department of Trade and Industry (DTI) to maximise the economic potential of biotechnology [1]. As the Research Councils are responsible to the Office of Science and Technology, which has been placed by successive governments within the DTI, it was hardly surprising that MRC should devote itself to servicing the needs of the pharmaceutical industry. To this end, MRC has been siphoning off huge sums of public money into establishing a strong research base for biotechnology and instituting a host of mechanisms to commercialise research results. The division of MRC Technology [MRCT] was set up specifically to offer research methods and products to prospective partners eager to muscle in on a world market estimated to be worth $500bn over the next three years [2]. MRC labs and expertise have been given over entirely to developing a new generation of genetic medicines. A DTI funded programme and magazine, *Biotech Means Business*, dating from 1998, anticipated that by 2000, UK revenue from biotechnology would be £9bn [3].

MRC's strategic plan for 1999-2003 [4] was to "encourage knowledge transfer, commercial exploitation and provision of scientific advice for the benefit of national wealth and health." Note how 'health' comes after 'wealth' in MRC's national priorities. "Investors are looking at the MRC…to see what research there is that could provide the basis for new biotech companies" said Sir George Rada [5]. However, decades of investment and research in biotechnology resulted in just *twenty* genetically modified medicines hitting the market [6].

Anticipating the new growth-industry of bio-informatics on the heels of the Human Genome Project [HGP], MRC is increasing the number of grants for training places in the field [7]. It has already invested more than £150m over the past three years into HGP [8], and a further £120m was allocated last year to building new synchrotron facilities for studying proteins [9].

MRC places great emphasis on the development of patents and licensing portfolios. It has set up a special UK Medical Ventures Fund with a current holding of £40m, and an MRC owned company, Medical Ventures Management [MVM LTD], to facilitate the establishment of 'spin-out' and 'start-up' companies [10].

For example, Celltech Group was founded in 1980 to develop and exploit MRC research findings. Mergers with Chiroscience and Medeva over the past two years turned Celltech into one of Europe's biggest biotech consortium. Celltech's activities are wide, and include gene therapy and cancer treatments. Patent licensing also provides strong revenues.

Another company doing well out of publicly funded research is AERES Biomedical Ltd, launched in February 2000. It arose out of MRC's Collaborative Centre (MRCCC), which was a precursor of MRC Technology. The Antibody Engineering Group, one of the core groups at MRCCC, was set up in to develop and exploit the new technologies of CDR-grafting, invented at the MRC laboratory of Molecular Biology by Dr. Greg Winter in 1988, and patented by the MRC under the 'Winter' patent. AERES was created to develop and commercialise the invention. Working with business partners, AERES has 'humanised' 20 mouse antibodies. Six therapeutic anti-bodies have already gone into clinical trials [11].

Last year, MRC increased its licensing and patents income by selling off another company, Cambridge Antibody Technologies (CAT). Like other companies evolving out of MRC research, CAT is largely privately owned though MRC retains an interest, partly through shares, partly through income generated in the first place.

For MRC, income from patents has increased from 3m in 1999 to 7.6 in 2000. In comparison, Celltech is floating on the stock market with a capital rating of £3.229bn, while CAT's market value is £1.38 bn [12].

MRCT advertise "Licensing Opportunities" on their website. These include items such as "Porcine Endogenous Retrovirus Typing" (a patented method of determining which particular PERV

virus is active in xenotransplantation attempts). Markers for Major Affective Disorders, collaborative research into transgenics and so on [13]. Nowhere will you see on MRCT's website any indication of research in Environmental Medicine or Nutrition. In fact, both areas were part of MRC's research profile as recently as 1998, but have been handed over to other bodies since. At the time of their discontinuation [1998-99] Environment and Nutrition *combined* received £10m out of a total annual budget of more than £250m [14]. This is a paltry sum, and especially so when compared to spending in all areas relating to genetics and rapidly expanding genomics (see below). There is no funding for research into holistic health or complementary medical research at all.

MRC has worked closely with industry to build an infrastructure to exploit the next wave of genetic medicines. Celltech and CAT are the flagship companies, and MRC is receiving increasing funding from Government. On the back of New Labour's ascent to power in 1997, a Comprehensive Spending Review (CSR) awarded an additional £90m to MRC over three years, and another, more recent, CSR has led to a further increase of £89m over the coming three years [15]. As a consequence, MRC investment in biotech has exceeded any reasonable outlay for such an uncertain venture.

The interests of the drug giants are well represented in MRC. The Molecular and Cellular Medicine Board includes a representative from Aventis Pharmaceuticals. The Neurosciences and Mental Health Board includes Dr J Hunter from SmithKline Beecham. The biotech company Zeneca has Dr I Kimber in the Department of Toxicology. George Poste, Chief Science and Technical Advisor at SmithKline Beecham was, until recently, a member of MRC's Strategy Development Group [16].

Last November, MRC pledged £1.9bn over the next four years to help finance and exploit the findings of HGP in 'health genomics'. This is in addition to the £675m already earmarked for constructing high tech facilities to study genes and proteins. As part of the £1.9 billion package for 'health genomics', a Population Biomedical Collection will be established by the Wellcome Trust, a charity, in collaboration with the Departments of Health. The MRC's contribution to that project will be approximately £20m [17].

Sir George Radda, speaking for the MRC, assures us that, working out the functions of genes is " the key to designing new approaches to detecting illness early and to preventing and treating diseases. "The Collection promises to be one of the most exciting scientific initiatives of recent times" he said, "It could deliver benefits for the health of many generations to come". The study will, in the first instance, involve half a million volunteers donating blood samples from which their DNA would be extracted. The same volunteers will provide lifestyle information to the researchers. Over a period of years, this information would be tracked against their medical records. A small number of regional centres across the UK will be set up to recruit volunteers, with the overall study centrally managed and co-ordinated.

These studies have already raised concerns over the invasion of privacy and the erosion of civil rights. The database can fall into the hands of a private company and its contents sold to subscribers. Critics have call these studies "seriously misplaced", as they are based on the assumption that genes are what makes us tick, ignoring complex interactions between genes and the environment [18], except in so far as individual 'lifestyle' is being taken into account. They run the risk of marginalising and victimising those most in need of care and treatment.

The overwhelming causes of ill health are environmental and social. The health of nations will be infinitely better served by devoting resources to disease prevention, not just by advocating healthy lifestyles, but to phasing out the hundreds of known carcinogens and systemic poisons among industrial and agricultural chemicals. At the same time, we need to diversify public research efforts, especially into areas that do not result in expensive patented medicines and treatments, such as environmental and holistic health-care.

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Taking Science Seriously in the GM Debate

Dr. Mae-Wan Ho *summed up the state of the GM debate when she was invited to present evidence in a Workshop on Agricultural Bio-technology, Health, and the Environment, organised by the US National Academy of Science, 16 April 2001.*

Science in crisis

If there is one thing that distinguishes the Third World from the industrialised countries, it is that they take science a lot more seriously than we do in the GM debate.

I was researcher and university lecturer of genetics throughout the mid-1970s to the early1980s when new discoveries on the fluid genome made headlines every week. Researchers back then were building a new paradigm, dispelling once and for all the notion that a gene is constant and independent of context. The thought that a gene could be patented as an invention probably never crossed their mind. And if it did, they would have dismissed it as a joke. Craig Venter of Celera may have only just discovered that genetic determinism cannot deliver the goods after he's sequenced the human genome. But many of us knew that genetic determinism had died with the revelations of the fluid genome, if not before [1]. And now, almost two decades later, science is in crisis in more ways than one.

The paradigm change that should have occurred, did not. On the contrary, the scientific establishment remained strongly wedded to genetic determinism, which has misguided genetic engineering, making even the most unethical applications appear compelling, such as 'therapeutic' human cloning, for one [2]. Bioethics became a contradiction in terms as rampant commercialisation of science took hold.

Since the 1980s, preoccupation with patenting and start-up companies has compromised the quality of molecular genetics research, stifling basic science and innovation, and failing to serve the public good. Worse still, many scientists are consciously or unconsciously ignoring scientific evidence of the hazards. I got involved in the genetic engineering debate in 1994, to try to inform our policymakers and the public, and to start debate and discussion from within the scientific community.

For the past seven years, I have had to follow developments in genetic engineering science much more carefully and extensively than many of the practitioners, only to find that all my fears concerning the problems and dangers of genetic engineering are being confirmed. I shall highlight some of these before going to discuss what needs to be done.

Genetic engineering superviruses

The top news in the Jan. 13 issue of the *New Scientist* [3] was on a deadly virus created accidentally by researchers in Canberra Australia, who were trying to genetic engineer a contraceptive vaccine for mice [4]. They spliced a gene for the protein interleukin-4 (IL-4) into a relatively harmless mousepox virus in the hope that IL-4 would boost the immune system. When they injected the recombinant virus into mice belonging to a strain genetically resistant to mouse-pox virus, all the mice died. IL-4 suppressed both natural killer cells and cytotoxic lymphocytes responses to viral infection. The recombinant virus also killed 50% of the genetically resistant mice that were immunized against mouse-pox virus.

That is not all. The IL-4 gene, spliced into the vaccinia virus, was found to delay clearance of the virus from experimental animals, and to undermine the animals' anti-viral defence [5,6]. Vaccinia and mouse-pox both belong to the family that contains the human smallpox virus, raising the spectre of biological warfare. But the far greater danger lies in the unintentional creation of deadly pathogens in the course of apparently innocent genetic engineering experiments. Some scientists are already creating viruses deliberately in their laboratories, just to show it could be done, or in the course of cloning existing viruses [7]. And dangerous recombinant viruses and bacteria may also be inadvertently created in making vaccines against AIDS, as Yugoslav virologist Veljkovic has been warning since 1990 [8].

The *New Scientist* editorial [9] accompanying the report remarked that five years ago, when biomedical researchers were asked if genetic engineering could create “a virus or bacteria more virulent than nature’s worst”, they replied it would be “difficult if not impossible”.

Some of us have been warning of ‘accidents’ such as this for at least the past six years. The basic tools of genetic engineering are bacteria, viruses and other genetic parasites that cause diseases and spread drug and antibiotic resistance. All that fall into the hands of genetic engineers are exploited. Genes from dangerous agents, including antibiotic resistance genes, are profusely mixed and matched, or recombined. As every geneticist should know, recombination of genetic material is one of the main routes to creating new strains of bacteria and viruses, some of which may be pathogens. (The other route is mutation.) Moreover, the predominant orientation of genetic engineering in the past two decades has been to design artificial GM constructs and vectors that cross species barriers and invade genomes, both of which will enhance horizontal gene transfer and further increase the chance for recombination.

We published a detailed review on the possible links between genetic engineering and the recent resurgence of drug and antibiotic resistant infectious diseases in 1998 [10]. We were by no means the first. Those who pioneered genetic engineering declared a moratorium in Asilomar in the mid- 1970s precisely because they were concerned about this dire possibility. Unfortunately, overwhelming pressures for commercial exploitation cut the moratorium short. The scientists set up guidelines, based largely on assumptions that have all fallen by the wayside as the result of new scientific findings. The two most important findings are the persistence of nucleic acids in all environments including the gut of animals, and the ease with which nucleic acids can get into all cells, especially those of human beings, as shown in so-called gene therapy research [11].

Instead of tightening the guidelines, our regulators have relaxed them. Transgenic wastes are being recycled as food, feed, fertilizer and landfills under the current EC Directive on Contained Use [12], and I would not be surprised if this applies also in the US. There is a lesson to be learned from the 650 or more adverse reactions associated with gene therapy trials, including several deaths. The same kinds of constructs are made, whether it is to genetic engineer human beings or plants and animals, and the same crude first generation technology is used.

The instability of transgenic lines

The instability of transgenic lines has been well known since 1994, particularly in connection with gene silencing. This not only affects agronomic performance, but also safety. We have drawn attention to the *structural* instability of GM constructs in general, which may enhance horizontal gene transfer and recombination, especially because the cauliflower mosaic virus (CaMV) 35S promoter, present in practically all GM crops already commercialized or undergoing field trials, actually has a recombination hotspot. We raised our concerns in a series of scientific papers [13 - 16].

In the course of debating with plant molecular geneticists in UK's top research institute, the John Innes Centre (JIC), we discovered that the CaMV 35S promoter is active, not only in all plants, bacteria, algae and yeast, but also in animal and human cells [17,18]. None of our critics was aware that the promoter is active in human cells, including a molecular geneticist on the UK Agriculture & Environmental Biotechnology Commission set up to oversee our farmscale field trials [19].

This year, researchers in JIC admitted in their annual report that GM crops are unstable and prone to recombination. But when we pointed this out [20], they issued a strong denial, and accused us of ignoring one of their papers where they claim to have demonstrated that transgenic rice lines are stable. I have since reviewed that paper in detail [21] and concluded, “A generous interpretation of the data presented would suggest that 7 out of 40 (18%) transgenic rice lines may be stable to the R3 generation.” In other words, at least 82% of the lines are unstable. That paper is not at all exceptional in making claims in the abstract, and often in the title, which are not supported by the evidence presented [22]. No reply has yet come from the JIC since. My colleague, Prof. Joe Cummins has summarised more up-to-date literature showing that all GM crops may be unstable [23].

Roundup Ready soya has consistently performed less well than non GM soya over the years, and this year's seeds are experiencing problems in germination, according to a report from the University of Missouri [24].

Terminator crops at large

Last December, I was asked to act as expert witness in defence of citizens who have taken civil action against GM crops which they strongly believe to be a threat to health and biodiversity.

Among the crops were GM oilseed rape varieties used to produce F1 hybrids belonging to AgrEvo UK (now Aventis). At the time, I was also preparing a joint submission, with two other scientists, to the consultation document, "Guidance on Best Practice in the Design of GM Crops" put out by the UK Government's Advisory Committee for Release to the Environment (ACRE). One of the main 'enabling technologies' for 'best practice' suggested in the document is precisely Agrevo's seed/pollen sterility system, for it prevents GM gene flow.

It soon dawned on us that the GM oilseed rape lines undergoing field trials in the UK are engineered with 'terminator technology' - so named by critics because it renders harvested seeds sterile - for no other reason than to enforce corporate patents on GM seeds. Not only that, according to AgrEvo's application, similar crops produced by the company Plant Genetic Systems (PGS), a subsidiary of AgrEvo, have been undergoing field-trials in Europe since the beginning of 1990.

In the US, similar male sterile lines engineered with the 'terminator-gene', barnase have been tested at least as early as 1992. There have been 115 field trials, the vast majority done without risk assessment, as the first environmental assessment came up with 'FONSI' - Finding of No Significant Impact. Crops modified for male sterility include rapeseed, corn, tobacco, cotton. Brassica oleracea, potato, poplar, chicory, petunia and lettuce. The USDA commercial release data include 4 crops with barnase: a corn and a canola by AgrEvo, a chicory by Bejo, and another corn by Plant Genetic Systems.

Separately, the other genetic component in terminator crops, site-specific recombinase, has also been engineered into corn and papaya, and there have been 14 field trials between 1994 and 1998, with no environmental impact assessment at all.

There are more than 150 US patents listing barnase or site-specific recombination or both, the oldest, on site-specific recombinase, going back to 1987.

The first terminator patents that came to public attention were those jointly owned by US Department of Agriculture and Delta and Pine Land Company, which Monsanto had intended to acquire. The novelty in those patents is the proposal to combine the terminator-gene system with the site-specific recombinase system, giving the company complete control over the hybrids as well as proprietary chemicals that control gene expression.

As a result of universal condemnation and rejection, Monsanto had announced it will not commercialise terminator crops, to everyone's relief. Research and development, however, have continued unabated. Everyone has assumed such crops only exist in theory, when they have been out there for more than 10 years.

It is no coincidence that simultaneous consultation went on in the United States on the USDA-Delta and Pine terminator patents. The USDA has since committed itself to commercial development of the technology, and, like the UK ACRE, also argued in its favour because it could prevent GM gene flow. But it cannot [24], because male sterile lines will be pollinated by non GM crops, and there is no way to prevent horizontal gene transfer.

On the contrary, the increased complication of the constructs may enhance horizontal gene transfer and recombination. The genes and gene products themselves are also known to be harmful. The terminator-gene barnase kills cells by breaking down RNA, an intermediate in the expression of all genes. The recombinase, in theory, breaks and rejoins DNA at specific sites, but is far from accurate and can scramble genomes. A male transgenic mouse engineered with only one copy of Cre recombinase was 100% sterile, because the recombinase enzyme managed to scramble the genomes of both daughter spermatids when they are still connected by a cytoplasmic bridge [25]. The mouse genome does not even have the *lox* sites recognised by the Cre recombinase.

Terminator insects give wings to genome invaders

The US Department of Agriculture has approved field release of GM pink bollworms this summer, made with a mobile genetic element, *piggyBac*, already known to jump many species. The element was first discovered in cell cultures of the cabbage looper, where it caused high mutations of the baculovirus infecting the cells, by jumping into the viral genome. In experiments in silkworms, researchers already found evidence that the inserts were unstable, and had a tendency to move again from one generation to the next [26].

"These artificial transposons are already aggressive genome invaders, and putting them into insects is to give them wings, as well as sharp mouthparts for efficient delivery to all plants and animals... The predictable result is rampant horizontal gene transfer and recombination across species barriers. The unpredictable unknown is what kinds of new deadly viruses might be

generated, and how many new cases of insertion mutagenesis and carcinogenesis they may bring…" [27].

"Food biotech is dead"

I have presented only a small fraction of the scientific findings indicating problems and dangers specific to genetic engineering, which both the practitioners and regulators are ignoring or dismissing. These and other concerns have persuaded more than 410 scientists from 55 countries around the world to sign an Open Letter to all Governments demanding a moratorium on environmental releases of GMOs because they are unsafe, and a ban on patenting life-forms and living processes because those patents are unethical. They also demand support for non-corporate, sustainable, organic agricultural methods that can truly bring food security and health for all (www.i-sis.org).

Since we launched the Open Letter two years ago, the terms of the GM debate have shifted. It is no longer a moratorium that is needed. GMOs, as currently made, are unsafe and unsustainable, as well as immoral. We must abandon GM crops and all other attempts to genetic engineer plants, animals and human beings with a technology that is widely acknowledged to be unreliable, uncontrollable and unpredictable.

Even the corporations are coming around to the view that "Food biotech is dead" [28]. One by one, Aventis, Monsanto and Syngenta have announced they will concentrate on genomics and marker assisted conventional breeding. Though meanwhile, they are still forcing the world, especially the Third World to accept GM crops.

But the whole world is in revolt. The governments of Thailand and Sri Lanka, among others, have banned GM crops and GM imports. In Indonesia, armed guards had to be sent to protect Monsanto's shipment of cotton seeds, which have already been shown not to perform as well as the indigenous non GM variety [29]. In the Philippines, mass demonstrations are taking place against GMOs and the International Rice Research Institute (IRRI) by MASIPAG (Farmer Scientist Partnership for Development) and other ngos. They condemn IRRI for restructuring sound traditional practices over the past 40 years to make farmers dependent on chemical inputs produced by corporations, the same corporations that are now forcing GMOs on farmers with the help of IRRI [30]. People are demanding farmer's rights over the genetic resources in the collection and genebanks of IRRI and they renounce any form of IPR. Those sentiments are widely shared, not just all over the Third World, but in Europe and the United States.

The organic revolution

Europe is fed up with the intensive corporate agriculture that has brought BSE and the food and mouth epidemic now threatening to get out of control, and is going organic in earnest. The annual growth rate in organic agriculture in Europe from 1989 to 1999 averaged 25%, which, extrapolated forward, would lead to 10% of Western European agriculture being organic by 2005, and 30% by 2010 [31]. The same is happening in the rest of the world. As scientists, we must take all evidence seriously.

Organic and sustainable agricultural practices and technologies are succeeding, documented in study after study, despite the appalling lack of research funding compared to the hundreds millions that have gone into biotech. At least 3% of the arable land, some 28.9m hectares in Africa, Asia and Latin America are already farmed sustainably, with impressive gains in crop yield as well as social, economic and health benefits [32]. Organic farming is also working well in the United States and Europe, with yields matching and even surpassing agrochemical agriculture. Organic farms are good for wild-life, supporting many more species of plants, songbirds butterflies spiders, earthworms [33]. We need organic farming for the world to feed itself and for the planet to regenerate and thrive.

Sustainable agriculture is also important for alleviating, if not reversing global warming. A new report shows that sustainable agriculture can contribute significantly, not only to reducing consumption of fossil fuel, but increasing sequestration of carbon in the soil [34].

Sustainable agriculture is predicated on a holistic, ecological perspective anathema to reductionist mechanistic science. Mechanistic science has been thoroughly discredited in the course of the 20th century. Mechanical physics went first of all with relativity and quantum physics. Biology was the last to go with the new genetics.

The new genetics is radically ecological, organic and holistic. That is why genetic engineering, at least in its current form, can never succeed. It is based on misconceptions that organisms are machines, and on a denial of the complexity and flexibility of the organic whole.

The challenge for western scientists is to develop a holistic science to help revitalise all kinds of non-corporate sustainable agriculture and holistic medicine that can truly bring food security and health to the world.

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Corporate Science Kills

As academic institutions are getting into an orgy of incestuous relationships with industry, scientists find themselves testing drugs they have invented, sitting on committees approving the drugs and holding financial stakes in companies that stand to profit from them. ***Dr. Mae-Wan Ho*** *reviews reports on how scientists in the growing ‘academic-industrial complex’ are endangering lives.*

“All over the planet, especially in the majority world to which I belong, crimes are being carried out in the name of scientific and technological progress. Yet every few months conferences like this come together and do little more than discuss their fashionably abstract theories..” [1].

That sums up the rot in our academic institutions. For decades, the scientific establishment has been blithely hiding behind the façade of ‘scientific objectivity’ to declare “there is no evidence of harm”, to allow corporations to poison people and our planet with impunity. It is now saying the same about genetically engineered crops and medicines. This time round, big money is eating away the soul of science itself.

Two years ago, teenager Jesse Gelsinger died in a gene therapy trial at the University of Pennsylvania. Government regulators cited the researchers for numerous safety violations. The scientist overseeing that trial and the medical centre had financial stake in the therapy tested. The public enquiry which followed concluded that gene therapy has been oversold by the scientists themselves [2].

But that was just the tip of the iceberg. Here’s a litany of misconducts that recently came to light [3].

Doctors at the Fred Hutchinson Cancer Research Centre allowed a cancer experiment to go on for years, even though patients were dying at a higher rate than with standard therapy.

At least 20 patients died from causes directly attributable to the treatment. The Centre and some of its physicians had financial stake in the treatment.

A University of Pittsburgh scientist funded by several drug companies was accused in a lawsuit of manipulating a study of children’s ear infections and contributing to the dangerous overuse of antibiotics.

The FDA reprimanded a Tufts University researcher for improperly treating a cancer patient with a gene therapy that may have caused his tumour to double in size. Both the scientist and a Boston medical centre held large stake in the company developing the treatment.

Society has long relied on publicly funded institutions and universities to research and develop drugs and therapies. But these traditionally independent institutions are teaming up with pharmaceutical and biotech companies and metamorphosing into a monstrous ‘academic-industrial complex’.

Academic-industry partnership is not new. In the United States, it goes back to the 1862 federal legislation that created the land-grant universities [4]. But the partnership developed at a greatly accelerated pace with the passage of the Bayh-Dole Act in 1980, which for the first time, allowed universities to patent the results of federally funded research [5]. The Business-Higher Education Forum, a coalition of corporate and academic leaders, and similar groups lobbied to get universities joined up with the marketplace.

Since then, the US Congress has passed numerous other laws to cement university-industry ties, including generous tax breaks for corporations investing in academic research. From 1980 to 1998, industry funding for academic research expanded at an annual rate of 8.1% , reaching $1.9billion in 1997, nearly 8 times the level 20 years ago. Before Bayh-Dole, universities produced roughly 250 patents a year, many never commercialised. But in 1999, more than 120 US research universities filed a total of 7,612 patent applications. Licenses to industry generated $641 million for the universities - and about $40 billion in economic activity overall.

Another factor driving academic institutions into the maws of big business is the cut in public research budgets, which enables corporations to buy up departments and whole institutions for new ideas and prestigious labour at bargain prices.

Postdoctoral fellows earn as little as $15,000 a year working, at times, round the clock. Projects in a university lab typically costs about half what it would at a drug company. And the public has greater faith in research at universities than in private labs.

The Swiss drug giant Novartis is paying $24 million over six years to the University of Maryland's Psychiatric Research Center for access to its brain tissue bank and one of its labs. Novartis came at the invitation of Dr. William T. Carpenter Jr., Director of the Psychiatric Research Center. Carpenter was faced with budget constraints standing in the way of understanding schizophrenia, and approached the company's researchers at a scientific meeting several years ago.

The University of California at Berkeley, similarly, had suffered decades of financial cutbacks when Novartis agreed in 1998 to pay $25 million to be allowed to sift through the research of the department of plant and microbial biology, and license up to about one-third of the research results. Along with that, the company gains the right to sit on a committee deciding on the research of the department.

The company also pays $20 million a year for some research at the Scripps Research Institute in California and over the past decade has paid up to $100 million for research at the Harvard-affiliated Dana Farber Cancer Institute.

Scientists at other institutions are uneasy of such close links to industry. Dr. E. Fuller Torrey, Director of the Stanley Foundation Research Programs in Rockville, says his group shares its collection of about 400 brains with researchers around the world. There's only one requirement: that all research be freely published. He is worried that deals like the one at the Psychiatric Center in Maryland is constricting research.

Many researchers collect consulting fees. The chief of psychiatry at Brown University medical school received more than $500,000 in fees from drug companies in 1998, much of it from the makers of antidepressants he praised in journals [3].

So many prominent academic researchers serve as paid industry consultants that the Food and Drug Administration, in need of expertise, has to allow them to sit on drug approval advisory committees. Sometimes, half the members of a panel will have a financial stake in the outcome, through ties to the drug manufacturer or a competitor.

Universities in the US still receive most of their money for research from the National Institutes of Health. But drug companies spend about $30 billion a year on drug research and development, and some of that goes to academic labs. Large drug companies spend up to one-fifth of their research dollars at universities; and small biotech companies may do half of their research on campus. At many universities, corporate grants are growing faster than federal support.

Johns Hopkins University has clung onto its independent status for the longest time. It passed up the chance to patent a DNA-testing method that was subsequently turned into a $100 million product by a Bethesda company, but not any more. Today, it is fast becoming one of the nation's most entrepreneurial universities.

Scientists at Johns Hopkins serve as paid consultants and scientific advisers to corporations. The university filed more patent applications in 1999 than all but two other major research centres. It helped launch 18 companies in recent years, and corporate-sponsored research at the medical school has nearly quadrupled in the past decade.

Johns Hopkins is taking a permissive attitude towards its scientists researching products on which they have financial stakes. For example, a senior scientist was allowed to test an

experimental vaccine developed by a company he co-founded. Tiny Magnetic Resonance Imaging devices were tested on humans by scientists who invented the devices, developed by a company that the scientists and Johns Hopkins partly own.

Dr. Bart Chernow, then vice dean of research at the medical school, proposed a business partnership to Craig Venter of Celera, the private company that sequenced the human genome, back in 1998. He boasted that Johns Hopkins was “one of the biggest biotech companies in the world”, and suggested that the school could supply Venter with blood and tissue samples from some of the 100,000 patients that Johns Hopkins scientists see each year.

“There is this supposed immorality in trying to patent genes and develop new medicines,” Chernow said, shaking his head. But Johns Hopkins, he said, had finally recognised that industry was not its adversary but its greatest ally.

On 19 July 2001, the US government ordered a suspension of all clinical trials in Johns Hopkins following the death of a previously healthy 24 year old volunteer in an asthma experiment, for which the University accepted full responsibility. The shutdown lasted 3 days, but 2 200 research protocols will have to be reviewed by ethics board before they can recommence [6].

The unholy alliance of academia and industry is turning out some high profile science crimes and severely rattling public trust. The situation is so serious that British physicians are proposing the formation of a national panel to handle investigations of misconduct in biomedical research [7].

Researchers at the University of Alabama at Birmingham carried out tests on cancer patients with a drug they knew to be useless. But they had financial stakes in a company making the drug. The drug, BCX-34, was the first product developed by BioCryst, a biotech company co-founded in 1986 by Dr. Charles E. Bugg, a biochemist at the Birmingham school. Company officials traded 5 percent of BioCryst stock to the University Research Foundation in return for rights to university patents. Within a decade, the company was paying the university more than $500,000 a year for research. Faculty members moved freely between the university and industry.

BioCryst saw BCX-34 as a potential cure for a common skin disease, psoriasis, as well as a rare skin cancer. A dermatologist, Dr. W. Mitchell Sams Jr., a friend of Bugg was paid $2000 a month as consultant in two company-funded studies - one on 22 cancer patients at the Birmingham school, the other on 40 psoriasis sufferers.

As with many drug studies sponsored by the manufacturer, the company retained significant control. Sams provided the patients and oversaw the tests. But the company designed the study and analysed the results.

A lot hinged on BCX-34. BioCryst’s losses had risen from $1.3 million in 1991 to almost $7 million in 1994. The drug was the closest thing the company had to a product. Because cutaneous T-cell lymphoma is rare, the FDA could waive expensive large-scale clinical trials if early studies produced striking positive results.

Dr. Harry W. Snyder Jr., a scientist who taught at Cornell University medical school before working in the biotech industry, joined BioCryst in 1993 and was given responsibility for the trial. His wife, Renee Peugeot, a nurse, was hired to assist Sams. Both husband and wife held shares in BioCryst and stood to gain from favourable trial results, but Bugg was unconcerned.

Over the next two years, Snyder and Peugeot falsified the records and made exaggerated claims about the efficacy of the drug.

More than a month before the BCX-34 studies ended in January 1995, Snyder wrote to colleagues, claiming that the drug was working, even though it was supposed to be a blind study and he had no legitimate way of knowing the results. In early January, Peugeot and Snyder bought BioCryst stock, adding to their shares and options. At one point, they owned BioCryst stock and options worth $600,000.

When Snyder’s data were analysed at the end of the trial, BCX-34 seemed to have performed impressively. The company issued a news release in early February 1995, announcing that the drug had proven highly effective in treating psoriasis and, more important, the skin cancer.

About a week later, BioCryst told the FDA that the drug had reduced or eliminated the cancer in 59 percent of the patients. The company, it appeared, had found a cure for an incurable disease.

The company’s stock shot up - from less than $6 a share at the beginning of February 1995 to nearly $13 some months later. One investor bought $5.5 million worth of newly issued BioCryst stock.

In June, Dr. William J. Cook, hired from the university as BioCryst’s medical director and Snyder’s boss, decided to write up the scientific paper. He asked Snyder for the key to the blind trials and got a computer printout. Cook calculated the results, and was dismayed to find they did

not match those announced in February. He went to the trial co-ordinator for the original key, which was locked up safely, and repeated the calculations. The results were different again. In both the cancer and psoriasis trials, Snyder had made the results appear more favourable for the drug.

The company notified the FDA of the new results, but fell short of charging Snyder.

It took five more years and investigations by two federal agencies to bring Snyder and his wife to book. They were convicted last year of defrauding the U.S. Food and Drug Administration. Sams, one of the nation's top dermatologist, was banned from testing drugs for the FDA. Investors lost an estimated $34 million in the company. The National Institutes of Health accused the UAB of poor oversight and suspended enrolment of patients in 550 studies.

Across the Atlantic, things are no better, and possibly worse. Many fledgling companies in US test their new drugs in Germany to exploit loopholes to save time and cost [8].

Early in August, the German pharmaceutical giant Bayer was forced to withdraw its anti-cholesterol drug Baycol, with the admission that it might have killed 52 worldwide, with another 1 100 potentially crippled. Germany's health minister, Ulla Schmidt, accused Bayer of sitting on research documenting Baycol's lethal side-effects for nearly two months before the Berlin Government was informed. Bayer claimed it complied with EU rules when it reported the problems to the authorities in Britain where the drug was originally registered

Later in the same month, another case came to light in Germany over human experiments with a fraudulent "cancer vaccine". This vaccine came from a scientist in a prestigious university, who claimed to have discovered it, and was tested on more than 200 terminally ill patients at Gottingen University. It was an outright fake, and many of the first batch of human guinea pigs are already dead.

German scientist Alexander Kugler published a paper two years ago purporting to show that his fused cells had defeated kidney cancer. The crucial evidence was a photograph illustrating the miracle of vanishing cancer cells. There was no other proof, and no one else had duplicated his findings. Dr. Kugler received the prestigious Ernst-Wiethoff medical prize, and his group signed a deal with the German company Fresenius to manufacture and test the vaccine.

But Prof. Ulrich Zimmermann of Wurzburg, a leading authority in this field, had grave doubts from the start. He alerted his colleagues at Gottingen University of "accumulated errors" and "misinterpretations" in Kluger's paper. An investigation followed.

It turns out that the photographic 'evidence' came from the website of a US company, Molecular Probes. Nowhere in the world would this trial have taken place, Fresenius admits. But there is a loophole for "compassionate use". What was conducted was not a clinical trial but a 'healing experiment', claims Oliver Heick, a Fresenius spokesman. These experiments only have to be approved by local ethics committees.

Sams, the dermatologist in the UAB case, left the University and wrote an article for the Journal of the American Academy of Dermatology afterwards, in which he warned that "the very soul of medicine is corroding and eroding at an unprecedented pace." He lamented the medical profession's "convenient and sometimes excessively cozy relationship to ... industry."

"We let it happen. It happened slowly, by a sort of progressive creep," he wrote. "We succumbed to the siren songs of scientific advances, political power and, worst of all, financial success."

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Who Owns Scientific Knowledge?

Prof. Peter Saunders *calls on all scientists to resist the privatisation of scientific knowledge by refusing to publish in journals belonging to publishers profiteering from closing off free access to scientific archives.*

Patents and copyrights exist so that people can be rewarded for what they have invented or created. Recently, however, some corporations have been using them to gain ownership of things they didn't invent. No one invented the so-called breast cancer gene BRCA1 and the company that holds the patent didn't even do most of the work of discovering it; they only put the last piece into the jigsaw. No corporation invented the neem tree or Basmati rice. But that hasn't stopped them from filing patents. Now some publishers, notably Elsevier, are trying to do the same with scientific knowledge. They are setting up electronic archives that will effectively make them the owners of large amounts of scientific knowledge.

As with patents on genes, the problem arises largely because the law has failed to keep up with new technology. The scientific literature is vast, and it can be very hard to find the information you need. Most scientists know all too well that you can discover only by chance and often too late something it would have been very useful to know when you began your work. Someone may even have published essentially the same result a few years ago in a journal that your library doesn't take, and in an article whose title wouldn't have caught your eye even if you had seen it. Scientific results are generally picked up quickly, or not at all. If no one has cited a paper within two or three years of publication, the work it contains is very likely to be lost.

The development of highly efficient search engines will change this by making it possible to trawl through thousands of articles in an electronic archive and pick out the few that might be relevant to your work. This will greatly extend the amount of research that any scientist will be able to draw on and so makes the ownership of electronic archives crucial. Some publishers are now working hard to ensure that this knowledge belongs not to the scientific community, not to the general public, but to them. This is knowledge that they haven't even paid for.

It's important to remember that academic journals are not like other publications. The most obvious difference, and one that surprises outsiders, is that the authors are not paid. Neither are the reviewers, even though it is peer review that gives the journals much of their authority. The editorial board and the editors, too, generally receive no payment for their work. The publisher gets all that for free, and most insist that the author signs over the copyright as well.

The reason this arrangement has survived is that the journals have been the chief means of letting other scientists know about your work and of establishing your scientific reputation. The editors and reviewers, almost all in paid employment, have regarded their work for the journal as a part of their contribution to science. As long as the publishers made only reasonable profits, this was acceptable as payment for a useful service to the scientific community, though in recent years some commercial publishers have been raising their prices at rates far in excess of inflation or special costs like the price of paper.

As for the copyright, that didn't seem to matter too much. It doesn't cover the ideas in the paper, only things like the typesetting, the diagrams and so on. The chief effect of copyright was that anyone who wanted to reproduce the material in another publication (as distinct from merely using the results of the research) had to obtain permission and possibly pay a suitable fee. In recent years, it has become more important because it limited photocopying. That largely affected only teaching; there was relatively little effect on research.

Things are now changing. If material can be put on an electronic archive, and if almost every scientist will want to refer to the archive while carrying out research, then the copyright becomes very valuable. The copyrights that authors signed over without giving the matter much thought may now mean that the very results of their research are effectively the property of whoever owns the archive. Anyone will still be able to use the results for free, but only those with access to the archive will know they exist.

There's not much we can do about those papers for which the publishers already hold the copyright. They may not have paid for them, but the law says they own them. Scientists have just realised that their copyright is valuable, not because we expect to make money out of it ourselves, but because to assign it to a publisher may now mean that our fellow scientists will have to pay to use it.

The most vocal opponents to this privatisation of knowledge are a group who call themselves the Public Library for Science. They are demanding that all published papers should be placed on a free archive six months after they have appeared. They argue that this should not affect the sales of journals because people will still pay to see research as it appears, and they are asking scientists to sign a declaration that they will not publish in any journal that does not agree to this. So far almost 27000 scientists from 170 countries have signed. There is also a list of journals that have already agreed to make the papers they publish available after six months, and this includes the highly prestigious Proceedings of the National Academy of Sciences of the USA.

Setting up and maintaining an electronic archive is a considerable undertaking, and it is not clear what is the best way forward. Six months before access is free may be a long enough delay in some fields but not in others. It is not even obvious that there should be a single archive at all, whoever controls it. But at the very least, the Public Library of Science has drawn attention to the problem and well and truly thrown down the gauntlet: if what they are arguing is not practicable, then we have to find something better.

Over the past ten or twenty years there have been massive increases in the prices of many journals. Most university libraries have been forced to reduce the number of journals they take, which makes it harder for scientists to keep up with new work in their field. The publishers have thus increased their profits by providing not a better service to the scientific community but a worse one. We allowed that to happen by continuing to publish in overpriced journals. We must not repeat the mistake by allowing our work to disappear into overpriced archives. We must stop publishing in those journals.

(The Public Library of Science's policy statement and open letter can be found on www.publiclibraryofscience.org. For contributions from all sides of the debate, see for example www.nature.com/debates/e-access/index.html)

Organics Enter the Science Wars

Prominent scientists have been denigrating organic agriculture recently on both sides of the Atlantic. This debate has even reached the pages of the top science journals. ***Angela Ryan*** *reviews and rebuts the arguments put forward.*

Sir John Krebs, Head of the UK Food Standards Agency (FSA) said, "in my opinion and in the opinion of the FSA, consumers who buy organic produce are not getting value for money if they think they're buying food with extra nutritional quality or extra safety"[1].

Soon afterwards, as if on cue, an article appeared in *Nature* entitled, *Urban Myths of Organic Agriculture*, by Anthony Trewavas, Prof. of Plant Biochemistry, Edinburgh University. It sets out to refute a common argument "that organic farming is 'holistic' and superior to reductionist 'chemical' agriculture".

This dichotomy is false, and "neither is superior". He claims "there is very little science to organic farming" [2].

Organic agriculture bans the use of synthetic pesticides, herbicides, fertilizers, fungicides, veterinary drugs (antibiotics, growth hormones), synthetic preservatives and additives, and irradiation, many of which are associated with harmful effects on health and biodiversity. Not only that, a United Nations Food and Agricultural Organisation (FAO) 1998 report on organic farming suggests con-siderations like ethical values and sustainable production principles are gaining weight in the food sector as "integral product values" for consumers [3].

The former UK Ministry of Agriculture Fisheries and Food (MAFF) 1998 Review examined comparative studies on biodiversity, and concluded, "organic regimes have the greatest benefit for biodiversity at the farm level".

But according to Trewavas, organic farming practices do not "necessarily conserve the environment". He claims that "current synthetic pesticides are very unstable; only transient declines of most field insects are reported even at full pesticide dosage". And conjectures, "lower levels of aphids observed on organic farms could well reflect lower nitrogen and protein content of organic crops".

A new study comparing arthropod communities and pest damage levels to fresh market tomato, *Lycopersicon esculentum*, was carried out on 18 commercial farms in California, representing a range of management practices, half operating as organic and half as conventional [4].

The study found that insect pest damage varied across the spectrum of farm management practices and organic and conventional farms did not differ significantly for any type of damage to tomato foliage or fruit.

However, there was a significant difference between the actual community structures of arthropods. There was higher abundance of natural enemies, and greater species richness of herbivores, predators, parasitoids and others in organic farms where arthropod biodiversity was one-third greater.

Trewavas claims "developments in the past 25 years have shown how conventional agriculture can be much more sustainable and environmentally friendly than organic farming". He cites the Institute of Arable Crops Research (IACR) website as reference.

The scientific literature contradicts his claim. A new study in *Nature* compared the sustainability of organic, conventional and integrated apple production systems in Washington State from 1994 to 1999 and found the ***organic systems ranked first for environmental and economic sustainability, with the integrated second, and the conventional las***t [5].

The researchers measured soil quality, horticultural performance, orchard profitability, environmental quality and energy efficiency, which are all specific indicators of sustainability.

They found that all three systems gave similar apple yields. The organic and integrated systems showed higher soil quality and lower negative environmental impact. But the organic systems produced sweeter and less tart apples, higher profitability and were more energy efficient. Tree growth was similar for all three systems but analysis of fruit firmness at harvest and after storage showed that the organic fruit was firmer.

Environmental impacts were assessed using the rating index employed by scientists and growers. The total environmental impact rating of the conventional system was 6.2 times higher than that of the organic system, and the integrated system was 4.7 times higher.

Energy accounting was divided into inputs (labour, fuel, fertilisers and so on), output (yield) and output/input ratios (energy efficiency). Energy efficiency for the organic system was 7% greater than the conventional system and 5% greater than the integrated system.

Enterprise budgets were generated each year to calculate net returns from total costs and gross receipts. There was no price premium for integrated fruit but the price premium of organic apples averaged 50% higher than conventional prices. Hence, the organic system was more profitable.

The use of manure on organic farms results in higher, beneficial levels of biodiversity, especially earthworms, but Trewavas claims there are "numerous problems", including "possible effects on human health".

Manure is also widely used on conventional farms. Faecal matter is known to contain a range of human pathogens but properly treated manure is effective and safe. Furthermore, unlike conventional regimes, mandatory organic certification bodies inspect farms to ensure standards are being met.

Trewavas states, "ploughing in of legume crops on organic farms to improve soil fertility and continued manure breakdown leads to nitrate leaching into aquifers and waterways at identical rates to conventional farms".

The occurrence of nitrates is a major public health hazard as they can be converted to nitrosamines, which are carcinogens and nitrates impair the ability of blood to carry oxygen.

But FAO reports that nitrate content on organic farms is "significantly lower" due to absence of soluble fertilizers and the governments of Germany and France encourage conversion to organic farming in a bid to improve water quality in certain areas.

Furthermore, the use of 'biosolids' from wastewater treatment facilities (sludge) on conventional farms raises concern over heavy metals, toxic organic compounds, such as dioxin, PCBs and persistent microbial pathogen contamination. The Codex and EU organic standards prohibit the use of sewage sludge and the US National Organic Programme also bans it.

Organic regulations recommend hay for animal feeding, but Trewavas claims "hay-fed animals infected with *Escherichia coli* 0157 incubate this dangerous organism longer than conventional animals fed with grain".

FAO report that the US Centres for Disease Control (CDC) identifies the main source of *E. coli* infection as meat contaminated during slaughter. Virulent strains of *E. coli* such as 0157, develop in the digestive tract of cattle that are fed mainly with starchy grain [6]. Cows fed with hay generate less than 1% of *E. coli* found in faeces of grain-fed animals. FAO concludes, "ruminants like cattle and sheep fed in the organic system reduce the risk of *E. coli* infection".

Trewavas writes, "food mycotoxins from contaminating fungi definitely contribute to European cancer rates, and fumonisin and patulin are both reported to be higher in organic products". He claims "failure to use effective fungicides on organic farms has led to these farms acting as repositories of disease" and "organic farms may be protected from the full effects of disease outbreak because they are surrounded by conventional farms using proper fungicides."

Mycotoxins are toxic by-products of certain moulds that can grow on food. Since fungicides are not allowed in organic systems, many studies have investigated their presence in both organic and conventional foods [7]. From these, FAO conclude, “it cannot be concluded organic farming leads to an increased risk of mycotoxin contamination”.

FAO report two studies that found aflatoxin levels in organic milk were lower than conventional, suggesting additional risks involved with feeding mainly grain to conventionally raised livestock. Aflatoxins are most toxic and can induce liver cancer at low doses if ingested over time. The report states, “as organically raised livestock are fed higher proportions of hay, grass and silage there is a reduced opportunity for mycotoxin contamination.”

Several other hazards are associated with conventional food production. In Central and Eastern Europe, there are areas of high contamination due to industrial activities, from mining, smelting, the energy sector, agricultural practices and disposal of hazardous and municipal wastes.

FAO reports, “A more widespread use of organic agriculture would contribute to a reduction of environmental degradation, ultimately resulting in reduced levels of contaminants in food”. Furthermore, “EU member states increasingly see organic agriculture as a tool for improving rural economies and stability, while simultaneously increasing biodiversity and environmental sustainability”.

It is clear that holistic approaches that link ecology and economics benefit both the ecosystem and human health, and are competitive in commercial markets.

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