Arpad Pusztai's Feeding experiments of GM potatoes with lectins to rats: Anatomy of a controversy 1998 - 2009

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Contents

1. Introduction

The reason to take up the Pusztai controversy is not to justify the safety of GM crops, their success (James, 2008) tells its own tale. Regulation and biosafety research has made dramatic progress since 1997-1998, the time of communicating the first results of the pioneering work of A. Pusztai which caused a backlash and shock to the public, that after all, genetically engineered crops could develop into an unsafe products.

A new and well organized oppositions took happily up the arguments and with a nearly uncontrolled dynamics bitter and emotional disputes started around scientific arguments. These early disputes were organized in a suboptimal way to say the least. It's time to learn the lesson that many non-scientific factors are determining the debate, such as cultural, social issues, not to forget emotions.

But this strategic and tactical shift away from pure science in the dispute will not lead to easy and swift resolutions. It is fact, that opponents of the technology are abusing science, they use the language of science in order to appeal to emotions and to strike fear into the heart of lay people, who have a difficult time to make their own judgment confronted with highly complex matters of modern biotechnology. After all, - and this is somehow strange: politics and consumers still believe in science and its progress, although often denying it for non-rational reasons and proclaiming to be against technological progress.

This is the *real lesson* from the Pusztai affair: We have to realize that a highly scientific controversy triggered something like a turning point in the public opinion of the United Kingdom and sometime later in the whole of Europe.

Well organized opponents have built up a culture of website networks and worse: there are a number of scientists who blow the whistle for good and bad reasons, often in a pseudoscientific and alarmist way, some examples are given in the ASK-FORCE site of www.pubresreg.org , two typical recent cases are

- **(Dona & Arvanitoyannis, 2009)**
  with lots of erroneous statements and extremely selected bibliography, see the rebuttal
  http://www.botanischergarten.ch/AF-7-Dona-rebuttal/Ammann-et-al.-Rebuttal-Dona-AF-7-20090725.pdf

- **(Velimirov et al., 2008)** with a flawed concept of experiments with mice on GM food
  http://www.botanischergarten.ch/AF-5-Austrian-Micestudy-20081214/Austrian-Experiment-Background-1-open-source.pdf (including a list of similar cases)
  http://www.botanischergarten.ch/AF-5-Austrian-Micestudy-20081214/Austrian-Experiment-20081214-open-source.pdf

The above cited alarmist review and the prematurely published report on food safety experiments make it more and more into peer reviewed journals for various reasons, some are so ill-designed that they are – despite an intensive, although controversial website life – never making it into a good scientific journal, despite the fact that many editors in chief crave for more publications which make it into international

debate. Still, it should not be overlooked that in the process of the scientific regulatory process we should remain open in mind for new risks which need legislative reactions.

It is an illusion to seek the solution of ill-fated disputes by adding social and cultural aspects, or worse, that the dispute should so to say start from the other end of the controversy and appeal to feelings and emotions of the public and indulge into entertaining but ultimately meaningless discussions in order to catch the interest of the public. That said. this does not mean, that socio-cultural aspects *and* emotions should be neglected and more importantly it also does not mean that we should fall into the usual tennis matches of who is right or wrong – or worse, that specialists are teaching and preaching lay people, and as such creating a patronizing atmosphere which automatically creates resistance. Well designed schemes of enhancing the discourse are offered by (Rittel & Webber, 2005) (Ammann & Papazova Ammann, 2004) and (Osseweijer, 2006a, b), strictly based on good science.

Still, some of the most prominent critics of the deficit model such as (Sturgis & Allum, 2004) come to a surprising conclusion: They do not cast the rather simplistic *deficit model* that has traditionally characterized discussions alone, rather they propose to combine it with the *contextualist approach*, thus emphasizing the complex and interacting nature of the knowledge-attitude interface.

The still underestimated revolutionary introduction of the world wide web (only available since a few years with all its recent ramifications) invites to *collaborative* instead of *confronting* modi. It is offering in a strikingly democratic way access to a gigantic amount of knowledge, which we need to organize properly for easy and reasonable access and combine it with the experience of sustainable development activities into wisdom. It will be difficult to balance excellent science with a convincing and successful dialogue with consumers and politicians.

Mind-full of this introduction it is good to find back to the roots of the *science* of the food-safety debate, and we have to realize that one of the main starting points was the publication of A. Pusztai:

2. How it all started

Pusztai published papers on nutritional effects of lectins way before the he went to press with some results of his latest project, here just one example (Pusztai et al., 1990)

"The effects on the small intestine and the growth of rats of six pure plant lectins: PHA (Phaseolus vulgaris); SBL (Glycine maxima); SNA-I and SNA-II (Sambucus nigra); GNA (Galanthus nivalis) and VFL (Viciafaba), covering most sugar specificities found in nature, were studied in vivo. Variable amounts, 25% (VFL) to 100% (PHA, GNA) of the lectins administered intragastrically, remained in immunochemically intact form in the small intestine after 1 h. ***All lectins, except GNA, showed binding to the brush border on first exposure, although this was slight with VFL****. Thus, binding to the gut wall was not obligatory for resistance to proteolysis. Exposure of rats to lectins, except VFL, for 10 days, retarded their growth but induced hyper-plastic growth of their small intestine. The two activities were directly related. PHA and SNA-II, whose intestinal binding and endocytosis was appreciable after 10 days of feeding the rats with diets containing these lectins and similar to that found on acute (1 h) exposure, were powerful growth factors for the small intestine.* ***GNA, which did not bind at the start but was reactive after 10 days, and SNA-I, which behaved in the opposite way, induced changes in receptor expression in the gut. As they were bound to the brush border transiently, they were less effective growth factors.*** *VFL was not bound or endocytosed, was non-toxic and did not promote gut growth*."

The Rowett affair erupted on 10 August 1998, when Pusztai appeared on Granada's TV show *World in Action* (with the explicit permission of the director of his institute) and declared that transgenic potatoes had stunted growth and suppressed immunity in rats that had eaten them for 110 days. His statements were misunderstood by the press, their writers were not able to distinguish properly between the experimental details and the general assumption that GM food could be unsafe altogether.

This way the statements of Pusztai were spread without scientific scrutiny, a really unfortunate start for a debate which actually should be based on science. The irony is, that A. Pusztai used the jargon of science, used his reputation as a widely known food scientist, but was for months not called to order and submit his data to the often harsh process of scientific review. And as we will see from the press statement of the Rowett institute, he produced confusion by actually not really talking about transgenic potatoes but presented results of GNA (a lectin)- impact on transgenic potatoes. But the way A. Pusztai recalled his press conference is completely different as shown below in his own recollection from memory ten years later:

The way, A. Pusztai sees this starting point in the hindsight after 10 years (Pusztai, 2008).

From a letter of Pusztai he wrote at the occasion of the 10th anniversary of his first press conference [the sic!s are placed by K.A.]

*"On this anniversary I have to admit that, unfortunately, not much has changed since 1998. In one of the few sentences I said in my broadcast ten years ago, I asked for a credible GM testing protocol to be established that would be acceptable to th**e** majority of scientists and to people in general [sic!]. 10 years on we still haven't got one [sic!]. Instead, in Europe we have an unelected EFSA GMO Panel with no clear responsibility to European consumers, which invariably underwrites the safety of whatever product the GM biotech industry is pushing onto us.*

All of us asked for independent, transparent and inclusive research into the safety of GM plants, and particularly those used in foods. There is not much sign of this either. There are still "many opinions but very few data"; less than three dozen peer-reviewed scientific papers have been published describing the results of work relating to GM safety that could actually be regarded as being of an academic standard; and the majority of even these is from industry-supported labs. Instead we have the likes of Tony Trewavas and others writing unsupported claims for the safety of GM food and defaming people like Rachel Carson who can no longer defend herself; not that she needs to be defended from such nonentities."

"Dr Pusztai was interviewed for a program about GM food being made by Granada TV's 'The World in Action'. The filming took place in late June 1998 with the agreement of the director of the Rowett Institute, Professor James, and in the presence of the R"owett Institute's press officer. The World in Action interview was broadcast on the evening of Monday 10th August 1998.

Later that evening Professor James congratulated Dr Pusztai on his TV appearance, commenting on 'how well Arpad had handled the questions'. The next day a further press release from the Rowett noted that 'a range of carefully controlled studies underlie the basis of Dr Pusztai's concerns'. However, reportedly following two calls to the Rowett from the Prime Minister's Office, the Government, the Royal Society and the Rowett launched a vitriolic campaign to sack, silence and ridicule Dr Pusztai."

The interview was very short, 150 seconds, and, according to another Inerview Pusztai gave in Canada 2000 (Pusztai, 2000a):

"It is now over two years. With the consent of my director and my Institute I gave a very, very short interview for television. It was all of 150 seconds. I simply said, and this is on record, that we had done some work with one

particular GM crop we are not eating this and we found that when we fed this to rats, we had some problems. Some of the rats were not growing as well, some of the rats had problems in the development of the insides, the immune system. ***Our concern was that, even though this is not eaten, British public is already eating things that had not been tested by similar methods****. Because of this, as a publicly funded scientist, I should really raise my concerns. And that was it."*

He made, as you can see in the bolded text above, some really inflammatory statements without presenting the scientific data. The reaction in the press in the next days was indeed devastating for the whole method of genetic engineering of crops.

The press release of the Rowett Institute one day later on August 12, 1998 (Rowett Institute, 19980812) herefore followed swiftly and int was justified:

Genetically Modified Foods
Rowett Research Institute 12. August 1998
"This week's intense and global publicity given to Dr. Pusztai's work and its implications has led to the Rowett Research Institute's decision to carry out a fully audited analysis of the date before they are presented to MAFF and EU Committees dealing with the issue of the safety of genetically modified foods. This field is of exceptional importance to the public.

The Directors and the Senior Manager involved were therefore presented yesterday with a preliminary view of the primary laboratory data by Dr. Eva Gelencser, the member of the team who carried out the studies on immune responsiveness under the supervision of Dr. Pusztai. She had returned to the institute from abroad yesterday morning. ***By late yesterday it emerged that the relevant data provided by Dr. Pusztai referred not to experimental studies on potatoes with transgenic Con A but to GNA transgenic potatoes****. The detailed analyses on the transgenic GNA studies are due to be completed by Friday of this week and were not data, as originally suggested, which had been discussed extensively at scientific meetings involving UK collaborators and the Scottish Office in April of this year. All the preparations for the transgenic Con A feeding trials are complete but the only data available on Can A are, in practice, the long-term studies with Con A added to the potato based diets.*

This morning the director suspended Dr. Pusztai from all responsibility for Institute. UK and European studies on these issues and ***Dr. Pusztai will now retire from the Institute.*** *Dr. Andrew Chesson, a member of the EU's DG XXIV's working party on the safety of genetically modified foods will be put in charge of all data analyses and presentations to MAFF and the EU. Dr. Chesson will work in conjunction with a molecular biologist, Dr. Harry Flint, who has not previously been directly involved in this work. Collaborating Institutions will be asked to nominate an expert to audit the work.* ***The original decision by the Institute to allow Dr. Pusztai to respond to the "World in Action" request for information was based on the Institute's recognition of its responsibility not to suppress scientific views of importance in this, or any other, field****. It was recognized and agreed that previously published concepts relating to the use of lectins as transgenics could be discussed* ***but that it was improper to present data which had not been publicly scrutinized by a variety of international experts and published****. Senior Managers and special staff with responsibility for scientific issues of public interest were assigned to ensure that this agreement was adhered to.* ***It is therefore regrettable that discussions with the media at other times led to the presentation of information which misled everybody concerned****. The long and complex studies on the use of lectins in transgenic plants, including published as well as unpublished work, will now be reviewed to ensure the validity of the findings. The GNA transgenic studies and comparable experiments on diets where both GNA and Con A have been added to the potato mix will be collated for urgent transmissions to MAFF and the EU.* ***This morning it would be premature to conclude whether or not there are data of concern to those assessing the safety of foods with transgenic lectins****. The analysis of the new findings will not be released by the Institute but will be scrutinised by collaborating*

groups of scientists and official expert committees. The Institute will also arrange to do appropriate additional studies on these safety issues once the significance of the current findings is clear. The Institute regrets the release of misleading information about issues of such importance to the public and the scientific community.

The Rowett Research Institute is an independent government sponsored institution for nutrition and has a range of research concerned with assessing the risk of genetically modified foods. The Institute has the responsibility to help develop new and better approaches to the risk of genetically modified foods. The Institute's staff recognise the great potential value of genetically modified foods and collaborate with a wide range of scientists, companies and government around the world in helping to assess the value and safety of such products. (Rowett Institute, 19980812) Copyright 1998 Rowett Research Institute (Press Release) All Rights Reserved Press Release August 12, 1998, one day after Pusztai's going to TV

The way the Rowett institute describes the situation one year later: Press release: 16 February 1999 (Rowett Institute, 19990216)

"The intense publicity induced by the press conference in Westminster last Friday suggested that the Rowett Research Institute had limited Dr Pusztai's ability to express his concern about GMOs. The Institute has therefore decided the following:

1. We hereby release Dr Pusztai's October 22nd alternative report in its entirety. This report was requested by the Rowett in response to an audit committee's analysis of the validity of Dr Pusztai's statement on the World in Action programme on August 10th 1998.

2. This report was produced by Dr Pusztai himself. At no time were the participant collaborators in SCRI and Durham University involved in the production of this report.

3. The audit committee's response to the alternative report is also attached.

4. Dr Pusztai is no longer required to observe the usual conventions of many scientific research institutes in relation to public disclosure of unpublished work. The Institute can therefore no longer be responsible for his analyses or views.

The Institute does, however, require that Dr Pusztai's research findings be discussed with other participants in this project if papers are submitted for peer review.

The Institute has identified the studies (contained within the original audit report) which were used to produce a variety of tissues for histological analyses. The background to these studies will be sent to the Government's Advisory Committee on Novel Foods and Processes so that any results which they obtain from Dr Stan Ewen at Aberdeen Medical School can be seen in context.

Dr Pusztai has been repeatedly requested to provide papers for publication on all this work.

As yet he had not done so.

We are seeking independent external review of the specific areas covered by this research. We would expect the review to seek the co-operation of Drs Pusztai and Ewen in the assessment of their work.

The Rowett remains of the view that independent publicly funded research to improve the analytical approach to evaluating genetically modified foods is important. The Institute's function is to undertake research in the public interest. The Institute's strategy is not conditioned by political, industrial or vested interests. The Institute receives about 90% of its income from public sources with a subsidiary commercial company undertaking about 10% additional contract work. A current contract with Monsanto represents less than 1% of Rowett income. The research is looking at ways to improve the digestion of feed in cattle and is not related to the issue of genetically modified food.

The Institute considers Dr Pusztai as having undertaken valuable work over many years. His ideas on the use of lectins are important contributions. The basic research to develop better understanding of GM foods is continuing with Scottish Office and other funding at the Rowett and elsewhere."

The chronology of the correspondence can be seen on A. Pusztai's personal website: (Pusztai, 2009)

Probably the most accurate description of the events around the Pusztai press conference and the reaction of the Rowett Institute two days later and in the period until end of 1999 have been described by a sequence of articles in Science (Enserink, 1998; Enserink, 1999a, b, c).

The major reason why the statements of Pusztai based on his flawed experiments were so successful, is because the field was already prepared in 1998, things turned sour, despite the vote in Switzerland positive for Biotech, the situation got gradually worse, as nicely demonstrated by (Williams, 1998): The press conference of A. Pusztai on August 11 1998 came in a critical moment for the GM food debate in Europe and as it was shown over the years, his unfortunate statements with blunt generalizations had a devastating impact, and there was for a long period no peer reviewed publication available, which came as late as October 22 in a Research letter in Lancet (Ewen & Pusztai, 1999a), in fact too late to really influence the public opinion at that time.

The original research report of A. Pusztai can be downloaded from the Rowett Institute website, it is dated from 22. October 1998 (Pusztai, 1998).

Summary conclusions:

"After GNA gene insertion into potatoes changes in protein, starch, sugar, lectin and trypsin/chymotrypsin inhibitor levels were observed in the tubers of two generations of two GNA-GM lines suggesting "possible gene silencing, suppression and/or somaclonal variation" in the potato genome. The GNA-GM-potato lines investigated as part of the Rowett's work program in FF 818 were therefore not "substantially equivalent" to the appropriate parent tubers.
Four feeding trials were carried out with two lines of GNA-GM-potatoes. In all four experiments feeding transgenic potatoes to rats induced major and in most instances highly significant changes in the weights of some or most of their vital organs. This was not abolished even when high-quality lactalbumin supplied two-third of the protein in the diet (D249). Particularly worrying was the partial liver atrophy observed with cooked transgenic potatoes in all short-time (10 day) studies. Immune organs, such as the spleen and thymus were also frequently affected. These results therefore indicated that similar to the lack of equivalence in composition there is also a lack of equivalence in the metabolic consequences between feeding of GM and parent potatoes even though that "potato GNA" in GNA-GM-potato diets appears to show functional equivalence to "snowdrop GNA" in parent potato diets spiked with GNA. The growth rate of rats fed potato diets was slightly but significantly less than that of rats fed a high-quality control diet but the presence of GNA, whether added to potato-based diets or expressed in the transgenic tuber line 71/1, had no significant effect on weight gain and weight change compared to parent potato lines. However, in most instances the presence of GNA-GM potatoes in the diet caused some slowing down the digestion and absorption of nutrients in the gut in comparison with parent line diets. This was only observed with diets in which potatoes supplied the major part of dietary protein (D227 and D242) and the effect reached full significance in experiment D242.
Feeding rats with GNA-GM-potatoes significantly reduced their lymphocyte responsiveness to mitogenic stimuli after 10 days compared to parent controls that was not abolished by raising the high-quality protein (lactalbumin)

concentration to superoptimal nutritional levels. However, as in long-term feeding the lymphocyte proliferative response of all rats fed potato-based diets was reduced to non-stimulated levels, no significant differences were observed in lymphocyte responsiveness between GNA-GM-potatoes and their parent counterparts in long-term (110 day) feeding experiments.
Accordingly, the Coordinator of FF 818 SOAEFD commissioned program is of the opinion that the existing data fully support our suggestion that the consumption by rats of transgenic potatoes expressing GNA has significant effects on organ development, body metabolism and immune function that is fully in line with the significant compositional differences between transgenic and corresponding parent lines of potatoes."

Its conclusions are clearly contradicted, as we will see below in 4.2 and 4.3.

3. The Issue of the Rat Experiments of A. Pusztai as an example

In an article in Lancet by (Ewen & Pusztai, 1999a) which was published by the editor in chief Richard Horton on October 22, 1999 under the pretext that the public debate should be conducted on grounds of a journal publication:
"Diets containing genetically modified (GM) potatoes expressing the lectin *Galanthus nivalis* agglutinin (GNA) had variable effects on different parts of the rat gastrointestinal tract. Some effects, such as the proliferation of the gastric mucosa, were mainly due to the expression of the GNA transgene. However, other parts of the construct or the genetic transformation (or both) could also have contributed to the overall biological effects of the GNA-GM potatoes, particularly on the small intestine and caecum."
However, in the same journal (Kuiper et al., 1999c) published a rebuttal. after having been alerted by one of the numerous preprints of Ewen and Pusztai in hand (hardly legible due to multiple fax rounds):
"The experiments done by Ewen and Pusztai were incomplete , included too few animals per diet group, (OECD, 1998a) and lacked controls such as a standard rodent diet containing about 15% protein (lactalbumin) as a balanced source of amino-acids (National Research Council NAP, 2004) and a test diet with potatoes containing an "empty " vector. Therefore the results are difficult to interpret and do not allow the conclusion that the genetic modification of potatoes accounts for adverse effects in animals."

In a summary of the whole controversy related to the dispute about facts and results it can be said that the issue is basically settled, the concerns the way Pusztai generalized them can be dismissed. However, it remains fact that the Pusztai experiments per se have never been repeated – on one side this is deplorable, but keeping in mind that since the pioneering experiments of Arpad Pusztai the methodology of food biosafety research has made enormous progress, the original study became obsolete in specific research questions and in methodology. There is also another reason why the experiments have not been repeated: In Switzerland for instance rat experiments using such feed as raw (and also cooked) potatoes over extended periods of time would hardly pass scrutiny by the ethics committees on animal experimentation. As cited below, there are dozens of excellent experiments with the present day transgenes inserted into GM crops which demonstrate no detrimental effects for human consumption. The research protocols have been refined step by step (OECD, 1998a, b, c, d, 2007; Sesikeran & Vasanthi, 2008; Toyoda et al., 2000). A recent report summarizes good practice for animal experiments related to food safety: (Chassy et al., 2004; Chassy & Parrott, 2009).

The scientific assessment of the publication of Ewen and Pusztai remains critical and results did not convince the great majority of the scientific community involved in such research. The reason why ASK-

FORCE is taking up this "old hat" are given in the introduction: it's a learning piece of the GM food safety debate and also because it is still lingering in the websites of the opponents.

The reasons of the scientifically negative assessments of the Pusztai experiments are given below in chapter 4 and 5.

4. Background related to the publication process of the study of A. Pusztai in Lancet

It is interesting to know more about the background and reasoning of the original Lancet publication of the results. Richard Horton (Horton, 1999a, d), the editor in chief of Lancet gave the reasons, why he decided to publish the study of (Ewen & Pusztai, 1999a) in Lancet:

"The trigger for much of this despondency was the public debate that followed Pusztai's television revelations. The data on which this media furore was founded are published for independent assessment in this week's issue of *The Lancet*, 18 months after their first public release. The Research Letter by Stanley Ewen and Pusztai was received by the journal towards the end of 1998. Since then, it has been peer reviewed by six specialist advisers—a nutritionist, a human pathologist, a veterinary pathologist, an agricultural geneticist, a plant molecular biologist, and a statistician —who had several requests for clarification about the design of the study, the laboratory methods used, and the statistical tests applied. Some advised rejection; others encouraged us to go ahead and publish. The authors revised their letter three times to try to meet our reviewers' criticisms. The Royal Society's own internal review of the Pusztai data had led to the damning verdict that the study "is flawed in many aspects of design, execution, and analysis and that no conclusions should be drawn from it". So why publish the paper? The answer lies partly in a February, 1999, statement from the UK's chief scientific adviser, Robert May.(May, 1999) While criticizing the researchers' "sweeping conclusions about the unpredictability and safety of GM foods", he pointed to the frustration that had dogged this entire debate:

"Pusztai's work has never been submitted for peer review, much less published, and so the usual evaluation of confusing claim and counter-claim effectively cannot be made". This problem was underlined by our reviewers, one of whom, while arguing that the data were "flawed", also noted that, "I would like to see [this work] published in the public domain so that fellow scientists can judge for themselves . . . if the paper is not published, it will be claimed there is a conspiracy to suppress information". Publication of Ewen and Pusztai's findings is not, as some newspapers have reported, (Lean, 1999) a "vindication" of Pusztai's earlier claims. On the contrary, publication of a paper after substantial review and revision provides a report that deserves further scientific attention. Such wider appraisal begins in this week's *Lancet* with the commentary by Harry Kuiper and colleagues."

It should be noted, that after reading the rebuttal of (Kuiper et al., 1999b) it is an unacceptable euphemism to label his paper under a "wider appraisal", on the contrary, this is the first of a long series of clear-cut rejections of the original paper on multiple grounds.

The work of (Ewen & Pusztai, 1999a) claims to demonstrate some possible interaction between a lectin expressed in potato and alterations in the potato caused by the genetic engineering process. According to the study, diets containing genetically engineered potatoes expressing the lectin, *Galanthus nivalis* agglutinin (GNA), showed some effects on different parts of the rat gastrointestinal tract. Those effects fell into two categories, ones caused by the GNA transgene itself and others caused by pleiotropic effects of expressing the transgene. Two important excerpts from the conclusion part of their original text:

"Feeding rats on diets containing GM potatoes, irrespective of whether raw or boiled, had no significant effect on colonic crypt length compared with that in animals fed the corresponding parent-line potatoes (table 1). Rats fed on GNA-supplemented

parent potatoes had significantly shorter colonic crypt lengths than those fed on parent potatoes of GNA-GM potatoes; the reason for this finding is not clear.

In conclusion, the stimulatory effect of GNA-GM potatoes on the stomach was mainly due to the expression of the GNA transgene in the potato. By contrast, the potent proliferative effect of raw GNA-GM potatoes on the jejunum, and the antiproliferative effect of boiled transgenic potatoes on the caecum can be attributed only partly to GNA gene expression. Other parts of the GM construct, or the transformation, could have contributed to the overall effects. Once bound, GNA is internalized by endocytosis;2 some other component of the construct in the GNA-GM potato or its expressed gene product might also be able to penetrate and affect the rat mucosal cells in a similar manner. The growth-promoting effect of raw GNA-GM potatoes in the jejunum, evident as crypt hyperplasia, is probably due to a direct stimulatory effect on crypt cells; the increase in T lymphocyte infiltration may be important in the elimination of damaged enterocytes.3 The possibility that a plant vector in common use in some GM plants can affect the mucosa of the gastrointestinal tract and exert powerful biological effects may also apply to GM plants containing similar constructs, particularly those containing lectins, such as soya beans or any plants expressing lectin genes or transgenes."

5. Analysis of the Results of the Study of Ewen and Pusztai 1999

Analysis of the work of Ewen and Pusztai by the Royal Society 1999 and by (Kuiper et al., 1999a), and many others in an extensive controversy (Ewen & Pusztai, 1999c, f; Feldbaum, 1999a, c; Horton, 1999b, e; Malcom, 1999; Mowat, 1999b) indicates that the study lacked scientific rigor. The (Ewen & Pusztai, 1999d) reply was not very convincing, and later e.g. (McHughen, 2005) came to the same conclusions. For example, data concerning the biochemical composition of the potatoes used in the study show that the non-transgenic variety differed significantly from the transgenic variety. Consequently, the differences in the results could be attributable to natural variations in potato lines *and are not necessarily due to the genetic modification* (Kuiper et al., 1999b).

5.1. Rebuttal in the same Lancet Volume of H. Kuiper

A summary of (Kuiper et al., 1999c):

"Stanley Ewen and Arpad Pusztai report that , w**h**en fed to rats , GM potatoes containing the GNA lectin have proliferative and anti-proliferative effects on the gut. They suggest that several of these effects are due to alterations in the composition of the transgenic potatoes , rather than to the newly expressed gene product. However , data on the composition of the different diets are not reported in the letter. Pusztai has released some of these details on the internet http//www.rri.sari.ac.uk/gmo/ajp.htm . These details indicate that the content of starch, glucose-polymers , lectin , and trypsin and chymotryps-inhibitors in GM potatoes differed from that of the parental line. Unfortunately, these differences have not been examined further by analysis of an extended range of lines, for evidence on whether these differences are attributable to the genetic modification or to natural variations. Another shortcoming of the study is that the diets were protein deficient; they contained only 6% protein by weight . There is convincing evidence that short-term protein stress and starvation impair the growth rate , development , hepatic metabolism, and immune function of rats. (Konno et al., 1993) (le Moullac et al., 1992), Ewen and Pusztai say that the significant differences between diet groups in variables such as mucosal thickness or crypt length are evidence of the biological effects of the GM foods. Such a claim is easy to make but difficult to prove , because no consistent patterns of changes were observed in the study. Ingestion of potatoes maybe associated with several adaptive changes in the gut because of the low digestibility of raw or partly refined potato starch. In rats caecal hypertrophy is a common response to short - term feeding of various poorly digestible carbohydrates , such as raw potato starch .3 , 4 A physiological response of this nature is probably of little toxicological significance. Dose - response studies would have helped in the assessment of consistency of response.

The experiments done by Ewen and Pusztai were incomplete , included too few animals per diet group, (Gelbke et al., 2007; OECD, 1998a; Toyoda et al., 2000) and lacked controls such as a standard rodent diet containing about 15% protein (lactalbumin) as a balanced source of aminoacids6 and a test diet with potatoes containing an "empty" vector. Therefore the results are difficult to interpret and do not allow the conclusion that the genetic modification of potatoes accounts for adverse effects in animals. Similar criticisms of this work have been made by the Royal Society http://www.royalsoc.ac.uk/st_pol54.htm."

It is also interesting to note the basic difference between the original claims of Pusztai made in unpublished reports and media contributions and the claims Ewans and Pusztai published in Lancet, see the comments of Dixon (Dixon, 2003):

"Most reporters missed or ignored the simple fact that the paper did *not* support Pusztai's original claims at all (that raw GM potatoes impaired growth and immune responsiveness in rats). It was about something totally different : the microstructure of the small intestine. Moreover, the editor of *The Lancet* published this paper, against peer review advice, not because he believed the findings to be generalizable, but simply to place the authors' evidence in the public domain so that it could be evaluated."

5.2.The audit report of the Rowett Institute

A major blow to the Ewen-Pusztai study 1999 came from the audit report of the Rowett Insitute, which is now again available in a scanned copy, (Rowett Institute, 1998). The paragraphs referring to the Evaluation of the results is given here in extenso, p.3-4: It is clear-cut negative in the conclusions:

"Evaluation of the results by the audit committee

Attached is the formal report of the audit group. As is made clear in the Audit Report, one long-term feeding study and several short-term studies were made with potato tubers expressing GNA. These showed, as expected, no discernable effect on growth. No comparable experiments were made with transgenic plants expressing the Con A gene.

One long-term feeding study, however, was made with potato-based diets to which ConA had been added in a concentration some 5000-times that found in potato tubers expressing the conA gene. Addition of isolated conA at this concentration did cause a small depression in growth rate. Studies have been made on the effects of lectins on mammalian cells in laboratory

Experiments which have led to the observation that some lectin scan stimulate cell division (i.e are mitogenic). However, lectins from different sources have different properties and thus one lectin may be mitogenic, while another lectin is not. with the exception of several well-studied lectins, little is known about their precise effects when fed as part of the diet on the cells of the gut and immune systems of mammals. Given the interest in the possible future introduction of lectin genes to provide pest resistance in crops, it is important that suitable tools are developed to evaluate the potential effects of lectins on animals including any possible effect on the immune System.

Unfortunately in the course of developing appropriate tools, difficulties were encountered with the lymphocyte proliferation assay selected as a preliminary test of immune function These early results were far too variable to allow any conclusions to be drawn or even to allow any effects to be suggested. ***This led the Audit committee to their final conclusion that the existing data do not support any suggestion that the consumption by rats of transgenic potato tubers expressing GNA lectin has any effect on growth, organ development or immune function."***

5.3. The Audit Report of the Royal Society

The original Royal Society Audit report on the Pusztai experiments cannot be downloaded, but a comprehensive summary is available at http://www.royalsoc.ac.uk/st_pol54.htm (Royal Society, 1999). The result of the Royal Society Audit is clear: The published data demonstrate that they do not allow Pusztai's interpretation of detrimental effects on rat organs of GM potatoes and also they cannot be generalized as a major criticism of the regulation of GM food.

Excerpt of the audit summary:

- *"The safety of GM plants is an important and complex area of scientific research and demands rigorous standards. However, on the basis of the information available to us, it appears that the reported work from the Rowett is flawed in many aspects of design, execution and analysis and that no conclusions should be drawn from it.*
- *We found no convincing evidence of adverse effects from GM potatoes. Where the data seemed to show slight differences between rats fed predominantly on GM and on non-GM potatoes, the differences were un-interpretable because of the technical limitations of the experiments and the incorrect use of statistical tests.*
- *The work concerned one particular species of animal, when fed with one particular product modified by the insertion of one particular gene by one particular method. However skillfully the experiments were done, it would be unjustifiable to draw from them general conclusions about whether genetically modified foods are harmful to human beings or not. Each GM food must be assessed individually.*
- *The whole episode underlines how important it is that research scientists should expose new research results to others able to offer informed criticism before releasing them into the public arena."*

Regarding the methodology used, the comments are clearly negative in this report

"In summary, the data presented to the reviewers and Working Group are inadequate for the following reasons:

- *poor experimental design, possibly exacerbated by lack of 'blind' measurements resulting in unintentionally biased results;*
- *uncertainty about the differences in chemical composition between strains of non-GM and GM potatoes;*
- *possible dietary differences due to non-systematic dietary enrichment to meet Home Office and other requirements;*
- *the small sample numbers used in experiments testing several diets (all of which were non-standard diets for the animals used) and which resulted in multiple comparisons;*
- *application of inappropriate statistical techniques in the analysis of results;*
- *lack of consistency of findings within and between experiments."*

The report itself concluded that feeding transgenic potatoes containing a toxic snowdrop lectin gene GNA (*Galanthus nivalis* agglutinin) to rats resulted in cell proliferation of the gastric mucosa. According to Pusztai this effect could be attributed to GNA, since GNA added to normal potatoes had the same

effect. Increases in colonic crypt length of the jejunum and decreases in caecal mucosal thickness were suggested to result from the genetic transformation of the potato, rather than the presence of GNA per se.
For more details, go to the Royal Society Reviewer Reports http://www.botanischergarten.ch/Pusztai/Royal-Society-Reviewer-Reports-1999.PDF and go to the reply of A. Pusztai to the full report: http://www.botanischergarten.ch/Pusztai/Pusztai-Reply-to-Royal-Society-Report-19990518.PDF

A detailed account on the origin of the Pusztai debate has been published in Science (Enserink, 1998; Enserink, 1999a, b).

On February 12 1999, Professors Edilbert van Driessche and Thorkild C. Bøg-Hansen, colleagues who had collected the responses of their call for support of Pusztai to some colleagues, issued a memorandum supported by more than 20 other scientists who had studied Dr. Pusztai's findings (Gillard et al., 1999; Lee & Tyler, 1999; Van Driessche, 1999). Most of those scientist have not been in the possession of the full data set and were not really aware of the full controversy, they supported Arpad Pusztai as a good colleague and as a scientist with a good name as food scientist.

5.4. The Reaction of Arpad Pusztai

It is only fair to cite Arpad Pusztai's subsequent publications, where he admits quite frankly that some of the criticism is actually correct, his defense is also remarkable, insofar as he describes his work as pioneering experiments and needed correction during the course of experimentation, and also that subsequent experiments can be improved, as he suggested himself in (Pusztai, 2000b):

"I therefore suggested for the next stage in the regulatory risk assessment process an animal testing protocol based on methods already used in animal feedstuff evaluation. One group of young animals should be fed on carefully formulated diets into which the OM crop is incorporated. Their biological responses should be compared to those of two control groups of physically and genetically identical animals fed on diets that are the same except that they contain the same crop in non-GM form, with and without spiking with the isolated gene product, respectively. All three groups should be assessed over a number of generations using a variety of tests, such as monitoring weight and analyzing blood. urine and faeces on a regular basis. All experiments should include male and female animals and be followed by studies of reproductive performance for several generations. Evaluation should be by appropriate analysis to establish any significant differences. If there are differences between those animals fed on GM and unmodified diets, then the genetic modification must have had a effect on the utilization and nutritional value. Such a GM crop therefore could not be used in human or animal diets. If both the GM and unmodified diet spiked with the gene product show differences, the use of this gene is unacceptable. If spiking the non-GM diet with the gene product does not affect the animals, the harm caused by the OM diet is the result of unexpected effects of the gene insertion. If no harmful effects are detected in animals, the results will have to be validated using human volunteers, with the usual stringent safeguards - that is, clinical double-blind, placebo-type testing. I believe that if my critics are willing to embrace the concept of biological testing, these methods are available for the work to start. Alternatively, they are free to propose methods of their own. Either way, it must be done openly, transparently and inclusively to convince a skeptical public about the safety of GM food."

So, for some elements, he accepted the criticism by the Royal Society, for other elements he has some good arguments ready (it should be clarified whether the arguments below actually were not known to the Royal Society reviewers).

In his replies to various comments (see 2.3.) Pusztai also revealed more data, which shed some more light on his experimental activities: (Pusztai, 1998).

"The results clearly show that the contents of some or all of the constituents of major nutritional importance in GM-potatoes are significantly different from those of their respective parent lines. Thus, although the true protein content of the tubers of 71/1 lines (used in D227) is similar, the GNA-GM 74/2T potato line used in 3 of the main feeding trials (D237, D242 & D249), regardless whether raw or baked, contained nearly 20% less protein than its respective parent. The starch and/or glucose contents of the parent and GNA-GM tubers were also different. Similar findings were made for antinutrient contents. Thus, the potato lectin (PL) content of most GM lines was significantly different from the appropriate parent. Indeed, in one instance, the PL content of 74/26 GNA-GM line was well over double of that of the parent line. Similarly and almost without exception, contents of trypsin inhibitors and chymotrypsin inhibitors of the GM and appropriate parent lines were significantly different. The results of changes in protein, starch, sugar, lectin and trypsin/chymotrypsin inhibitor levels in potato tubers after GNA gene insertion taken in conjunction with the preliminary results by SCRI scientists (Interim SCRI Report - FF 818; April 1998) showing decreased foliar glycoalkaloid content in various lines of GM-potatoes clearly **"indicate possible gene silencing, suppression and/or somaclonal variation"** as a result of gene insertion. It is therefore clear that in contrast to the conclusions of the Audit Report the **GNA-GM-potato lines investigated as part of the Rowett's work programmed in FF 818** were not "substantially equivalent" **to the appropriate parent tubers."**

And:

"Summary conclusions:
After **GNA** gene insertion into potatoes changes in protein, starch, sugar, lectin and trypsin/chymotrypsin inhibitor levels were observed in the tubers of two generations of **two GNA-GM lines suggesting "possible gene silencing, suppression and/or somaclonal** variation" in the potato genome. The GNA-GM-potato lines investigated as part of the **Rowett's work programmed in FF 818 were therefore not "substantially equivalent" to the appropriate parent tubers.**
Four feeding trials were carried out with two lines of GNA-GM-potatoes. In all four experiments feeding transgenic potatoes to rats induced major and in most instances highly significant changes in the weights of some or most of their vital organs. This was not abolished even when high-quality lactalbumin supplied two-third of the protein in the diet (D249). Particularly worrying was the partial liver atrophy observed with cooked transgenic potatoes in all short-time (10 day) studies. Immune organs, such as the spleen and thymus were also frequently affected. These results therefore indicated that similar to the lack of equivalence in composition there is **also a lack of equivalence in the metabolic consequences between feeding of GM and parent potatoes** even though that "potato GNA" in GNA-GM-potato diets appears to show functional equivalence to "snowdrop GNA" in parent potato diets spiked with GNA. The growth rate of rats fed potato diets was slightly but significantly less than that of rats fed a high-quality control diet but the presence of GNA, whether added to potato-based diets or expressed in the transgenic tuber line 71/1, had no significant effect on weight gain and weight change compared to parent potato lines. However, in most instances the presence of GNA-GM potatoes in the diet caused some slowing down the digestion and absorption of nutrients in the gut in comparison with parent line diets. This was only observed with diets in which potatoes supplied the major part of dietary protein (D227 and D242) and the effect reached full significance in experiment D242.
Feeding rats with GNA-GM-potatoes significantly reduced their lymphocyte responsiveness to mitogenic stimuli after 10 days compared to parent controls that was not abolished by raising the high-quality protein (lactalbumin) concentration to superoptimal nutritional levels. However, as in long-term feeding the lymphocyte proliferative response of all rats fed potato-based diets was reduced to non-stimulated levels, **no significant differences were observed in lymphocyte responsiveness between GNA-GM-potatoes and their parent counterparts in long-term (110 day) feeding experiments.**
Accordingly, the Coordinator of FF 818 SOAEFD commissioned programmed is of the opinion that the existing data fully support our suggestion that the consumption by rats of transgenic potatoes expressing GNA has significant effects on organ development, body metabolism and immune function that is fully in line with the significant compositional differences between transgenic and corresponding parent lines of potatoes."

And in a direct response to the Royal Society Report:
http://www.botanischergarten.ch/Pusztai/Pusztai-Reply-to-Royal-Society-Report-19990518.PDF

5.5. Conclusions of A. Pusztai

> "In contrast to the conclusions in the RS Report which is based in most instances on poor refereeing and **using inappropriate internal reports** for their peer-reviewing, our data reliably and convincingly demonstrate that the inclusion of GM-potatoes in the rat diet has a number of harmful effects on growth, organ development and immune responses. Although these experiments were "preliminary", they were well designed, expertly carried out and subjected to correct statistical analysis. Thus, **the results could well serve as basis for further developments**. Had the RS taken up my offer of cooperation with them we could have arrived at the real significance of our work with GM-potatoes for GM-food testing generally. **Sadly, speed was more important for the RS than my cooperation and therefore we have missed a great opportunity for advance.** Thus, we now have to wait till the results of this and any follow-up studies are fully published."

The question actually is resolved, whether the Royal Society offered Pusztai an unlimited exchange of data as claimed, but explicitly complained in the short report that Pusztai did not comply in some instances, a situation which is denied by Pusztai himself, see above: "Had the RS taken up my offer of cooperation…".

(Royal Society, 1999) p.2 Methodology:
"Dr Pusztai indicated to us that further information existed, but did not provide it."

And further on (Bateson, 1999) made it crystal clear who failed to communicate properly, it was actually A. Pusztai who did not follow up the requests to deliver more data and even more so, he failed to react timely to the draft report of the Royal Society, which was delivered to him at the same time as the RS committee received it – so he had ample time to respond timely.

"Sir—In response to Stanley Ewen and Arpad Pusztai's letter on the health risks of genetically modified foods (Aug 21, p 684), (Ewen & Pusztai, 1999e) we would like to clarify several points about the methodology of our review of data on the possible toxicity of genetically modified (GM) potatoes. These workers incorrectly state that the Royal Society did not have access to the project proposal. In fact, as we made clear in our report, we had access to a range of sources of information which included a copy of the proposal. Pusztai received a list of all the information that we had available to us while the review was in progress. The Royal Society contacted several of organizations, including Pusztai, on March 5, 1999, requesting data or comments. We published our report on May 18, over 2 months later. This in our view, gave Pusztai more than adequate time to supply information. He received our referees' comments at the same time as the Working Group and should have had adequate time to respond. Indeed, Pusztai originally made his claims in the media in August, 1998, so the evidence must have been available at that time. **We do not know why Pusztai did not provide any data, information, or comments on the experimental work under review, despite being asked by us on several occasions**."

If you want to know in detail about minutes of the expert's interviews in the British Parliament, go to
http://www.publications.parliament.uk/pa/cm199899/cmselect/cmsctech/286/9030801.htm
The link also gives access to the memoranda of Pusztai, Ewans and the Rowett Institute.

The press releases of the Rowett Institute available, showing early developments of the case.
http://www.botanischergarten.ch/Pusztai/Rowett-Institute-Pressreleases-19980812-ff.pdf

The debate developed rapidly and heated up within days and weeks and most participants were not in the possession of all the detailed and in many cases not published data. An unfortunate and ill designed harsh political and general debate on GM foods created an explosive mix, highly welcomed by the Anti-GMO-activists. In this heated atmosphere out of control, mainly triggered by Pusztai's press releases including unjustified generalizations (Pusztai, 2000a), Arpad Pusztai did not hold back his bitterness about the blunt, unanimous and sometimes harsh rejection of his lectin biosafety experiments which

included his whole life time achievements, this despite a publication record which is quite remarkable and respectable as a whole: http://www.botanischergarten.ch/Pusztai/Pusztai-Bibliography-20090701.pdf .The rejection of his rat experiments and also the way how he was removed from leading project positions (nota bene research activities he continued after his official retirement) also pushed him in the camp of opponents and provoked statements, which are untypical for a well-known and respected scientist. (Ewen & Pusztai, 1999a, d, e; Pusztai, 2000b, 2001, 2002a, b, 2005; Pusztai et al., 1999; Pusztai & Bardocz, 1996, 2006; Pusztai et al., 2008; Roberts & Pusztai, 2001). See the hindsight statements of A. Pusztai in an article from the Guardian in 2008: (Randerson, 2008).

6.More scientific comments about the Ewen-Pusztai study

The debate *within* Lancet produced a series of published texts within the journal, here a complete list:

(Bateson, 1999; Crawford, 1999; Ewen & Pusztai, 1999a, b, d, e; Feldbaum, 1999b; Fenton et al., 1999a; Fenton et al., 1999b; FitzGerald et al., 1999; Horton, 1999a; Horton, 1999c; Horton, 1999d, f; Horton, 1999g; Horton, 1999h; Horton, 1999i; Kilpatrick, 1999; Klug, 1999; Kuiper et al., 1999b; Kuiper et al., 1999c; Lachmann, 1999; Morris & Powell, 2001; Mowat, 1999a; Pedrazzoli et al., 1998; Price, 1998; Pusztai & Hortobagyi, 1998a, b)

Many have already be treated in this contribution and in the comments of N. Fedoroff, other noteworthy ones are:

(FitzGerald et al., 1999) criticize the handling of parameters:
"(Ewen & Pusztai, 1999a) talk about "proliferative effects" when they have not measured intestinal cell proliferation but merely crypt depth. Crypt depth might reflect hypoplasia and hyperplasia but this has yet to be shown. Various methods can be used to measure intestinal epithelial cell proliferation, such as the numbers of dividing cells in optimally sectioned crypts, but for definitive conclusions we need measurements related to the rate of crypt or gland cell production;[2] the size of the epithelial population also needs to be assessed appropriately."

(Kilpatrick, 1999) report on lectins:
"Plant lectins are present in active form in a wide variety of "healthy" foods. Lectins in general are resistant to the digestive process, and a small proportion of any ingested lectin may be transported into the circulation. Undoubtedly, some ingested lectins (eg, pokeweed mitogen) could be very harmful; equally, others, like the tomato lectin, seem to be harmless."

According to Peter Lachmann, the flaws in this study have been pointed out repeatedly and the claims comprehensively demolished. See the two replies to Pusztai in Lancet (Lachmann, 1999) and his book chapter in "The Panic Nation" (Lachmann, 2005), presenting a full account on the Pusztai debate. In this chapter 18 within "Panic Nation" he also reveals and rebuts an unfair attack at hominem, that he allegedly threatened the editor Richard Horton of Lancet that publishing the Pusztai piece would have some negative influence on his personal position. This allegation has been made by a journalist of the Guardian, it was properly refuted by Horton himself.

Lachman advises further on : Anyone with lingering doubts about the Pusztai case would do well to read: (Gatehouse, 1999). The letter to Lancet written by Dr. John Gatehouse (who made the GM potatoes used in the study) (http://silver-server.dur.ac.uk/GMPlants.html) is presented here in extenso including some important references, because it has not been published by Lancet for unknown reasons, and it points to the major problem of the study, and for which Pusztai did not give satisfactory answers.

“Dear Sir,
As a former collaborator of Drs. Ewen and Pusztai, in a program funded by the Scottish Office which generated the transgenic potato material at the centre of the controversy which seems to have raged for a long time now, I was very interested to see a page proof of a forthcoming paper those gentlemen will publish in "The Lancet". This paper is based on the very same transgenic potato material which had been originally supplied to Dr. Pusztai, as part of that collaborative program, though this is neither credited in the page proof, nor is the material properly described.
Dr. Pusztai, in publicizing his work, has consistently failed to properly describe the material on which he has based his various claims. The transgenic potato plants and plant tissues supplied to Dr. Pusztai were experimental material. They were not intended for consumption by animals except as part of the feeding trials in the program, and were certainly not intended for human consumption, or for release as an agricultural or food product. This being the case, essentially no selection or testing had been carried out on the plant material, apart from confirmation that the transgene was being expressed. Because of the difficulties of propagating potato in any other way, each "set" of experimental plant material was generated from a single individual primary transformant plant, as regenerated from the transformation/tissue culture process. This means that the transgenic plant material would have a high probability of showing differences from the parental line, because of variability introduced by tissue culture; for other plant species this variation would be largely eliminated by passage through seed generations, but this was impractical for this potato material.

Two points thus follow on from the technicalities of producing the potato material Dr. Pusztai tested.
1. There is a high probability that the transgenic material differs from the parental line due to factors that have nothing to do with the introduced gene, and thus the parental line may not be an adequate control;
2. Unless a number of different "sets" of transgenic potato material, derived from different primary transformant plants, were tested, there is no way of establishing a causal relationship between an effect, and the fact that the potatoes contain an inserted gene. Since only a limited amount of material was supplied to Dr. Pusztai, this extended testing could not have been done.
As a consequence of failing to consider these issues, the article describes data that lack proper controls, and the results presented are essentially anecdotal. I cannot comment on the validity or otherwise of the results that are presented, but the version of the paper I have seen does not make any clear statement about any biological consequences of the observations made, and makes a large number of unsupported assertions or assumptions. In any case, there is a basic failure as (pointed out above) to demonstrate causal relationships between any effects observed and the presence/expression of the transgene. There has also been a total failure to take the established US FDA safety assessment protocols for transgenic crops into account in either designing the experiments, or evaluating the data.
A key question which the article leaves unanswered is:
"Are the effects observed any different from what would be expected from natural variation between potato tubers of different varieties, grown and stored under different conditions?"
There are numerous reports of other components (principally glycol-alkaloids) in potato which can affect body tissues in higher animals (1) and levels of these components are known to be altered by stress, etc. (2). Asserting that there is some undefined problem with transgenic plants in general on the basis of the data presented by (Ewen & Pusztai, 1999a) (which, even if it is accepted at face value, cannot be shown to be due to the transgenic nature of the material) is simply unscientific; it is the attitude of the medieval witchcraft trials.
There is, of course, the strong possibility that the popular press will have another field day with this article, and to an extent the process has already started. I regret very much that what was set up as a serious scientific project has been hijacked by a scientist who has betrayed the trust of his former colleagues. **No scientific evidence has ever been produced to support views reported as being those of Dr. Pusztai, saying that "GM food will stunt your growth" or "GM food will damage your immune system"; and yet the present rather modest contribution is being reported to vindicate Dr. Pusztai's claims**. To be blunt, no-one is saying that it would not be possible to produce transgenic plants that would be harmful to higher animals if eaten - there are plenty of naturally occurring plants that are poisonous already. What needs to be said, loud and clear, is that there is not the slightest shred of evidence that GM crops being used currently are harmful to higher animals (as shown by the experience of the USA), nor is there any reason to suppose that crops that were harmful will be introduced. **The scientific programmed I was involved in set out to investigate various testing procedures for transgenic plant material; what has subsequently resulted has been a travesty of the original aims.**
In some ways it's a shame "The Lancet" has chosen to perpetuate the silliness generated by the Pusztai affair, but on the other hand, perhaps it is better to get it out in the open. There has been an atmosphere of hysteria about this whole affair from the beginning, carefully fostered by a number of pressure groups. Let's at least not lose sight of the fact that science is about finding out the truth.

Literature cited by J. Gatehouse in his unpublished letter
1. Biological activity of compounds: (Friedman & McDonald, 1997; Gee et al., 1996; Plhak & Sporns, 1997)
2. Variability of compounds with stress etc.: (Papathanasiou et al., 1999; Percival, 1999; Smith et al., 1996)

See also the published letter to Chemistry and Industry: Pusztai's misconceptions: (Gatehouse, 2000)

Dr. John A. Gatehouse
Reader, Crop Protection Group
Department of Biological Sciences
University of Durham"

One wonders why this letter, maybe even timely sent to the editor of Lancet before the Ewen-Pusztai paper went to press, was not published. Read the explanations of Peter Lachman in his book chapter 18 (Lachmann, 2005) why the letter was withheld from being published in Lancet – it does not shed the best light on the publication policy of the journal:

"For unknown reasons, and from a source that has never been revealed, corrected author proofs of this paper were widely circulated before it was published. This caused there to be considerable protest even before the paper appeared. Most significantly, John Gatehouse wrote to Richard Horton explaining where the work was faulty and dissociating himself from it. Under the guidelines of the Committee on Publication Ethics (of which Richard Horton was a member) this made the paper unpublishable since all significant contributors to work must give their consent to its publication. This letter is said to have reached the Lancet after it had gone to press, but there can be no excuse for its not subsequently being published and the paper withdrawn. Horton declined to do this on the grounds that, since parts of the letter had appeared in the Independent, it could not be published in the Lancet."

Many more comments on the experiments of Arpad Pusztai have been published subsequently after the first two years, here a few important ones: Cellini et al. (Cellini et al., 2004) suggest that carbohydrate profiling and chemical fingerprinting in some incidences, together with appropriate extended controls, might at least limit animal feeding studies when testing for unintended effects. Another comprehensive review with numerous experts in the field of food safety has been published in 2004 by Bruce Chassy et al: (Chassy et al., 2004). Again, there is nothing detrimental about regulated GM food to be noted in this review.

As chairman of international conferences on GM food Sir John Krebs published a balanced report on the Pusztai debate in Great Britain: (Krebs, 2000).

More, not yet mentioned comments have been made by the following authors:
(Crawford, 2000; Ferber, 1999; Gavaghan, 1999; McHughen, 2005; Rhodes, 1999).

Finally, one of the best summaries has been published by Nina Fedoroff (Fedoroff & Brown, 2004) as a special chapter in her book "Mendel in the Kitchen", the chapter can be accessed on the internet. http://www.botanischergarten.ch/Pusztai/Fedoroff-The_Pusztai_affair-1.pdf . The chapter has been put on the internet by Fedoroff herself.

7.Summary of Nina Fedoroff

The author of this ASK-FORCE piece considers her comments highly qualified, actually the best account available on the background of lectin science and, including the final comments on the experiments themselves, they are worth-wile to be quoted here extensively, including the references:

"Sensibly, the Scottish Office Agriculture, Environment and Fisheries Department (SOAEFD) commissioned a 3-year study in 1995 titled "Genetic engineering of crop plants for resistance to insect and nematode pests: effects of transgene expression on animal nutrition and the environment." Its objective was "to identify genes encoding anti-nutritional factors which will be suitable for transfer into plants to enhance their resistance towards insect and nematode pests, but will have minimum impact on non-target, beneficial organisms, the environment, livestock fed on these plants, and which will present no health risks for humans either directly or indirectly through the food chain." The University of Durham and the Scottish Crop Research Institute were to provide the transgenic plants and the Rowett Research Institute was to do a chemical analysis of the transgenic plant materials. They were also to do both short-term (10 day) and long-term (3 months) rat feeding trials to determine whether the effect of the transgenic plant materials was similar to that of the parent lines.

The chemical analysis of the transgenic plants showed them to be quite different from the parent lines (http://www.rowett.ac.uk/gmo/ajp.htm) – although the audit report curiously concludes that they weren't (http://www.rowett.ac.uk/gmoarchive/gmaudit.pdf). The researchers measured total protein concentration, as well as the content of several relevant proteins, including GNA, potato lectin and several others. All of these differed between transgenic lines and in comparison with the parental lines. Rats in Pusztai's study were fed either raw or cooked potatoes. Non-transgenic potatoes were supplemented with GNA. The results showed that rats fed the transgenic potatoes had significantly lower organ weights. They found that GNA added to the potatoes made the animal's lymphocytes, which are cells in the immune system, more responsive to stimulation by other lectins. By contrast, lymphocyte responsiveness was depressed in the animals fed the transgenic potatoes expressing GNA.

What these studies basically showed was that the transgenic potato lines were different from each other, as well as from the parental potatoes. A later study on transgenic potatoes came to the same conclusion (Down et al., 2001). Here Pusztai jumped to the conclusion that these differences must be attributable to the fact that the plants were transgenic – and he went public with his conclusion. What he probably didn't know – because he was neither a plant breeder nor a plant biologist – was that the very process through which the plants are put during the introduction of the transgene – culturing through a callus stage and then regeneration of the plant – can cause marked changes in both the structure and expression of genes.

The variation that arises as a result of passage through tissue culture is called "somaclonal variation" and is both a nuisance and a potent source of new materials for plant breeding. The variation is both genetic (single base changes, deletions, insertions, transpositions) and epigenetic – this means modifications that can affect expression of genes, but not their structure. For plant breeders, this means that new materials and new varieties derived using culturing techniques must be evaluated for both their growth and their food properties. This is particularly important for potato breeding, because potatoes produce toxic substances called glycoalkaloids (Kozukue et al., 1999). Glycoalkaloids are normally present in potatoes, can contribute to inflammatory bowel disease, and are concentrated by frying potatoes (Patel et al., 2002). So potato breeders must carefully monitor these compounds, irrespective of the means by which new potato varieties are generated.

Unfortunately, Pusztai's analyses of the chemical composition of the transgenic lines were rather superficial. And his quick leap to the conclusion that the variation he observed was attributable to the fact that they were transgenic was simply unwarranted. This mistake has proved costly to Pusztai himself. And unfortunately, the expertise battle that sprang up around the experiments has obscured the importance of carrying out well-designed experiments to evaluate the food qualities of transgenic crop plants expressing proteins that have the potential of affecting human health. Lectins are clearly in this category.

Pusztai has been criticized severely for the quality of his experiments. His experiments have been attacked for their small sample sizes, the use of inappropriate statistical procedures, and the fact that a diet of raw – or even cooked – potatoes is a bad diet for rats (people too), even when supplemented with a bit of extra protein. **But oddly enough, in all that has been written about these experiments, no one seems to have seen their central flaw, which was that he did not use appropriate controls. A "control" is the part of an experiment that allows the researcher to examine the consequences of just the change (in this case) or the treatment (in the case of a drug) under study. In Pusztai's experiments, the control potatoes had a different history than the transgenic potatoes and, in particular, that history included a culture procedure that induces somaclonal variation.** The likeliest source of the variation he detected – and of the differences he attributed to the fact that they contained foreign DNA – was the culture procedure itself. In order to be able to attribute the deleterious effects of the transgenic potatoes to the newly introduced gene or to some other part of the introduced DNA, he would have had to make a comparison

between potatoes that had the very same history, but either had or lacked the transgenic construct. This can be done, but the study that Pusztai participated in was simply not designed for such a test."

8.Background related to GM food in general

The safety of food derived from GM crops is scientifically proven and in many cases it can be said that GM food is safer or at least as safe as food derived from crops from conventional breeding methods.

Several peer reviewed publications, based on extensive research and reviewing the existing literature on food safety, but not directly related to the Pusztai study, have been published subsequently, only a few are named here: (Aumaitre et al., 2002). Based on an important multiannual research program of the EU, ENTRANSFOOD from 2004, (Konig et al., 2004) and a very extensive report on food safety by the National Academy of Science of the US from 2004: (National Research Council NAP, 2004), here the most interesting paragraphs on the comparison of traditional and biotech breeding and its safety consequences on pages 179 ff:

"All new crop varieties, animal breeds (see cloning subreport), and microbial strains carry modified deoxyribonucleic acid (DNA) that differs from parental strains. Methods to genetically modify plants, animals, and microbes are mechanistically diverse and include both natural and human-mediated activities. Health outcomes could be associated with the presence or absence of specific substances added or deleted using genetic modification techniques, including genetic engineering, and with unintended compositional changes.

The likelihood that an unintended compositional change will occur can be placed on a continuum that is based on the method of genetic modification used (see Figure 3-1 and comment http://www.botanischergarten.ch/Pusztai/NAS-Excerpt-Continuum-fig3-2004.pdf). *The genetic modification method used, however, should not be the sole criterion for suspecting and subsequently evaluating possible health effects associated with unintended compositional changes.*

All evidence evaluated to date indicates that unexpected and unintended com positional changes arise with all forms of genetic modification, including genetic engineering. Whether such compositional changes result in unintended health effects is dependent upon the nature of the substances altered and the biological consequences of the compounds. ***To date, no adverse health effects attributed to genetic engineering have been documented in the human population***."

A further extensive report taking care of many other potential risks of GMOs has been published by the Flanders Interuniversity Institute for Biotechnology (Custers et al., 2000). As a whole, there is a rich literature on food safety published, and it is generally accepted in the academic community of food safety researchers that food derived from GM crops is as safe as conventional food. Pusztai complained in the ninties often about the lack of proper food safety research procedures, but this has been properly taken care of in the meanwhile: (EFSA, 2007; OECD, 1998a, b, c, d, 2003, 2007).

In many debates on the food safety of transgenic herbicide tolerant soybeans there is word on the experimentation with rats of the team of Malatesta et al. (Malatesta et al., 2005a; Malatesta et al., 2003; Malatesta et al., 2008; Malatesta et al., 2002a, b; Malatesta et al., 2002c; Malatesta et al., 2001; Malatesta et al., 2005b; Malatesta et al., 2002d; Trabalza-Marinucci et al., 2008; Vecchio et al., 2004). Those results are often interpreted as showing clear-cut detrimental effects on rat organs due to

transgenesis. Although Malatesta concluded in a prudent way, leaving open other interpretations for the detrimental effects, it has to be said that criticism about her experimental layout and procedures are serious (Bruce Chassy by email):

There are about a dozen things wrong with those lines that totally invalidate any study that follows.

1. What is the hypothesis and what is the power of the experiment? Is 12 animals per group enough for the magnitude of changes observed?
2. The soybean varieties are neither described nor is it known if they are isolines. It is also not known if they were cultivated in the same fields during the same growing season.
3. The compositional analysis of the diets is not presented
4. The isoflavone content of the experimental and control diets are not reported. Isoflavones can produce the observed effects and are known to vary wildly in soybeans
5. The growth parameters and food consumption of each animal is not reported
6. In the analysis statistical significance of differences is reported. One should not draw conclusions based on P values. See attached articles David Tribe shared last week.
7. The experiments do not follow internationally accepted protocols for such feeding studies. No dose effect is evaluated. Without a dose effect study changes are as likely to be normal biological variation as they are real effects.

And a final remark on animal experimentation with whole food by Bruce Chassy, one of the most experienced food scientists:

"*When should animal studies be done?*

Most people agree that it is wrong to test potentially toxic substances in humans, and some think it's also wrong to use animals. Proponents of animal studies say that they save human lives and relieve suffering, while opponents say that it's not right to use animal testing for any reason. The debate cannot be settled here, but there are clear ethical issues involved when animals are used for studies that cannot hope to provide answers. Therefore, many animal feeding studies with whole foods appear to be ethically unjustifiable and should be greeted with skepticism, if not criticism, by the general public and scientific community."

In a recently published electronic (draft)-contribution (Chassy & Parrott, 2009) define on how animal experimentation for testing GM food should be done:

"The book *Tomorrow's Table* provides readers a check-list for deciding if a study is believable (Ronald & Adamchak, 2008). These points boil down to the following:

1. "Determine the primary source of information"
2. "Check if the work was published in a peer-reviewed journal"
3. "Check if the journal has a good reputation for scientific research"
4. "Determine if there is an independent confirmation by another published study"
5. "Assess whether a potential conflict of interest exists"
6. "Assess the quality of institution or panel"
7. "Examine the reputation of the author"

In some final remarks, (Chassy & Parrott, 2009) boil down some of the scientific criteria respected by doing animal experiments on food safety:

"As mentioned previously, animal feeding studies with whole foods are especially difficult to perform and are particularly prone to errors. Animal studies can be used to provide vital information about new drugs, the nutritional value of foods and feeds, and the potential toxicity of certain substances. Valuable information can be obtained if they are done correctly and follow the recommended guidelines. Animal studies with whole foods should only be done when there is a clear scientific hypothesis that can be tested by the study design. Most of the studies that claim adverse effects of feeding GM foods that have been sensationalized in the media do not meet the criteria of proper study design and conduct, do not test a hypothesis, and do not perform appropriate statistical analysis. Some have also not been published in the peer-reviewed literature. A study that fails to meet any of these criteria should be disregarded no matter how scary the claim."

Below a selection of papers which propose the solution by introducing new analytical methods on the level of various omics:. (Ferrer et al., 2009; Kok et al., 2007; Kok et al., 2008; Kolar & Rusche, 2008; Kuiper & Kleter, 2003; Kuiper et al., 2000; Kuiper et al., 2001, 2002; Kuiper et al., 2004; Kwiatek et al., 2008; Lauri & Mariani, 2009; Liu-Stratton et al., 2004; Mosiello et al., 2009; Perreten et al., 2005; Puttamreddy et al., 2008; van Dijk et al., 2009; Zdunczyk & Pareek, 2009). Some of those authors have hopes that biosafety assessment could be enhanced with those innovative methods, but according to Bruce Chassy (email) and (Lay et al., 2006) this is not advisable:

> 1. Analytical chemistry has spent several hundred years honing its paradigm. Paramount to the paradigm are accurate, precise, sensible and reproducible measurements of many examples performed by standardized and validated methods using trained personnel in approved laboratories. Robust statistical and documentation procedures exist. All of these are required for the analysis of a single analyte to be used in a safety assessment but omics meets none of these requirements. Moreover, from a philosophy of science perspective, -omics runs counter to the logic of analysis. We believe that we can measure one or a few compounds very well using the aforementioned procedures, whereas in -omics we measure many things once and poorly. In omic analysis it is not uncommon for many analytes to be unknowns and it is not uncommon to have large errors associated with each measurement. Thus, -omics are more like abstract art than they are a photo of reality.
>
> 2. The statistics of doing many analytes with large variation and poor precision and accuracy are impossible. It is exceedingly hard to do any analysis. It has been shown using Bayesian analysis that the correlation of transcriptomics with disease genes is in fact more likely to arrive at an incorrect association of a gene with a specific disease than it is to identify the gene responsible for a disease. There are a number of examples where this has proven to be true. As applied to food it means that an observed omic change that is correlated with some potential risk is more likely to be not connected than connected.
>
> 3. Omics are also not methodologically ready. While transcriptomics is in pretty good shape, in proteomics only a few hundred of the cells thousands of proteins are measured. Metabolomics is much worse off and the term is a misnomer. Nobody can measure more than a few dozens of the thousands of metabolites in one plant in a single analysis. It is an illusion that Dr. Spock will waive his Tricorder at a potato and instantly know its total composition.
>
> 4. Plants have enormous natural variation. We have no good databases that document that for every analyte for every crop. When we do we will discover that the 95% confidence interval for any analyte is enormous. We can't use omics until we have catalogued plants.
>
> 5. All the evidence we have to date is that conventional breeding produces more variability than GM breeding. (Batista et al., 2008; Baudo et al., 2006) There is nothing inherently risky or different about GM breeding in the first place (Arber, 2000, 2002, 2003) so it should not be surprising that thus far omic analysis has pointed to fewer differences rather than greater differences. The call for omics is based on an incorrect hypothesis that a set of analytes could be out of the normally observed range in a GM plant in a way that would not be observed in conventional breeding.
>
> 6. Finally, the call for omics is an attempt to address a non-existent problem. It is virtually anti-science and anti-rational. By this I mean that we have spend several hundred years learning what the most common and most important compounds are in each different food plant. We know which provide energy or essential nutrients. Which know which we need and which we dont. We know which are harmful and which are not. We understand the nutritional and safety implications of hundreds of metabolites in each plant and we can select which 100-150 we need to measure to assess the nutritional value and safety. We have other indicators such as phenotype to support our analysis. There is nothing flawed about the analysis and no new methods are needed to say a plant is safe. Remember always the prime directive that there is no reason to believe a GM plant should be treated any differently than any other. If omics are applied simply to reassure people that even one more modern method has been used it will be expensive, it will contribute nothing to the analysis, and it will not reassure. It will be just another act of the emperor's new clothes.

With this view it is clear that with the new omics methods applied to biosafety of foods you just end in the devils kitchen.

9.Background Lectin Science

A comprehensive account has been given by (Fedoroff & Brown, 2004), a short summary may be enough for this contribution:

"Plants – no less than animals – have mechanisms for defending themselves from microorganisms and insects. Plant produce lectins as one of their defense strategies against insects (Carlini & Grossi-de-Sa, 2002). Indeed, a good deal of evidence has accumulated that GNA, which binds specifically to a sugar called mannose, is rather toxic to certain kinds of insects pests of important crop plants, including rice (Du et al., 2000); (Fitches et al., 2001) GNA does not seem to affect ladybird beetles, considered to be a beneficial insect (Down et al., 2001), although it does affect parasitic wasps, also considered to be beneficial insects (Romeis et al., 2003). Some lectins, including ricin, are quite toxic because they're taken up by cells and block protein synthesis (Olsnes & Kozlov, 2001). These are called ribosome-inactivating proteins or RIPs. But GNA doesn't have this activity (Battelli et al., 1997).

Better yet, Pusztai's own studies showed that purified GNA wasn't toxic to rats (Pusztai et al., 1990). In fact, he and his colleagues had shown that GNA had a protective effect against bacterial infection with *Salmonella*, a nasty intestinal bug (Naughton et al., 2000). All of this made the gene coding for GNA an attractive choice for increasing the insect resistance of crop plants. To test this possibility, the gene was introduced into a number of different crop plants, including potatoes and rice. And it does, indeed, increase their resistance to some important insect pests (K. V. Rao et al., 1998); (Foissac et al., 2000). Because GNA binds to the surface cells of insects guts and enters their blood stream, it is also thought to have potential as a vehicle for delivering more toxic peptides to insects (Fitches et al., 2002).

10.The Role of the Opponents

Some activists spontaneously and enthusiastically declared that they will support Pusztai, most probably without having the details ready for the scientific debate: http://www.botanischergarten.ch/Pusztai/Greenpeace-Support-Pusztai-1999.PDF.

One of the worst examples of polemically presenting the case of the Pusztai experiments is given by Jeffrey M. Smith in his first book "Seeds of Deception", a highly biased narrative without giving a shred of precise scientific evidence, leaving out all the scientific doubts and shortcomings of the study, but written like a crime story, a highly inflammatory piece creating nothing but hatred against the multinational companies and disgust about GM food (Smith, 2003), created in the usual manner of neo-Marxist views, actually an insult to historic Marxism…

Another typical example of unanimous and uncritical approval of Pusztai's work was produced by a consortium of authors with a well known profile of GM food opponents (Suurkula J. ed. et al., 2000) from the global network Physicians and Scientists for Responsible Application of Science and Technology.

On web-Google you have under A.Pusztai today July 27, 2009 some 260'000 hits, the usual potpourri of negative statements against GM foods and feeds.

Some NGOs notoriously opposed to GMOs try from time to time to disqualify the science behind the many studies disproving the results from Pusztai's experiments, they usually concentrate on citing biased studies, often not even published, and for which it usually takes at least a few weeks until the rebuttals are published. A typical case related to GM soybeans has been purported in numerous websites by Dr. Irina Ermakova (to whom the activists wrongly attribute membership in the Russian Academy of Science): Herbicide tolerant GM soybeans supposedly show detrimental effects in rat feeding experiments. These statements in the Russian and international press have been hotly debated in hundreds of activist websites and in the local press. Amazingly enough, it has not been published regularly in a peer reviewed journal. This is why the editor in chief of Nature Biotechnology has taken another avenue of bringing the case in a peer reviewed journal in order to debate it using scientific criterions by learning from the Pusztai/Lancet case: He *interviewed* Ermakova and confronted her with the opinions of reputed experts, the result is clear cut negative for Ermakova's interpretations: (Marshall, 2007). The case is treated extensively with more details in a separate ASK-FORCE contribution. http://pubresreg.org/index.php?option=com_content&task=view&id=62

The Social Issues Research Centre http://www.sirc.org/ provides enlightening information about the community and names of opponents of genetic engineering and their activity supporting Pusztai: http://www.botanischergarten.ch/Pusztai/SIRC-Statement-Pusztai-1999.pdf

11.Concluding remarks:

Starting from a text of one of the most important accounts on food safety from the National Academy of Sciences Committee on Environmental Impacts (2000) (National Academy of Sciences Committee on Environmental Impacts, 2000) we can summarize the contemporary situation as follows: p. 68-69

"The potential for transgenic pest-protected plants to pose a threat to human or animal health must be considered against the background of existing information. To date no such effects have been shown with commercialized transgenic crop plants."

The safety of food derived from regulated GM crops is scientifically proven, the cases of the herbicide tolerant soybeans and Bt maize have been made this clear with numerous publications in peer reviewed journals, and in many cases it can be said that GM food is safer or at least as safe as food derived from crops from conventional breeding methods.

A detailed account on the whole bitter debate was delivered as a bulky thesis of 450 pages by (Delborne, 2005) with lots of details, concentrating on the way, how the scientific "establishment" is looking at dissenting scientists. There is a detailed chapter on the Pusztai case, in the environment of a predominantly promotional atmosphere of agricultural biotechnology, how *contrarian* science appears, and how, at a first spark of dissent, it is confronted with myriad challenges to its credibility. After describing the mechanics of the scientific debate, the thesis engages in how dissenters are enacting performances of *dissent science* as a form of scientific dissent that takes on an explicitly political character and challenges conventional relationships among scientists, publics and politics. So far, so good, but in my view the extensive and impressive documentation does not concentrate enough on the scientific arguments and is neglecting the role of the NGOs with their dissemination of pseudoscience.

Instead of giving a truncated account on the debate, it would be much better to offer some solutions, such as debate procedures in a *discourse*, which should be organized along the lines of the *systems approach* of Horst Rittel, see below.

There are some unfortunate final outcomes to be noted on this incident in the hindsight: In 1998 and 1999 it would have been better to reconcile the contrasts of opinions and statements on experimental details by listening more properly to each other, in particular the author is not in a position to resolve the fact that both sides, the Royal Society and A. Pusztai accuse each-other vice versa of not playing with open cards. Had there been more transparency in the beginning controversy, had both sides taken more time for a scientific discourse in the sense of Horst Rittel (Ammann & Papazova Ammann, 2004; Osseweijer, 2006a, b; Rith & Dubberly, 2007; Rittel & Webber, 2005), the dispute could have been more constructive.

The report concludes with the remarks of one author of the Royal Society audit reports, Prof. Rebecca Bowden – words to heed carefully:
http://www.botanischergarten.ch/Pusztai/Royal-Society-Reviewer-Reports-1999.PDF

"I can add little to what has already been written about these studies at the Rowett Research Institute but I have two small comments.

- The first concerns the diet fed by Dr Pusztai to his rats: Potatoes are a very inadequate diet for rats. Dr Pusztai was aware of their low protein content and made up some of the deficit with lactalbumin. However, the protein uptake of the rats was probably still well below the requirements. Dr Pusztai says nothing about minerals and vitamins, but potatoes would not provide rats with their requirements for these nutrients. It is possible that he gave the rats a mineral and vitamin supplement, but I can find nothing about this in the text. My personal comment - there appears to be no group of rats on a normal rat diet so it is impossible to tell how much the normal growth and development of the experimental animals was retarded on any of the potato diets.
- I do not think the problem about transgenic foods will make much further progress towards solution by going over and over the experiments made at the Rowett Research Institute. This was pioneering work, but more research needs to be done. Since it is only plant foods that are involved I suggest that a herbivore e.g. the rabbit, might be a better experimental animal than the rat. Herbivores have a digestive system which is adapted to deal with the large amounts of plant foods that have to be eaten to provide for the animal's requirements. The staple food of rabbits is leafy plants. I do not know how easy it would be to produce a transgenic leafy plant, whether vegetable or not, but if this could be done dietary supplements would be unnecessary. If experiments on rats are to continue, with potatoes as the 'test' food. I suggest that the animals be fed some of the food normally fed to laboratory rats along with potato."

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