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The Biotechnology Bubble *

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Biotechnology crisis management

One sign of big trouble in the biotech industry is when EuropaBio, a non-Government organization representing the interests of the industry, launched its multi-million pound campaign to win over European consumers last summer by engaging the services of Burson Marsteller [1], the leading consultancy firm for worldwide crisis-management. The clientele of the firm included Babcock and Wilcox during the Three Mile Island nuclear crisis in US in 1979, Union Carbide after the Bhopal disaster in India which killed 15 000, and oppressive regimes in Indonesia, Argentina and South Korea. According to a leaked document from Burson Marsteller, plans drawn up to change perceptions on genetic engineering advised the industry to stay quiet on risks of genetically engineered foods, as they could never win the argument, but to focus instead, on "symbols, that elicit hope, satisfaction and caring". It also advised that the best way of eliciting a favourable response to new products must be to use regulators and food producers to reassure the public.

Let the regulators reassure the public

And regulators have been most obliging, starting at the highest level. The Food and Agricultural Organization (FAO) and World Health Organization (WHO) issued a joint Safety Report on genetically engineered foods, as the result of an expert consultation held in Rome in October, 1996. The Report sets international safety standards by WHO's Codex Alimentarius Commission, which will determine, not only the safety of genetically engineered foods, but also world trade. It will be illegal for any country to ban imports of genetically engineered foods, so long as the Codex considers them safe [2].

According to the Report, risk assessment is to be based on the "principle of substantial equivalence". A product assessed to be substantially equivalent is regarded as safe and fit for human consumption. But, substantial equivalence can be claimed in advance, in which case, subsequent risk assessment is most perfunctory. Furthermore,"substantial equivalence" does *not* mean equivalence to the unengineered plant or animal variety. The genetically engineered food could be compared to any and all varieties within the species. It could have the worst characteristics of all the varieties and still be considered substantially equivalent. It could even be compared to a product from a totally unrelated species or collection of species. Worse still, 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 toxins and allergens could easily escape detection. A genetically engineered potato, grossly altered, with deformed tubers, was nevertheless tested and passed as substantially equivalent.

Risk assessment based on the principle of substantial equivalence is the stuff of farce. It is designed to expedite product approval with little or no regard for safety. It is a case of "don't need -- don't look -- don't see", effectively giving biotech companies *carte blanche* to do as they please, while serving, indeed, to diffuse and allay legitimate public fears and oppositions.

Meanwhile, the European Commission has set up a European Federation of Biotechnology Task Group on Public Perceptions on Biotechnology to deal with public resistance to biotechnology, which is seen to be the biggest problem for the industry. Generous research

grants are given to support public understanding, and to professors who promote public understanding, one of whom is John Durant.

Corporate scientists speak for the industry

John Durant is not just a Professor of Public Understanding of Science, he is also Chairman of the European Federation of Biotechnology Task Group, a member of the UK Advisory Committee on Genetic Testing and Assistant Director of the Science Museum in London. The Museum is currently mounting a major exhibition promoting biotechnology, which includes a woolly jumper knitted from the wool of Dolly the cloned sheep, designed by the winner in a children's competition. In a public debate with one of us, [3] he denied that he was working to overcome public resistance to genetic engineering. But he did assure the audience that the technology was absolutely safe, so segregation and labelling of genetically engineered products were unnecessary. He was also opposed to any moratorium on releases of genetically engineered organisms, as it would slow down development and compromise the competitiveness of the industry in Europe.

Professor Durant is not alone. There is now a sizable clone of corporate scientists, not necessarily all working officially for the biotech corporations, who go about promoting and defending the industry in roughly the same manner. They dismiss all risks as non-existent or negligible, while offering caring promises of feeding the starving billions of the Third World, greener agriculture, cleaning up the environment, miracle cures for cancer and other diseases, gene therapy... Some of us have heard those promises for nearly 30 years, and still, the only real success that they can come up with is genetically engineered insulin. It has been an endless summer of hype and promises that have yet to bear fruit.

The biotechnology bubble

It is clear that everyone is in it for the money. The risks can be dismissed by appealing to the benefits, and when the benefits are not forthcoming, the promises have to be kept alive. Biotechnology is the South Sea Bubble at the end of the millenium [4]. Billions have already been invested, and companies are desperate to recoup their losses before the whole enterprise collapses.

The biotechnology bubble may be about to burst. "Investors have been stunned more by the absence of profits in their investments than by medical progress in the sector" [5]. According to Investor's Business Daily's rankings, the sector has hovered in mediocrity for more than a year. Within a week this March, biotech stocks slipped from 77th among 197 industry groups to 95th. German economist Ulrich Dolata reported [6] that the original estimates of US$100 billion in world markets for genetically engineered products by year 2000 is now revised downwards to $48 billion, of which only $1 billion will be in food and agriculture. He also noted that the maximum number of jobs likely to be created in Germany, assuming all goes well, is 40 000, which does not take account of jobs eliminated or substituted by gene technology. However, he ended on a cheery note, and suggested that the sector may become more "dynamic" in the near future.

We very much doubt it would. Why? Because the current approach is entirely misguided by a crude, outmoded, reductionist view of organisms, and the technology is hit or miss, as well

as dangerous.

Reductionist science and hit or miss technology

This is what the public is told:

"Research scientists can now precisely identify the individual gene that governs a desired trait, extract it, copy it and insert the copy into another organism. That organism (and its offspring) will then have the desired trait.." [7]. This description is typical of literature supposedly "promoting public understanding", and neatly encapsulates the bad science of genetic determinism.

It gives the highly misleading impression of a precise technology, implying that,

1. Genes determine characters in linear causal chains, one gene giving rise to one character;
2. Genes are not subject to influence from the environment;
3. Genes remain stable and constant;
4. Genes remain in organisms and stay where they are put.

This is the most extreme version of the classical genetics which has dominated biology roughly from the 1930s up to the 1970s when genetic engineering began. It is so extreme that no biologist would *admit* to actually subscribing to it. But, why else would they suggest that by manipulating genes, practically all the problems of the world can be solved?

Genetic determinism goes counter to all the scientific evidence accumulated especially within the past 20 years, which gives us the new genetics. What is the new genetics of the present day *really* like?

- No gene ever works in isolation, but in an extremely complicated genetic network, the function of each gene is dependent on the context of all the other genes in the genome. So, the same gene will have very different effects from individual to individual, because other genes are different. There is so much genetic diversity within the human population that each individual is genetically unique. And, especially if the gene is transferred to another species, it is most likely to have new and unpredictable effects.

- The genetic network, in turn, is subject to layers of feedback regulation from the physiology of the organism and its relationship to the external environment.

- These layers of feedback regulation not only change the function of genes but can rearrange them, multiply copies of them, mutate them to order, or make them move around.

- And, genes can even travel outside the original organism to infect another -- this is called horizontal gene transfer.

- The new picture of the gene is diametrically opposite to the old static, reductionist

view. The gene has a very complicated ecology consisting of the interconnected levels of the genome, the physiology of the organism and its external environment [8]. Putting a new gene into an organism will create disturbances that can propagate out to the external environment. Conversely, changes in the environment will be transmitted inwards and may alter the genes themselves.

- Genetic engineering profoundly disturbs the ecology of genes at all levels, and that is where the problems and dangers arise.

- Genetic engineering is a crude, imprecise operation

First of all, we must dispel the myth that genetic engineering organisms is a precise operation. It is not. The insertion of foreign genes into the host cell genome is a random process, not under the control of the genetic engineer, it is done by means of artificial vectors for horizontal gene transfer (see Box 1) [2, 8-10].

Box 1

Genetic engineering involves transferring genes horizontally between species that do not interbreed. Horizontal gene transfer is naturally done by infectious agents such as viruses and virus-like elements that are passed from cell to cell, from organism to organism, many causing diseases including cancer and spreading drug and antibiotic resistance genes (Fig. 1).

Fig. 1. How vectors can transfer genes. The gene(s) to be transferred (dotted line) are usually integrated into the genetic material of the vector; viruses can also transfer genes that are not integrated, but merely packaged within the protein coat.

Natural agents are limited by species barriers, and all cells have mechanisms that break down or inactivate foreign genes. However, genetic engineers make artificial vectors for transferring genes by joining together parts of the most agressive agents to overcome all species barriers. Most of the genes causing diseases are removed, but the antibiotic resistance genes are left in so that cells carrying the vector can be selected with antibiotics (Fig. 2).

Fig. 2. Genetic engineering makes use of artifical vectors for replicating and transferring genes. The gene to be transferred (transgene) is inserted into a vector containing one or more antibiotic resistance marker genes which makes it possible to select for cells that have taken up the vector carrying the transgene. The vector carrying the transgene and marker gene(s) can either be replicated many times in the cell or become integrated into the genome. The integration is random and not controllable by the genetic engineer.

Artificial vectors and the genes they carry have the potential to spread horizontally to a wide range of species, to recombine with their genes to generate new viral and bacterial pathogens. It is this very danger that persuaded molecular geneticists to impose a moratorium on genetic engineering in the Asilomar Declaration of 1975 [11]. But commercial pressures soon intervened. Regulatory guidelines were put in place, and commercial production began. Those guidelines are far from adequate in the light of recent scientific evidence as eight scientists have argued in a new report which links genetic engineering biotechnology to the recent resurgence of infectious diseases [9].

This gives rise to correspondingly random genetic effects, including cancer [12]. Furthermore, and this is important, the foreign genes are equipped with very strong signals, most often from viruses, called promoters or enhancers, that force the organism to express the foreign genes at rates 10 to 100 times greater than its own genes. In other words, the genetic engineering process, both by design and otherwise, completely upsets the first two levels in the ecology of genes -- the genome and the physiology -- with dire consequences.

Unsustainable and unwholesome

There are many signs of the problems caused in genetic engineering organisms. For every product that reaches the market, there are perhaps 20 or more that fail. It is particularly disastrous for animal welfare.

- The "superpig" engineered with human growth hormone gene turned out arthritic, ulcerous, blind and impotent [13].

- The"supersalmon" engineered, again, to grow as fast as possible, with genes belonging to other fish, ended up with big monstrous heads and died from not being able to see, breathe or feed properly [14, 15].

- The latest clones of the transgenic sheep Polly are abnormal and 8 times as likely to die at birth compared with ordinary lambs [16].

  Even products that reach the market are failing, including crops that have been widely planted.

- The Flavr Savr tomato was a commercial disaster and has disappeared [17].

- Monsanto's bt-cotton, engineered with an insecticide from the soil bacterium *Bacillus thuringiensis*, failed to perform in the field in both US and Australia in 1996, and suffered excessive damages from bt-resistant pests [18].

- 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 are seeking compensation for losses [19].

- 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 [20].

- A number of different viral-resistant transgenic plants engineered with a viral gene actually showed increased propensity to generate new, often super-infectious viruses by recombination [21-24].

- There is widespread instability of transgenic lines, they generally do not breed true [2, 8, 25].

According to Bill Christison, a representative of family farmers from the United States, who

attended a recent Conference in the European Parliament on genetic engineering biotechnology, [**6**] transgenic crop failures are under-reported.That, plus the restrictive contracts on transgenic crops imposed by the biotech companies -- which make it unlawful for farmers to save seeds for replanting -- have drastically reduced uptake for 1998. For example, transgenic soybean, unlike transgenic cotton, has not been reported as having any problems, and it was anticipated that 30% of soybeans planted in 1998 will be transgenic. This has now been revised downwards to around 25% at most. One reason is that in Missouri, the transgenic crop is showing a five bushels per acre disadvantage in yield compared with the non-transgenic.

It is important to realize that the failures are not just teething problems. They are systematically caused by a reductionist science and a hit or miss technology. The transgenic foods created are unwholesome, because they involve stressing the developmental and metabolic system of organisms out of balance. There are bound to be unintended effects including toxins and allergens, which current risk assessments are designed to conceal rather than reveal [**2**].

The major problem is the instability of transgenic lines.

Beware of transgenic instability

Traditional breeding methods involve crossing closely related varieties or species containing different forms of the same genes, and selection is practiced over many generations under field conditions, so that the desired characteristics and the genes influencing those characteristics, *in the appropriate environment* , are tested and harmonized for stable expression over a range of genetic backgrounds. Different genetic combinations moreover will vary in performance in different environments. This "genotype-environment" interaction is well-known in traditional breeding, so it is not possible to predict how a new variety will perform in untested environments. In many cases, new varieties will lose their characters in later generations as genes become shuffled and recombined, or as they respond to environmental changes.

This problem is greatly exacerbated in genetic engineering, First of all, completely exotic genes are often introduced into organisms. Secondly, the procedures for creating transgenic organisms inherently generate increased genetic instability, In plants, the genes are often introduced into cells in tissue culture, and transgenic plants are regenerated from the cells after selection in culture.

- The tissue culture technique itself introduces new genetic variations at high frequencies, these are known as *somaclonal variations* [**26**]. That is because the cells are removed from the internal, physiological environment of the plant which, together with the ecological environment, keep gene expression, genes and genome structure stable in the cells and the organism as a whole. Unilever used tissue culture techniques to regenerate oil palms for planting in Malaysia several years ago. This has now been abandoned as many plants aborted in the field or failed to flower [**27**].

- The process of gene insertion is random and many secondary genetic effects can result, as mentioned earlier.

- The extra DNA integrated into the transgenic organism's genome disrupts the structure of its chromosome, and can itself cause chromosomal rearrangement, further affecting gene function.

- The integrated vector containing the transgene(s) and marker gene(s) has the potential to move out again or reinsert into another site, causing further genetic disturbances [2, 8, 9].

- The highly mosaic character of most vector constructs make them structually unstable and prone to recombination [9]. This may be why viral-resistant transgenic plants generate recombinant viruses more readily than non-transgenic plants (see earlier).

- The use of aggressive promoters and enhancers to boost expression of transgenes stress and unbalance the physiological system and increases instability, as already stated before.

- All cells have mechanisms which silence foreign genes [29]. One common mechanism is methylation -- a chemical reaction that adds a methyl group to the base adenine or cytosine in the DNA (there are 4 bases in DNA, adenine, cytosine, guanine and thymine) -- as the result of which, the gene is no longer expressed.

Transgene instability occurs both in farm animals [30] and plants [31]. The transgenic sheep Tracy, engineered to produce human alpha-antitrypsin at high levels in her milk, failed to reproduce a single female offspring that matches her performance. That is why cloning techniques that resulted in Dolly was contemplated. Much more is known about instability in plants. In tobacco, 64 to 92% of the first generation of transgenic plants become unstable. The frequency of transgene loss in *Arabidopsis* ranges between 50 to 90%. Instability arises both during the production of germ cells and in cell division during plant growth. It can be triggered by transplantation or mild trauma [18].

Transgenic lines, therefore, often do not breed true. A typical case [32] is the supposedly non-allergenic rice produced in Japan, [33] which turned out to be both ineffective and unstable. The transgenic plants of the second and third generations showed only 20-30% reduction of the allergens. The project has been abandoned since [34, 35]. The instability of transgenic lines create difficulties in quality control and traceability. It also raises serious safety concerns. A transgenic variety with a certain gene insert may be assessed safe, and completely change in characteristics when the insert moves to another position in the genome.

At a seminar given by scientists working for the biotech industry during the Biosafety Meeting in Montreal in May, 1997, a delegate from West Africa asked, "How old is the oldest transgenic line?" None of the scientists answered the question. There is, in fact, no data documenting the stability of any transgenic line in gene expression, or in structure and location of the insert in the genome. Such data must include the level of gene expression as well as genetic map and DNA base sequence of the insert and its site of insertion in the host genome *in each successive generation*. No such data has ever been provided by the industry, nor requested by the regulatory authorities.

One does not have to be prescient to see that transgenic instability makes biotechnology a bad investment. It may well ruin our agriculture and food supply.

Agricultural gene technology destroys biodiversity

Agricultural genetic engineering destroys biodiversity because ecological relationships are ignored.

- Broad-spectrum herbicides used with herbicide-resistant transgenic crops, such as glufosinate [36] Novartis' Basta and glyphosate [37] (Monsanto's Roundup) destroy plants indiscriminately, many of which are habitats for wild-life. They are toxic to animals and human beings. Glufosinate also causes birth defects and glyphosate is mutagenic [38]. Yet, the European Commission has approved 4 transgenic crops which are resistant to these toxic herbicides [39].

  Resistant transgenic plants can become weeds themselves or cross-pollinate with wild-relatives, creating resistant weeds [40].

- Food plants are now being engineered to produce industrial chemicals and pharmaceuticals. These will surely cross-pollinate and contaminate our food supply for years to come [2].

- Transgenic plants with insecticidal genes not only harm beneficial species directly, but also indirectly down the food chain, such as lacewings and ladybird eating prey that have fed on transgenic plants [41, 42]. In a field trial of Bt-cotton in Thailand, 30% of the bees around the test-fields died [43].

- Transgenic crops with insecticidal genes or herbicide resistance genes actually favour the evolution of resistances [8]. In other words, they exacerbate the problem they are supposed to solve.

Pesticide resistance, a major and persistent problem in intensive agriculture, has become a textbook example of the supposed power of natural selection to increase rare random mutations. That is a myth. In reality, pesticide resistance turns out to be a classic case of feedback regulation in the ecology of genes of the new genetics. It is due to genetic changes that can occur in most, if not all individuals in pest populations in response to sublethal levels of pesticide. They do not have to wait for rare random mutations. This has been known for more than 10 years. The genetic changes are part and parcel of the physiological mechanisms common to *all* cells challenged with toxic substances, including anti-cancer drugs in mammalian cells or antibiotics in bacteria [8, 9]. Similarly, resistance to herbicides readily arises in plants exposed to the herbicides [44]. So, using herbicides with resistant transgenic plants will also hasten the wide-spread evolution of herbicide tolerance among weeds, *even in the absence of cross-pollination.*

For all those reasons, agricultural biotechnology is a bad investment which will kill off all the wild-life, until nothing is left but pests and weeds. So much for the supposed benefits of biotechnology in food and agriculture. What about human genetics and medicine?

The human genomania

We must expose some of the most outrageous myths that have been perpetrated, before dealing with the more serious propositions [8]. The greatest myth is that the human genome project will uncover the genetic blue-print for making a human being, so that one can recreate the whole human being from the DNA sequences. In fact, the isolated DNA can do nothing by itself. Nor can one deduce from the sequences anything about the human being. There are at least 10 000 genes in the human genome, each with hundreds of variants. The number of possible combination of genes, assuming only 10 variants for each gene is 10^{10000}. For comparison, the total number of particles in the universe is 10^{80}. There is no doubt that each person is genetically unique, as mentioned before, and it is thus impossible to predict the life of the individual from the DNA sequence of the genome, even if one believes that genes determine our destiny. Furthermore, 95% of the DNA in the genome is so-called "junk" DNA, because no one knows what it does.

For the same reasons, it is outrageous to suggest that there can ever be a completely "personalized medicine" that matches a person's DNA. The thoroughly immoral suggestion of cloning headless human embryos to supply organs and cells for custom-made transplantations is also highly impractical [45]. The technique, which made Dolly, involves transferring a nucleus from a cell of an adult to eggs from which the nucleus has been removed, and allowing the egg to develop into an embryo. The success rate is less than 1%, so an army of human female donors will have to be lined up to provide "empty" eggs. There is much current doubt as to whether Dolly was in fact cloned from the nucleus of an adult cell [46]. Adult cells accumulate systematic and nonsystematic changes in the DNA which make it very unlikely to support normal development [8].

Gene therapy suffers from all the problems associated with making transgenic organisms. The technology for inserting genes into the genome is hit or miss, There has not been a single case of documented success in gene therapy [47]. On the contrary, severe, nearly fatal immunological reactions have developed to at least one gene therapy vector, [48] while the dangers of generating viruses from gene therapy vectors cannot be lightly dismissed [8]. Naked viral DNA is much more infectious than the virus itself, [9] and there are many dormant viral sequences in all genomes with which gene therapy vectors -- all derived from viruses -- can recombine to generate new viruses.

What about mass-screening programmes for so-called single gene diseases? Sickle cell anaemia is a recessive condition among Afro-Americans, which means that an individual has to have two copies of the mutant gene to have the disease. Screening programmes for this condition has already resulted in individuals who are asymptomatic carriers of the condition (with only one mutant gene) being discriminated against in employment and in health insurance [49]. This is socially unacceptable and economically unsound, and has no scientific basis whatsoever, for the reasons already stated: it is impossible to predict a person's health from just one single gene when the other genes are different.

Two cases may be described to illustrate the fallacy of genetic determinist thinking [8]. The first is cystic fibrosis, a recessive condition like sickle anaemia, which requires two copies of the mutant gene to become expressed.The severity of the disease is extremely variable. Furthermore, there are now more than 400 variants of the gene identified, whose effects are

largely unknown. The gene is extremely long, and many more variants are likely to be isolated. While the common variant results in cystic fibrosis in the North European population, it is not associated with the disease at all in the Yemanite population. In the latter population, clinical conditions diagnosed as cystic fibrosis are associated with a different gene altogether. The same goes for the so-called cancer gene, *BRCA1*. A certain mutation in the gene is associated with 40% of breast cancers in women who have a family history of cancer -- which make up only 5% of all breast cancer cases in women -- but has no association with familial breast cancer in men.

Genetic screening is most often limited to members of families which already have a history of the condition. But, couples have been subject to pressures to abort affected foetuses whether they want to or not. Enormous efforts are now concentrated into hunting for genes for every conceivable human condition -- homosexuality, shyness, criminality, intelligence, alcoholism where the connection with individual genes become more and more remote and dubious.

It is all too easy to slide insensibly into what constitutes a harmful or undesirable gene, and to practice "therapeutic" abortions on that basis.

Can we afford to let genetic determinist science continue to dominate our social and health policies? The dangers of genetic discrimination and eugenics are real. From the 1930s to the 1970s and in some cases right up to the 1990s, tens of thousands of people, the majority of them women, have been sterilized by force in US, Canada, Australia, Sweden, Denmark, Finland, Italy, Switzerland, Japan, Norway, France, Germany and Austria, on the basis of "undesirable" racial characteristics or otherwise "inferior" qualities including poor eyesight and "mental retardation" [50].

What about genetically engineered insulin? Certainly, it gives life support to those suffering from insulin-dependent diabetes. But that does not help the vast majority of diabetics that are controllable by diet, nor those that are independent of insulin.

The more general point is that debilitating genetic diseases which can be attributed to mutations in single genes constitute less than 2% of all human diseases [51]. How can this justify the current overwhelmingly biased investment in genetic medicine? The last issue of *The Ecologist* (Vol 28 No. 2, Mar/April) documents the dubious record of cancer research. Billions have been invested into cancer genes and the genetics of cancer, and still the rates of most cancers are increasing year by year. Tens of billions have been made in the "healthcare market" for diagnosing and treating cancer patients to little avail. At the same time, the impacts of environmental carcinogens and mutagens are consistently overlooked by the cancer research establishment. It is estimated that approximately 1% of all genetic diseases are due to new mutations [8]. Are these the result of environmental mutagens?

The investment in genetic medicine is bad in all senses of the word. It is a drain on public resources to the overwhelming benefit of the biotech corporations. At the same time, ever-dwindling public resources are being misdirected away from the real causes of deteriorating public health. It is disastrous from the social point of view in promoting genetic discrimination and eugenics.

Before the bubble bursts . . .

Before the bubble bursts, we suggest that the biotech industry should

- Stop throwing good money after bad. Take stock of existing projects and discontinue those that have all the signs of going down a blind alley, which may include most projects on genetically engineering organisms. Don't fool yourselves. Convince yourselves with good data that the transgenic lines created are genuinely stable and wholesome.

- Stop wasting money on expensive campaigns to change public perception. The public are smarter and more discerning than you think.

- Stop corrupting our scientists and support research scientists to do good research.

- Invest in basic research to discover appropriate and safe ways to use genetic engineering technology.

- In the meantime, don't forget to look out for alternative investments into other technologies that are genuinely environmentally friendly, caring and sustainable.

In fact, biotech companies would achieve the best public relations and serve their own interests by supporting a five year moratorium on releases. This would create a breathing spell for stock-taking and for honest scientists to do the necessary research.

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