Wholesome, Holistic and Holy: Controversies over Biotechnology and Food

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We are now ten years into the public debate over modern biotechnology applied to food production, a debate that pivots as much on fears, perceptions and values as on safety (1). In the mid 1980's, the development of bovine somatotropin (BST, also called bovine growth hormone, or BGH) as a method to increase milk production made news. So did plans to test in a California field whether a bacterium modified by cut-and-splice gene technology could reduce frost damage when sprayed on crops. The legacy of this decade includes cartoons of emaciated drugjunkie cows, and images of Moon-suited scientists walking on Earth among rows of crops. There is another part of the legacy. We are now five years into the era of commercial foods produced using such recombinant DNA technology. Less than a dozen such products have jumped the hurdles faced by any new food going from lab bench to the kitchen table: feasibility, safety and quality assurance, profitability, test marketing.

These foods have also passed through a series of regulations that some describe as a maze, others as an unnecessary gauntlet (2), and still others as inadequate relative to public health and input (3). Products of a new tool of genetic manipulation, they have been more controversial than the several thousand new food products placed in US supermarkets every year.

Three federal agencies share in the regulation of new foods developed using rDNA techniques: the FDA under the Food, Drug and Cosmetic Act; the USDA, principally under the Plant Pest Act; and the EPA under the Federal Insecticide, Fungicide and Rodenticide Act and the Toxic Substances Control Act. The agencies split the responsibilities according to policies originally described in a "Coordinated Framework" in 1986.

In the coming few years, the number of foods produced using gene-splicing techniques will likely double or treble to 20 or 30. Most public attention has focused on two pioneering products: BST and the "FlavrSavr" tomato. Consumer concern, at least as measured by news coverage, about foods introduced later has diminished.

This article will review the stories and the controversies of the first 10 years, compare the issues raised by the first five foods produced using recombinant DNA brought to market, assess the current situation, and seek ways to accommodate a range of values regarding food. One way to express the spectrum of attitudes towards food is the phrase "Wholesome, Holistic and Holy." The "Wholesome" point of view asks, "Is this food safe and nutritious?" These are questions that experiments and experimentalists can address and sometimes answer. The "Holistic" viewpoint asks not only about safety and nutrition, but also questions such as "Who made this food? How? Where? At what social cost? At what environmental cost?" These are not always answerable by experiment. The "Holy" viewpoint asks, "Is this food made in accordance with my religious

dietary laws, or in a manner consistent with my profound spiritual beliefs?" Questions of faith such as these cannot be answered by experiments.

Food: Symbol in the Sustenance. Raised a Catholic, I was astonished at my first Seder to see the origin of the use of unleavened bread and wine so familiar to me from the Christian Eucharist. The Last Supper was really the Last Seder, and even two thousand years ago it was no ordinary meal but an extraordinary remembrance of the formative event in the birth of a nation and its covenant with its God.

Few traditions demonstrate the role of food in spiritual as well as physical life as does the Passover Seder observed by Jews each spring. Based in history, held at home, centered around the family, its ritual foods symbolize the struggle from bondage to freedom.

The power of food as symbol is not limited to religion. John Tallmadge, in a review of two books examining the role of new technology in agriculture, notes that "biologically and culturally, we become what we eat, so we should choose our food with care" (4). Religious or moral restrictions, such as keeping kashrus or choosing vegetarianism, often impose a restraint on the sweep of human action, reserving some actions to God or to Nature, and thereby distinguishing the human from the deity or the natural. These restrictions also serve to set one group apart from another. Such self-imposed restraints can be embraced by some people as a liberating source of humility, humanity and humaneness. But when applied by compulsion rather than persuasion, other people chafe at the same restraints.

Food: Fuel and Building Blocks for Life. What we eat literally does become what we are, in the biochemical building-block sense. Food is also the physiological fuel that drives our lives. And almost all food eaten by humans comes from other living things: plants, animals, microbes. These living things are the common ground linking food and biotechnology.

Definitions of Biotechnology. The word "biotechnology" is a lexicographic amoeba. It's also politically-charged. So it is prudent to be aware of a range of meanings and connotations. Biotechnology derives from three ancient Greek words: bios, life; teuchos, tool; logos, meaning 'study of' or 'word' or 'essence.' Thus extracted etymologically, it becomes 'the study of tools from living things.'

Historically, Robert Bud of the Science Museum in London has traced the use of "biotechnology" at least as far back as 1917. During the World War, it referred to the use of **industrial fermentations** to produce industrial feedstocks, such as acetone used to make cordite, an explosive. Now "biotechnology" can encompass ancient uses such as microbial fermentations to flavor and preserve foods, including leavening bread, brewing beer, and making cheese and yogurt.

Biotechnology tools also include **selection and breeding, chromosome analysis** (such as used to diagnose Down Syndrome), **tissue culture** for growing tissues or cells in glass jars (used in

plant propagation and in producing drugs such as penicillin and monoclonal antibodies), and **DNA analysis** (for example, DNA fingerprinting, or massive DNA sequencing efforts such as the Human Genome Project). But for many people, biotechnology means **recombinant DNA and genetic engineering**.

Gene Transfer: The Crucial, Controversial Tool. During the 1970's scientists and reporters used "biotechnology" as shorthand for "recombinant DNA techniques." With these cut-and-splice tools developed in the early 1970's, researchers can cut a copy of a segment of DNA containing a gene, and paste it into another segment of DNA.

The power of this tool is that the DNA segment can come from any organism, and can be transferred to any organism. The gene on the transferred DNA can be active in the recipient organism, and the gene can be inherited by the offspring of the recipient. This means researchers can transfer a copy of a gene from a bacterium to a bull--or from a bull to a bacterium. Scientists and writers commonly refer to this cutting-and-splicing as genetic engineering. A term coined by a Danish microbiologist in 1941, its meaning has mutated from its original reference to the precise selection of yeast strains.

"Genetic engineering" generates a gut-level reaction among some consumers. Ironically, the two words are related. Ask most consumers for the name of the first book of the Bible, and they can answer "Genesis." It's about origins, beginnings, and inheritance. Knock off the "-is" and you get "genes". Rub the right lamp and you get a "genie". If the genie is real smart, it's a genius. If it's good with its hands and its head, it's ingenious and shows ingenuity. In French (and almost every other language of Western Europe save English), ingenious people are called "ingenieurs". In English, the word is engineer--one who designs and builds. The string of ideas from Godly creation to human manipulation helps explain the concern of consumers reacting to the words and the concepts of genetic engineering.

Critics of biotechnology have used other symbols from mythology and literature to express their concern or opposition. "Frankenfood" is a coinage notable for its impact and its chief invoker--Jeremy Rifkin (5). Mary Shelley's book has spawned a genre of movies that focuses on the monster more than the man, on the creation more than the creator. Yet in the book, the monster is just a supporting role; the leading man is the scientist-surgeon. In both the book and the movies, the monster provides the gore; the man provides the horror. Frankenstein counterposes humility and hubris.

Likewise, "Frankenfood" is ambiguous, and therefore more effective. Is the concern about the creation or the creator? About the tool or the toolmaker?

First Use: A Human Protein from Bacteria. In 1982 Eli Lilly & Co. successfully introduced the first commercial product of genetic engineering: human insulin made by bacteria given a copy of the human gene for insulin . This technical and commercial success in high-profit pharmaceuticals suggested that the same technology could be used to produce proteins valuable

in food production. The success did not suggest, however, that it would take eight years to emulate.

Cases of Foods: The First Five Products. The first two products of recombinant DNA technology in the US food supply actually resulted from a gene transfer from 'bull to bacterium'. But the first was not the infamous hormone BST. In 1990 Pfizer, Inc. introduced "CHY-MAX" brand chymosin, a protein purlfied from bacteria given a copy of the chymosin gene from cattle. Traditionally extracted from "chyme" or stomach slime of suckling calves, chymosin is not a hormone but is an enzyme that digests milk proteins. Chymosin is the active ingredient in rennet used by cheesemakers to coagulate milk into curds and whey. CHY-MAX extracted from bacteria grown in a vat is identical in chemical composition to thechymosin extracted from cattle.

In the late 1980's Pfizer's analyses showed that the product met the industry standard of care for a new food additive. Under the Food, Drug and Cosmetic Act, FDA requires a sponsoring company to establish the safety, efficacy and quality of the additive. Pfizer demonstrated that the composition and activity of its protein was identical to that extracted from calves, and that bacterial DNA could not be detected in the product. After preparing the data to gain approval as a food additive, the FDA approval actually came as acceptance of GRAS status: Generally Regarded as Safe. Ironically, because it was indistinguishable from chymosin from stomachs, the bacterial chymosin therefore did not require certification as a food additive.

Pfizer's product quickly won over half the market for rennet because cheesemakers found it to be a cost-effective source of high-quality chymosin in consistent supply. Before CHY-MAX, the sole source of chymosin was the stomachs of slaughtered suckling calves--calves usually less than 10 days old. This meant the supply of chymosin fluctuated with the supply of suckling calves. Moreover, the traditional source of chymosin also kept cheese from being kosher. Such cheese was considered a mixture of milk and of flesh, and violated kashrus. Some vegetarians also refused to accept cheese with calf-rennet. Jewish rabbis and some vegetarian groups gave an unanticipated benefit to Pfizer by approving cheese made with rennet from bacteria.

Unlike BST, under development at the same time, CHY-MAX made few headlines. It was a protein produced through gene transfer, but it was an enzyme and not a hormone. It was identical to chymosin produced by calves. It offended the values of few people. It did not threaten the health of consumers, the wealth of cheesemakers or family dairy farmers, or the well-being of cattle. Finally, it did not threaten the image of milk as "nature's most perfect food." rBST was suspected of all that, and more.

rBST. BST is a protein that functions as a hormone in cattle but not in humans. BST occurs in trace amounts in cow's milk. Fifty years ago experiments with BST extracted laboriously from cattle pituitary glands showed that injections of BST into cows increased milk production.

Recombinant DNA technology provided an alternative and plentiful source of the protein hormone: bacteria given a copy of a BST gene to make "rBST" protein.

Just as words in English are written using strings of letters selected from a 26-letter alphabet, proteins are chains composed of links or building blocks called amino acids. The "protein alphabet" contains 20 amino acids. Cattle make four similar but distinct versions of BST. Each is 190 or 191 amino acids long. Beginning in the early 1980's, Monsanto developed a recombinant DNA-derived version called rBST that differed from one of the four naturally-occuring versions only in the addition of one amino acid at one end. Introduced in 1994 under the tradename Posilac, farmers inject the drug into a cow starting at 60 days into her milking period (feeding rBST to animals is ineffective because the protein is degraded in the cow's stomach). Injections can increase milk production up to 20% compared to untreated animals.

rBST: A Decade in Development and Review. FDA is empowered by the Federal Food, Drug and Cosmetic Act to review new animal drugs before approval for commercial sale. The sponsoring company must demonstrate to FDA's satisifaction that the drug is safe to humans and to livestock, that it is effective at the administered dose, and that the drug can be produced with consistent and adequate quality.

Many rBST opponents have argued that these three criteria are inadequate. They support the addition of a Fourth Criterion: an assessment of the economic and social impact. Although Congress has yet to authorize such a criterion, nevertheless during the late 1980's critiques of rBST raised a spectrum of objections. They claimed that it was not safe for cows because it caused mastistis or other ailments; that it was not safe for humans; that the drug was not effective; alternatively, that the drug was too effective, and that the increase in milk supply would drive down the income of family farms; that even if the drug were safe and effective, its commercial use would preferentially benefit large corporate dairy farms its commercial use would ruin the dairy industry; and that its use would ruin small dairy farms because opinion polls predicted a 10% drop in demand for milk. During the late 1980's the issue burned in dairying regions but was not yet sign)ficant nationally. Then in the spring of 1990, Wisconsin passed a one-year ban on the drug, blocking its experimental use there. In August 1992 the federal General Accounting Of fice issued a report criticizing the FDA's review of BST, and recommended that approval be delayed until FDA resolved issues of mastitis (an udder inflammation) in treated cows. Also in November 1992, Wisconsin voters elected Russell Feingold, a state senator and a leading opponent of rBST, to the US Senate.

In March 1993 FDA convened an advisory panel to review issues raised in the GAO report. The panel concluded that aufficient safeguards were in place to ensure the safety of the milk supply. During August, Senator Feingold, who considered the issue more about milk and Monsanto than about biotechnology per se, sponsored an amendment to the federal budget bill that delayed commercial sale of rBST for 90 days following FDA approval. On November 5, 1993, FDA

announced approval of Monsanto's rBST product; commercial sales were delayed until the following February.

During the 90 day moratorium, the Executive Branch of the federal government compiled a wide-ranging assessment of rBST, including economic impacts. The report confirmed the FDA's conclusion that rBST was safe and effective, and discounted the predictions of severe economic upheaval in the dairy industry. Opponents of rBST criticized the report's analysis and conclusions. In early February 1994 national news media intensely covered the start of sales of rBST. However, the steep drop in consumer demand for milk predicted by some opinion polls never materialized, and demand remained steady.

Labeling. Another sharp issue over rBST was labeling: should labeling milk from cows treated with rBST be compulsory, permitted or prohibited? Based on what criteria? Proponents of compulsory labeling of milk held that those who used the new product should have to bear the burden of labeling their milk, and that consumers have a "right to know" about processes used to produce food. Proponents of BST argued that the FD&cC act requires labels only when composition of a food is changed, and since rBST did not change the composition of milk, there were no grounds for FDA to mandate a label. The FDA kept its own counsel until it published labeling guidelines in the Federal Register on February 14, 1994.

The FDA "found that there was no sign)ficant difference between milk from treated and untreated cows and, therefore, concluded that under the Federal Food, Drug and Cosmetic Act, the agency did not have the authority in this situation to require special labeling...." In this sentence, the FDA answered two key questions: milk composition was unchanged, and by implication, the milk was not adulterated.

The FDA also permitted voluntary labels for dairies wishing to accomodate consumer concern by selling milk from untreated cows. All label claims must be both true and not misleading. Furthermore, the FDA advised that both "the presence and the absence of information are relevant to whether labeling is misleading." To meet these tests, the FDA recommended a two-part phrase: "Milk from cows not treated with BST. No sign)ficant difference has been shown between milk derived from rBST-treated and non-BST-treated cows." The FDA also suggested that, in assessing a label statement (should a producer choose a phrase different than the one recommended in the guidelines), "available data on consumers' perceptions of the label statements could also be used to determine whether a statement is misleading." Apparently, a label-writer is responsible not only for what the label language implies, but also for what the consumer infers from the label.

States have the option of establishing their own label standards. Vermont has enacted a law that compells mandatory labeling of milk from cows treated with rBST. The label must include the "no signicant difference" disclaimer. In August 1995 US District Judge J. Garvan Murtha upheld

the law in deciding a lawsuit brought by the International Dairy Foods Association and five other groups (6).

The First Whole Food: FlavrSavr Tomato. Also in the spring of 1994, Calgene's FlavrSavr tomato entered the final stages of FDA review. FlavrSavr was the first whole food from plants reviewed under the policy issued by the FDA in May 1992.

In the debate whether regulation should be based on "the product or the process", the FDA decided to continue to base its judgements on the product. The policy assessed new foods from all genetically mod)fied plants based on the expected characteristics of the food and the genetic makeup of plant used to produce the food, including any introduced genes, regardless of the genetic techniques used to introduce the gene. Thus, the mere use of rDNA techniques would not trigger any unique regulations. Nor did FDA require special labeling of foods developed using recombinant DNA techniques. The policy included special provisions to safeguard against the potential transfer of an allergen from one food plant to another. For example, a tomato containing a peanut gene would have to be shown not to cause an allergic reaction in people known to be allergic to peanut. Calgene, headquartered in Davis, California, developed a tomato that remained firm even as it turned red and tasty as it ripened. Researchers inserted two genes linked together in tandem. One gene was a tomato gene modified to keep the tomato firm. The other gene was a tag, a "selectable marker" that enabled the researchers to find which plants received the two linked genes. The gene was originally found in bacteria in nature, so the use of the gene in tomato did not introduce a new gene to nature. In January 1993, Calgene asked the FDA for a two-track review. Calgene asked that the tomato itself be reviewed under the the May 1992 policy; and it asked for a review as a food additive of the "selectable marker" gene and its protein. Calgene's decision to submit the selectable marker gene and its protein to stringent review as a food additive was the most cautious approach to approval. It was also the most expensive approach, one intended to maximize consumer confidence in a pioneering product. Some observers expressed concern, however, that Calgene's approach might set a precedent that other companies would be expected or even obliged to follow. On May 18, 1994, the FDA reached two conclusions: 1) the mod)fied plant is a tomato and is as safe as other tomatoes, and 2) the selectable marker gene and its protein product were established as safe and effective. The addition of the selectable marker gene originally found in bacteria and the presence of the protein from the selectable marker gene did not constitute either a sign)ficant change in composition or an adulteration. Nor did the genetic manipulations cause any unintended change in nutrient composition, and the company had satisified the industry standard of care in looking for such a change. Furthermore, as expected the FDA did not require Calgene to include a label stating that the tomato was mod)fied by recombinant DNA techniques. Lastly, since the tomato a whole food, and since the FDA does not require ingredient labels on whole foods, the agency did not require the company to include a label listing the selectable marker gene and its protein products as a food additive. **Virus-resistant Freedom II Summer Squash.** Late last year the USDA cleared for commercial use a squash resistant to two types of virus (7). Developed by Asgrow

seed company of Kalamazoo, Michigan, the squash is remarkable in containing three genes instead of just two: a selectable marker, and one gene each from the two similar but distinct viruses. Because of the use of plant virus genes, the squash was the first time that the USDA, rather than the FDA, was the lead regulatory agency based on authority given in the Plant Pest Act. Farmers try to control the virus diseases and the aphids that spread them by spraying their crops with insecticides. Breeders have had diff~culty developing aphid-resistant plants as well as virus-resistant plants using genes from wild and cultivated relatives of squash. Recombinant DNA techniques enlarged the breeders' gene pool. Work started in the laboratory in 1986 to find, copy and move the genes into greenhouse plants. No longer limited to squash for sources of resistance, researchers inserted into plant's chromosomes a copy of gene from each virus to make plants resist the virus. They also used the same "selectable marker" or "tag gene" used by Calgene to find plants in which the three linked genes were inserted successfully. Beginning in 1990 Asgrow tested the squash in field trials every growing season. Asgrow formally petitioned the USDA in 1992 to declare the squash a "non-regulated article," the clearance needed to commercialize the squash. The petitioning process requires the USDA to announce in the Federal Register the company's request for "non-regulated article" status. Any interested person can then submit comments for a period after the announcement is published. USDA sent Asgrow's petition through three rounds of comment. USDA asked Asgrow for more analysis in response to each round of comments. USDA was at first concerned with molecular aspects, which inforamtion was easily answered. Later USDA expressed concerns about weediness, spread of the resistance gene by pollen, and possible acceleration of new strains of the virus. After reviewing Asgrowis additional analyses, USDA declared in late 1994 the squash and any hybrids developed from it to be "non-regulated articles." **New Leaf Potato.** A common soil bacterium named Bacillus thuringiensis produces a protein toxic to many plant-eating pests but harmless to beneficial insects such as honeybees as well as to humans. "Bt" is available as a commercial pesticide registered by the EPA. When dusted on potato plants, a specific strain of Bt kills Colorado potato beetle. The dust is effective for only two to three days. In the mid 1980's several companies, including Agracetus, Agrigenetics (now part of Mycogen) and Monsanto, transferred a copy of the Bt gene into plants. The goal was to produce plants resisted insects by producing the Bt protein. The EPA has been the lead regulatory agency reviewing these plants. On May 5, 1995, the EPA announced the registration of Monsanto's "NewLeaf" potato, making it the first registration of a "plant-pesticide." This action cleared NewLeaf potatoes, a type of Russett Burbank potato, for commercial production in 1995. They were marketed without any special label or segregation. The USDA had also previously de-regulated Monsanto's variety.

Summary: "What No Change in Sense Discern" These first five food products are remarkable in that, contrary to Frankenfood expectations, they look just like their counterparts. No monsters, no killer tomatoes. After wading through the empirical evidence, the emotional arguments, the issues of values, and the blatant scare tactics, it's not surprising to hear a consumer with a transgenic tomato in hand ask, "So what was all the fuss about?" **Scientifically sound regulations.** Scientific organizations such as the National Research Council have concluded that

the use of rDNA techniques poses no special risks not also posed by other genetic manipulations (crop hybridization, for example). If so, then why have special regulations triggered by the use of rDNA? (8) **"Reassurance Regulations"** One reason to support rDNA-triggered regulations is to reassure the public that each of the pioneering products of new technology are safe. Ironically, these regulations serve to protect biotechnology from the public, rather than to protect the public from biotechnology. They can impede university researchers and small companies with small budgets, and give the public an unfounded feeling of improved safety. The regulations do not reduce real asks but they do increase real costs, effectively barring smaller companies from entering the market (9). **There is surprisingly little litigation.** Yet the threat of litigation by people seeking more stringent regulation of rDNA technology is constantly affecting the decisions of federal policymakers and commercial developers. **How to accomodate people with profound concerns unfounded by the data?** rBST was among the most thoroughly tested and reviewed drugs ever, yet some consumers conclude it is not safe enough. Permitting specially-labeled alternative sources of foods produced in accordance with those concerns has proven practical. But in these cases, one can argue based on economic justice that those who value the extra information about the product should pay for the information. **Fire in the Cave.** A little saying: when people first brought fire into the cave, it was the end of cold nights--and the beginning of emphysema. The criteria we choose to assess the risks and benefits of new tools will profoundly affect the personal choices and the public policies surrounding biotechnology and food. **"Outreach is Key to Acceptance."** This mantra is overstated and misses the mark. A person may completely understand molecular biology and yet reject its application to food based on one's personal values. It is essential to provide information, point out misconceptions, and refute alarmist misinformation, not so much to assure public acceptance as to ensure public empowerment. On a topic as basic as food, the challenge is to accomodate personal values, but without capitulating to emotional or alarmist arguments that would deny other people access to a safe source of food. For those with a higher sense of values, let them persuade rather than compel those with differing views.

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