

# Mendel in the Kitchen: A Scientist's View of Genetically Modified Foods (2004)

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### POISONED RATS OR POISONED WELLS

*The increased public awareness of food allergy has arisen from a combination of three factors: reasoned concern, fear through ignorance, and political motivation.*

—Bob Buchanan (2001)

On August 10, 1998, Arpad Pusztai was interviewed on the British TV show “World in Action.” Pusztai studied lectins, sugar-binding proteins found in peas and beans, cereals and potatoes. In his 35 years at the Rowett Research Institute in Aberdeen, Scotland, he had written three books on lectins and published 270 research papers. Because of his expertise, he had been asked to test the safety of a potato variety that had been genetically engineered to produce its own pesticide. That pesticide was a lectin from a flower, the snowdrop. Pusztai fed the genetically modified potatoes to rats. His experiments, he told the television audience, showed that the GM potatoes damaged the rats’ immune systems and stunted their growth. He himself would not eat GM food, Pusztai said. He found it “very, very unfair to use our fellow citizens as guinea pigs.”

Pusztai’s study made headlines around the world. It came to be called “the poisoned rat debate.” According to a news report in the journal *Science*, the Rowett Institute was flooded with calls from reporters even before the television show aired. The Institute was faced with “a megacrisis we didn’t remotely anticipate,” said director Philip James. When James examined Pusztai’s experiments, he found them a “muddle.” Pusztai’s laboratory was sealed, his notebooks were turned over to an audit committee, and Pusztai himself was put on indefinite leave—he was out of a job. The audit committee’s report, released in October 1998, concluded that Pusztai’s data did not support his conclusions.

Forbidden to talk to the press, Pusztai asked a number of scientists to review the audit committee’s report. In February 1999 they posted a memorandum, supported by more than 20 scientists, on the World Socialist Web Site. “Those of us who have known Dr. Pusztai’s work or have collaborated with him,” the memorandum stated, “were shocked by the harshness of his treatment by the Rowett and even more by the impenetrable secrecy surrounding these events. It is an unacceptable code of practice by the Rowett and its director, Professor James, to set themselves up as arbiters or judges of the validity of the data which could have such a profound importance not only for scientists, but also for the public and its health.”

One scientist stressed that “there is enough strong evidence that the work of the audit group was not objective and per se dangerous, not only for Dr. Pusztai, but generally for free and objective science.” Another thought the Rowett Institute’s treatment of Pusztai was “a great injustice.” Even Kenneth Lough, who had been the Rowett’s principal scientific officer from 1956 to 1987, said, “The Institute is at risk in sending the wrong signals to scientists in this field of research that any sign of apparent default [that is, any error in judgment] will be treated with the utmost severity. The awareness will of course act as a strong deterrent to those who wish to conduct research in this vitally important field.”

Pusztai’s study was also reviewed by a committee of six members of the British Royal Society. They sent out material from Pusztai, the Rowett Institute, and other sources to scientists with expertise in statistics, clinical trials, physiology, nutrition, quantitative genetics, growth and development, and immunology. The committee concluded that Pusztai’s experiments were poorly designed; the statistics he used were inappropriate and his results were inconsistent. They recommended that the experiments be repeated and the results be published.

Pusztai jumped to his own defense with a detailed response circulated on the Internet. He and a colleague with whom he had worked for several years published their original study in the medical journal *Lancet*. For this *Lancet* also came under criticism. The U.K.'s Biotechnology and Biological Sciences Research Council called the journal "irresponsible." *Lancet's* editor, Richard Horton, stood by his decision. Five of six reviewers had favored publication, and he believed that it was appropriate for the information to be available in the public domain.

The lectin in question is called the *Galanthus nivalis* agglutinin, after the Latin name of the snowdrop, *Galanthus nivalis*. It is abbreviated GNA. Like other lectins, it recognizes and binds to sugars on other proteins. Although lectins were first discovered in plants, we now know that there are many different kinds of lectins in animals as well. Many proteins—in all kinds of organisms—are decorated with sugar molecules. Some, called glycoproteins, carry long strings or branches made of several sugar molecules. Each glycoprotein has a different complement of sugar molecules, depending on what it does and where. The sugar signature works like a zip code in the cell, determining where the protein is delivered by the machinery that produces it.

Lectins read these sugar codes. They serve many functions, one of which is to recognize disease-causing bacteria and viruses. For plants, lectins are a defense against insects. GNA, for instance, is mildly toxic to some pests of rice and other important crops. It does not affect ladybird beetles, considered to be beneficial insects, although it does affect parasitic wasps, which are also beneficial. Other lectins, including one called ricin, are quite toxic. When taken up by cells, ricin blocks the synthesis of proteins by inactivating the ribosomes. GNA does not have this property. Pusztai's own studies showed that rats could safely eat purified GNA. Moreover, he and his colleagues found that GNA protected the rats against infection by *Salmonella* bacteria, the intestinal bug often found in raw eggs and on uncooked chicken. When the gene coding for GNA was introduced into potatoes and rice, it increased the plants' resistance to insect pests. The next question was how a plant that produced GNA would affect a human gut. This question Pusztai tried to answer using rats as stand-ins for humans.

People already eat lectins. They are present in most plants, and are especially abundant in seeds, including cereals and beans, and in tubers such as potatoes. They tend to survive cooking and digestive enzymes. They occasionally cause symptoms of food poisoning. A lectin called phytohemagglutinin or PHA, for example, is a normal component of kidney beans. Allergist David Freed recounts an incident in 1988 when a hospital had a "healthy eating day" in its cafeteria at lunchtime. Thirty-one portions of a dish containing kidney beans were served. Over the next several hours, 11 people experienced typical food-poisoning symptoms, including vomiting and diarrhea. All recovered by the next day, but no pathogen was found in the food. It turned out that the beans contained an abnormally high concentration of PHA.

Studying PHA in the early 1990s, Pusztai and his colleagues found that it caused the cells lining the surfaces of a rat's intestines to die off and be replaced more quickly than usual. The rats became more susceptible to an overgrowth of the common gut bacterium, *Escherichia coli*. *E. coli* is harmless in small numbers, but causes stomach upset if it multiplies. The younger replacement cells on the tiny surface projections, or villi, of the intestines, Pusztai and his colleagues found, had a high proportion of proteins with mannose sugars on the ends of their sugar signatures. Because *E. coli* has projections, or fimbriae, that recognize and bind to mannose, the bacterium could grow more easily. (Pusztai also found that including the lectin GNA in the rat's diet reduced the extent of bacterial overgrowth, because the GNA binds to the mannose and keeps the bacteria's fimbriae from using it.)

As they do in insects, some lectins can get into and through animal cells and enter the bloodstream. Some are potent allergens. So even though GNA appeared to be relatively benign, there was no doubt that a food containing it needed careful testing. Sensibly, the Scottish Office of the Agriculture, Environment, and Fisheries Department commissioned a three-year study in 1995. The University of Durham and the Scottish Crop Research Institute were to provide the transformed potatoes, and the Rowett Institute was to do a chemical analysis of them. Pusztai was also to do both short-term (10-day) and long-term (3-month) rat feeding trials. In these he would compare the effects of eating potatoes from the transgenic plants with the effects of eating potatoes from the parent lines, that is, from the plants that provided the cells transformed by recombinant DNA.

The rats in Pusztai's study were fed either raw or cooked potatoes. If they ate ordinary, nontransgenic potatoes, their diets were supplemented with pure GNA. The results of the

experiment showed that the organs of the rats fed transgenic potatoes weighed significantly less than the same organs from control animals fed nontransgenic potatoes. In this control group—the rats fed purified GNA and ordinary potatoes—the lymphocytes (cells in their immune systems) were more responsive to stimulation by other lectins. By contrast, the lymphocytes were depressed in the animals fed the transgenic potatoes. It seemed that the potatoes expressing the GNA protein were somehow poisonous, while the ordinary potatoes—although spiced with pure GNA—were not.

Since he knew GNA wasn't toxic, Pusztai jumped to the conclusion that the new gene itself—or perhaps the other DNA introduced along with it—was causing the problem. He went public with his conclusion on "World in Action." What his experiments actually showed was that the genetically modified potatoes were different from each other, as well as from their parent lines. When the potatoes were chemically analyzed, the researchers measured total protein concentration, as well as the content of several relevant proteins, including GNA and potato lectin. All of these differed between the unmodified and modified potatoes, as well as between the different lines of modified potatoes. A later study on genetically modified potatoes found the same thing. Rather than the effects of the introduced DNA, what Pusztai was most likely seeing were the effects of somaclonal variation, the variation that arises as a result of tissue culture.

Plant breeders have known about somaclonal variation for decades. The techniques of tissue culture come from the 1950s, when Miller and Skoog identified the ingredient in old herring sperm that would make a plant cell divide and form a callus. Callus culture is commonly an intermediate stage between *Agrobacterium*-mediated transformation and the regeneration of transformed plants. With the right mix of hormones, callus cells divide for a long time; weaned off hormones, the callus turns into a plantlet, with roots, a shoot, and leaves. By 1981 the fact that different regenerated plantlets from a single callus were not identical was well-enough known to be given a name. Somaclonal variation was both a nuisance and an aid. Through screening, breeders could pick and choose among the changes, discarding the bad ones.

Some of the changes, scientists have since learned, are epigenetic, meaning that the modifications affect the expression of genes, but not their structure. These changes can be caused by differences in how the DNA is methylated. Attaching methyl groups to genes shuts them down, silences them, makes them sleep. Taking the methyl groups off awakens them. These changes, though, tend to right themselves quickly once the plants are propagated sexually or through cuttings. More stable genetic changes—deletions, insertions, single base changes, and rearrangements—also arise. Therefore, every new plant derived using tissue culture techniques must be evaluated both for how it grows and for its food properties. Potato breeders know to be especially careful of the toxic glycoalkaloids that potatoes naturally produce. These chemicals, which contribute to inflammatory bowel disease, are concentrated—not destroyed—when potatoes are fried.

Pusztai's conclusion that the variation he observed was due to genetic engineering was unwarranted. His mistake proved costly—and not just to his reputation. Pusztai's experiments have been attacked for their small sample sizes, for the use of inappropriate statistics, and for the fact that a diet of raw—or even cooked—potatoes is bad for rats, even if supplemented with a bit of extra protein. But oddly enough in the entire poisoned rat debate no one seems to have seen the central flaw in Pusztai's experiments: the absence of appropriate controls. The control in an experiment is the material that allows a good comparison to be made in order to understand the consequences of the experimental treatment being studied. In Pusztai's experiments the control potatoes had a different breeding history than the transgenic potatoes, so they couldn't be compared directly to those being tested. Only the genetically modified potatoes had undergone tissue culture. To blame the new DNA for the potatoes' effects on his rats, Pusztai needed control plants that had also come out of tissue culture and were exactly the same as the ones being tested—except for the new genes. Pusztai didn't use such plants.

To a fellow nutritionist, Pusztai's conclusions might have seemed justified. A plant breeder, familiar with the tissue culture technique, would have seen instead the signs of somaclonal variation. The tissue culture-derived potatoes were very different from those the experiment had been started with. It is quite likely that it was the changes that occurred in culture that were responsible for Pusztai's results, not the introduced gene. Perhaps we will never know. But it is quite clear that the expertise battle that sprang up around Pusztai's experiments obscured an important point. When plants are engineered to express new proteins that could affect human health—and lectins are clearly in this category—the foodstuffs produced from them must be analyzed carefully.