

Genetic Engineering and the Allergy Issue

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Although much has been learned since the field was put on a scientific basis at the turn of the last century, our knowledge of food allergies is far from complete. It is still unclear, for example, why only certain individuals are affected and why, even among them, the problem is often restricted to childhood. It is also not clear why the allergies caused by various nuts and aquatic animals tend to persist and be lifelong. Milk, egg, soy, and wheat are the major food allergies in children, whereas peanut, tree nuts, shellfish, and fish are most prevalent in adults.

The field is complicated by the fact that many more people believe they suffer from food allergies than is actually the case. Thus, although up to 20% of Americans have a perceived food allergy, the problem can be medically diagnosed in only about 2% of the population (Altman and Chiaramonte, 1996). The issue is further clouded by confusion with food intolerance and by evidence that allergies are increasing rapidly in developed countries for reasons that are only beginning to be understood. These factors collectively contribute to the lack of understanding that has long been a part of the food allergy field.

Aside from limited attention drawn to the increased prevalence, food allergy has historically attracted little notice. However, with the advent of genetic engineering and its application to the production of food, the situation has changed dramatically. The development and commercialization of a variety of food crops with transgenes has thrust the allergy issue onto a public stage and given the field unprecedented exposure worldwide. Although not yet apparent, I believe the allergy and food technology fields will benefit from this attention in the long term, akin to the progress made in understanding the cellular immune system as a result of publicity brought by the acquired immune deficiency syndrome epidemic.

WHY THE SUDDEN INTEREST?

The increased public awareness of food allergy has arisen from a combination of three factors: reasoned concern, fear through ignorance, and political motivation. The first two factors are expected and limited in scope. The third, which was unanticipated and amplifies the second, stems from the goal of certain individuals and environmental organizations to delay the commercial development of genetic engineering, especially as applied to food. The allergy issue was selected because of its vulnerability: In addition

to its enigmatic nature mentioned previously, opponents of genetic engineering recognized early on that it is difficult to determine with absolute certainty whether a protein introduced into a food by genetic engineering is a potential allergen. In retrospect, one wonders why the allergy issue was not raised earlier—for example, in the countless plant breeding programs since World War II—that significantly have not converted nonallergenic into allergenic foods. A new allergen has been introduced independently of plant breeding. The introduction of kiwi, a relatively obscure fruit, led to the development of a new allergy in the general population of the developed world.

Interest in the allergy issue has been heightened by knowledge that a protein known to be an allergen in one species remains an allergen when transferred by genetic transformation to a second species. An example of such a protein, now widely known, is the Brazil nut allergen (2S protein) transferred to soybean. The allergenicity associated with the original 2S protein in Brazil nut was found to be retained after it was overexpressed in soybean (Nordlee et al., 1996). Although not surprising, this example is reassuring in documenting that the scientific community is capable of detecting and identifying a known allergen that has been transferred from one species to another by genetic engineering. As a result of the allergy tests, the transgenic soy product in question was not further developed as a commercial product.

In this commentary, I shall identify the issues surrounding the allergy issue and discuss their scientific validity, rather than the production of hypoallergenic foods by genetic engineering—a research focus of a number of laboratories, including ours. I then turn to a discussion of the tools available to address the concerns and where we are in their resolution. It will be seen that a solution to this problem appears to lie on the near horizon.

WHAT ARE THE ISSUES?

Concern about the genetic modification of food appears to stem from three questions: Is the protein of interest an allergen? Has the protein of interest become an allergen as a result of the transformation and selection process? Has the transformation and selection process in some unknown way altered a normal cellular protein so that it has become an allergen?

SCIENTIFIC BASIS FOR THE CONCERNS

The first question, whether a particular protein is an allergen, is valid and should be answered. The second question, based on the conversion of the protein of interest into an allergen (for example, by glycosylation) also relates to a change that is biochemically feasible. One would think that indications of such a change would have surfaced with significantly abundant proteins in earlier plant breeding programs. Nonetheless, this point should be tested, at least until we have a greater understanding of the fate of transgenic proteins in plants. The last question, which raises the possibility that a given protein of the cell could become an allergen as a result of transformation and selection, is less tenable. However, this question, like the other two, will continue to be raised until additional experience has been gained and consumers have expressed confidence in genetically modified foods, especially those based on a protein to which the human population has not been previously exposed.

CURRENT TOOLS FOR SOLVING THE PROBLEM

The question of whether a transgene product is an allergen or whether its presence unintentionally renders a food product more allergenic than its nonengineered counterpart is addressed in several ways, including: (a) comparing the predicted amino acid sequence of the transgene product with that of known food allergens; (b) determining the abundance of the protein in food as significant food allergens typically represent one percent or more of the total protein; (c) examining the expressed protein for characteristics often associated with known food allergens, such as glycosylation, heat stability, and presence of disulfide bonds; and (d) monitoring the digestibility of the transgene product in simulated mammalian gastric and intestinal fluids.

Although numerous nonallergens show one or more of the properties often associated with allergens, each analysis provides indirect evidence that is of some predictive value. Moreover, the tests to determine these properties were included in a decision tree that was proposed by Metcalfe et al. (1996). As far as I know, the protocol suggested in that tree has been closely followed in the industrial development of transgenic food products.

However, as a result of recent problems in introducing new transgenic foods, it has become clear that an additional test is needed, namely an animal model for testing genetically modified products.

An animal model is needed to provide a direct test of the allergenic properties for proteins showing potential evidence of allergenicity. Such tests cannot be done on humans directly, ethical considerations aside. Present populations have not been exposed to the engineered food in question and, as a result, would not show an adverse reaction, even if the food con-

tained an allergen. In developing the decision tree, Metcalfe et al. (1996) pointed out the desirability of including an animal model, but did not do so because none "have been shown to predict the allergic potential of introduced proteins." Animal models were also a major topic of discussion at a recent conference dedicated to allergy issues, "Assessment of the Potential Allergenicity of Genetically Engineered Foods" held December 5 and 6, 2000, at the National Center for Food Safety and Technology (Summit-Argo, IL). The advantages and disadvantages of each model were considered at the meeting: Brown Norway rat, guinea pig, dog, pig, and various mouse models. To be beneficial, it was considered that an animal model should: (a) show an allergic response to allergens in humans, but not to nonallergens; (b) show an allergen profile similar to that of humans—for example, the response to a strong allergen (peanut) > moderate allergen (milk) > a nonallergen (spinach leaf); (c) have a gastrointestinal system similar to humans; and (d) ideally, show an epitope response similar to humans. This latter feature was considered a desirable but not a mandatory feature in view of the wide range of epitopes that humans can recognize.

The advantages, disadvantages, and current status of each model were discussed in Summit-Argo. It was agreed that, although decisive progress has been made, none of the current models meets these criteria because characterization and testing is still ongoing. Therefore, at this point it is not clear which of the models will prove to be of most value in detecting and assessing food allergens.

I am personally prone to the dog because, perhaps as a reflection of having a gastrointestinal system similar to humans (Strombeck and Guilford, 1990), it is unique among animal models in having natural allergies as far as is known. The dog shows clinical symptoms typical of food allergy in humans, i.e. vomit and diarrhea (Ermel et al., 1997; del Val et al., 1999). Advances made using the dog will, therefore, benefit dogs as well as humans because of similarities in their allergic response. In recognition of these features, our laboratory started a project to determine the suitability of the dog as a predictor of allergens in humans in collaboration with Dr. Oscar L. Frick (University of California, San Francisco) and Drs. Laura Privalle and Greg del Val (Syngenta, Research Triangle Park, NC). Initiated 3 years ago, this study is now entering its final stage and is yielding encouraging results. The results, which will be published when the study is complete, suggest that the dog will be useful as an animal model. That point notwithstanding, the other models mentioned above warrant continued study, because, in the end, each of several could present a particular advantage in detecting and characterizing allergens in humans.

One precautionary note seems in order. While proceeding with allergy testing, we must be careful not to overregulate and impose undue restrictions to sti-

file innovation. Rather, we should seek to formulate a balanced policy that insures food safety without hindering product development.

CLOSING COMMENTS

Great strides have been made in our understanding of food allergy since the problem was originally recognized by Hippocrates almost 2.5 millennia ago. Despite this rich history, large gaps remain in our knowledge and they are of such nature as to lend an element of mystery to the field. These features have led certain individuals and environmental groups to target food allergy in an effort to slow the commercial development of genetically modified crops and foods and, at the same time, utilize the issue as a fund-raising mechanism. Their efforts have been successful not only by having the intended effect, but also by negatively influencing science funding, especially in Europe. The net result has been that the participating organizations have experienced financial gain and genetically modified crops derived from research in developed countries are now being grown disproportionately in the developing world. For example, between 1999 and 2000, the area used for growing transgenic crops increased by 2% in industrial countries, whereas the area in developing counterparts, although still relatively small in total hectares, grew by 51% (James, 2000). The long-term economic effect of the shift in emphasis to developing countries could significantly impact research on transgenic crops in developed countries unless the situation changes. Such an impact on research would eventually adversely affect hunger and nutrition worldwide because, as recently pointed out in this series (e.g. Borlaug, 2000), continued progress in the genetic engineering of crops is critical to feeding future world populations.

I believe, however, the problem to be transitory and that, once appropriate allergen testing capability is in place, health concerns will abate and the development of transgenic foods will continue apace. As seen above, the needs to bring about this change are not extensive. What seems to be most lacking at this stage is an animal model to identify transgenic plant proteins that either are, or have become, allergens in

humans. Such a model is especially important for proteins to which humans have not been exposed. Had a reliable model been available, it is likely that StarLink corn could have avoided current problems (for example, see Barboza, 2000). Animal test data would have been available to allay consumer concern once the product was on the market. I am confident that, with progress now being made, one or more animal models will soon be available to serve as a reliable indicator of allergens in human and that a safe but reasonable testing policy will be formulated. Once such testing capability is in hand, the public will respond in a positive manner. In the long term, the food allergy and technology fields will likely benefit, rather than suffer, from this pause in their development.

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