Genome Editing and Engineering
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Module - 01
Introduction to genetics and genetic engineering
Lecture - 03
Advantages and Limitations of Genetic Engineering

Welcome to my 3rd lecture on Advantages and Limitations of Genetic Engineering.

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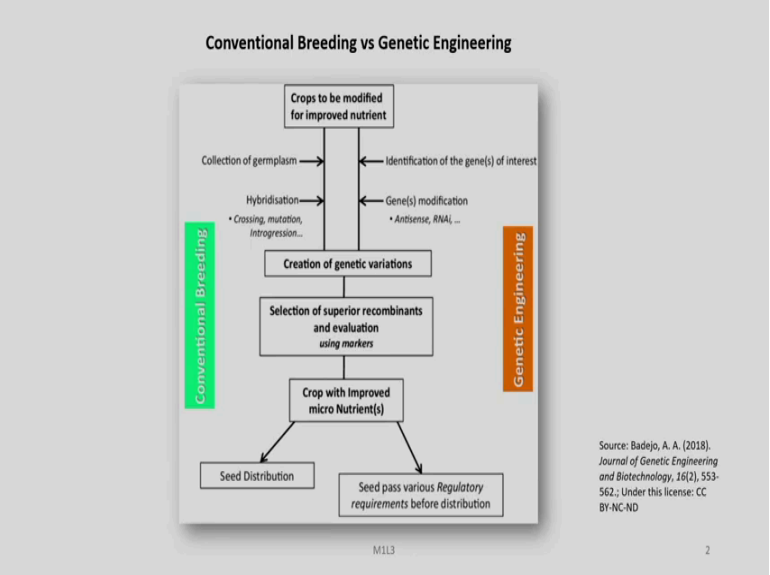

Let us first examine the differences in commonalities between conventional breeding and genetic engineering. Both have a goal to achieve for example, we have some crops which need to be modified for improved nutrient. We can do this by either way that is by conventional breeding and by genetic engineering.

If we want to go to the path of conventional breeding, we need to start with the collection of germplasm. Then we select germplasm on the basis of favorable characters and carry out some hybridization program and this can involve crossing, mutation and introgression. This finally, will give us some genetic variations in a population. Alternatively, we may like to go for genetic engineering under certain circumstances.

For example, if in the germplasm the favorable characters are not available then we have to look for the gene of interest in unrelated varieties or even species. Once we do that, we isolate that particular gene of interest and that particular gene we may transfer to the targeted crop plant and this may involve different technologies which may be antisense RNAi in the case of silencing of genes or it may be recombinant DNA technology to transfer favorable genes into the crop germplasm.

This will also give us genetic variations in a population of plants. Now, after the creation of genetic variations by either way the conventional breeding and genetic engineering, we can follow a common path that is the selection of superior recombinants and evaluation and this we do with the help of markers. Now, once we get our favorable desired traits in particular individuals of the crop plants under development, say for example, here our original goal was to have a crop with improved nutrient.

And after all testing in validation, we came up with those individual crop members which have indeed improved nutrients. In the case of conventional breeding, we can go for the seed distribution and raising the crop; although field level trials and certain quality assurances has to be taken care of.

And in certain cases, as in national law may be there which may be complied to. In the case of genetic engineering, we need to pass the crop plants so developed through stringent regulatory requirements are before distribution.

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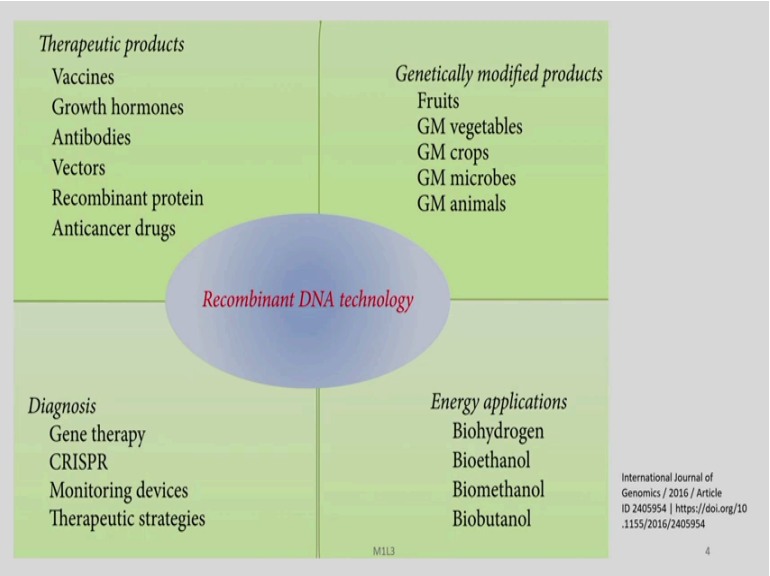

So, these are the pathway to crop improvement through the conventional breeding and genetic engineering pathways. Let us focus on the potential of recombinant DNA technology. How DNA technology has influenced the various fields particularly whether it is health or food or energy sector? You can see here from the earlier discussion we were interested to develop some crop varieties with improved nutrients.

Similarly, we may have other such priorities we may want to develop beautiful flowers or flowers with beautiful colors. So, in this case we may go for recombinant flowers or we may want to develop fruits with very very favorable taste or more pulp. So, we may go for developing genetically modified fruits, we may go for developing genetically modified vegetables, genetically modified microbes as well and even genetically modified animals.

Similarly, recombinant DNA technology has lot of application in the energy sector which is one of the most important sectors at today's date; like the production of biohydrogen or bioethanol, biomethanol or biobutanol. Therapeutics is one area where recombinant DNA technology has played a huge role like in the case of vaccine development, production of growth hormones, antibodies which are used for therapy and are known as therapeutic antibodies. We may also develop antibodies for diagnosis.

So, those will be known as diagnostic antibodies. Then the development of vectors for transferring genes from one organism to another, then development of recombinant proteins vaccines can be recombinant proteins, antibodies in fact are recombinant proteins, but we may have other proteins a nutritional food protein for example, casein and those can be recombinant protein products as well.

Other important products under therapeutics is development of anticancer drugs where recombinant DNA technology play a very big role. When it comes to diagnosis we may develop various molecular markers which we use for the detection of certain diseases in the recent case of the covid pandemic all of you know about the RT-PCR technology and similarly there are other many areas for example, development of recombinant antigens and antibodies which can be helpful in detecting certain diseases.

So, overall recombinant DNA technology is a very important technology platform which contributes directly to food security our health security as well as energy security and there are many other such areas where we can found its use. Let us go to some interesting topic of this year.

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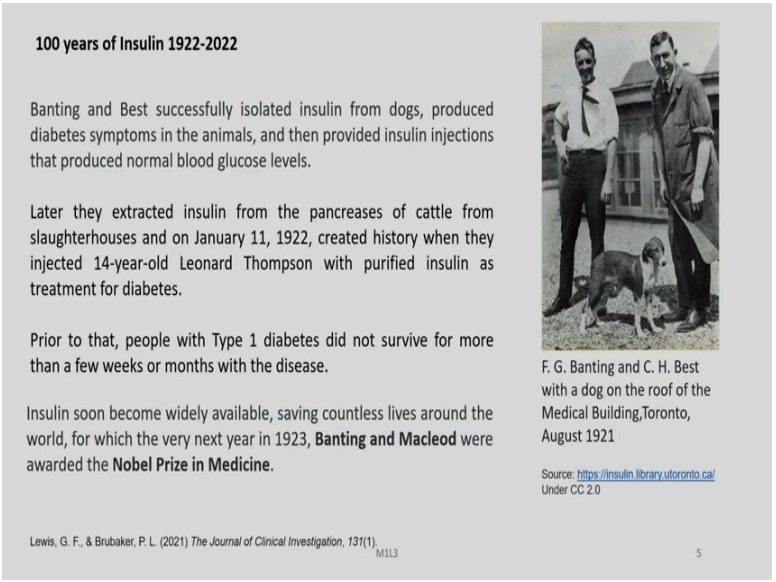

In 2022, we have been celebrating the 100 years of insulin discovery. In 1922, Banting and Best successfully isolated insulin from dogs, produced diabetes symptoms in the animals and then provided insulin injections that produce normal blood glucose level. So, with this discovery a giant leap was made forward towards the treatment of diabetes. Later on, they extracted insulin from the pancreas of cattle from slaughterhouse.

And on January 11, 1922 they created history when they injected a 14-year-old boy Leonard Thompson with purified insulin as treatment for diabetes. Now, prior to this people with Type 1 diabetes did not survive for long because there was no any known cure for that disease and they used to perish within months of the development of the disease.

Soon insulin became widely available and it saved countless lives around the world for which the very next year in 1923, Banting and another worker Macleod who had equal contribution in the development of therapy of diabetes were awarded the Nobel Prize in Medicine. In this picture, on the right you can see F. G. Banting and C. H. Best with a dog on the roof of the medical building in Toronto in August 1921, where they develop these insulins.

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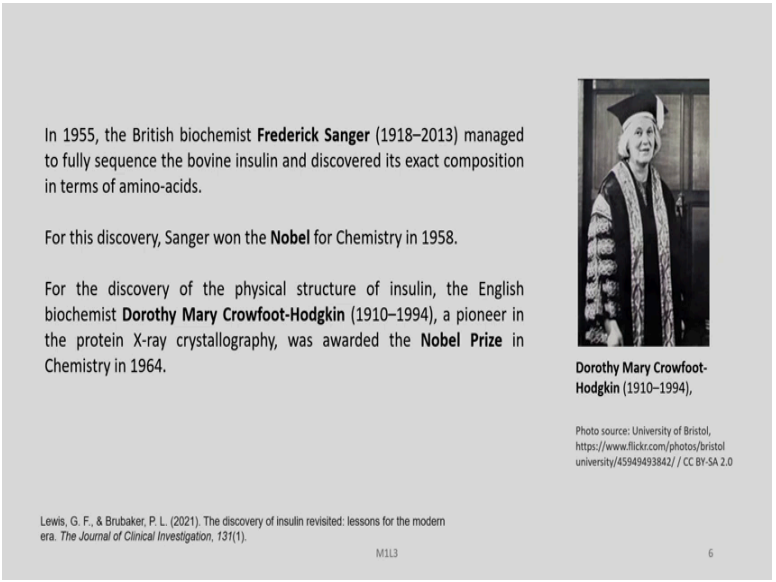

Later on in 1955, a British biochemist named Frederick Sanger managed to fully sequence the bovine insulin and discovers its exact composition in terms of amino-acids. These are very important discoveries on the path to the betterment of diabetes care. For this discovery, Sanger was awarded the Nobel Prize in Chemistry in the year 1958.

For the discovery of the physical structure of insulin another English biochemist Dorothy Mary Crowfoot-Hodgkin a pioneer in the protein X-ray crystallography was awarded the Nobel Prize in Chemistry in 1964. So, you can see that insulin diabetes has been such an important area of work. All the pioneer workers were awarded with the Nobel Prize starting from Banting and Macleod.

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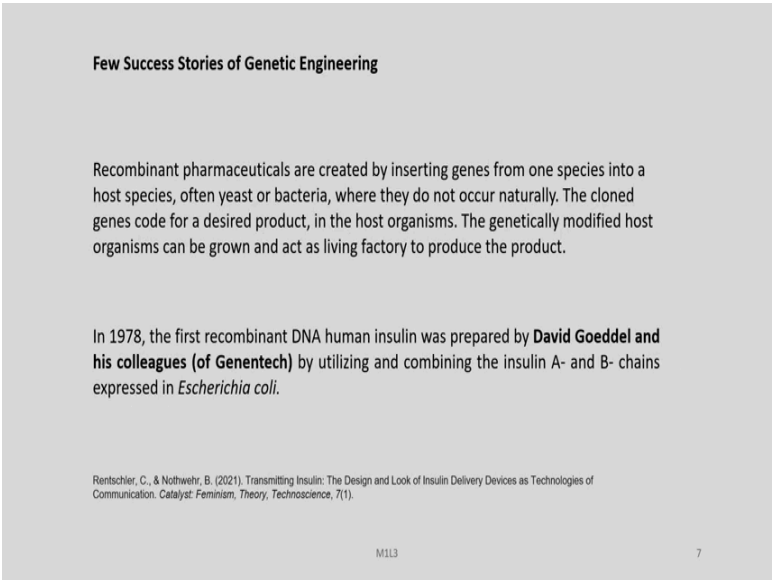

Let us now discuss a few of the success stories of genetic engineering. What are recombinant pharmaceuticals? We already discussed in one of the slides about the therapeutic importance of recombinant DNA technology. We know that the recombinant DNA technology can produce vaccines, antibodies as well as cancer drugs so on and so forth. So, these recombinant pharmaceuticals are created by inserting genes from one species into a host species often yeast or bacteria where they do not occur normally.

The cloned genes code for a desired product in the host organisms. The genetically modified host organisms can be grown and act as a living factory to produce the product. In 1978, the first recombinant DNA human insulin was prepared by David Goeddel and his colleagues working in Genentech by utilizing and combining the insulin A and B chains expressed in *Escherichia coli*.

The human insulin protein has two sub units; one sub unit is known as insulin A and the another sub unit is known as insulin B. The genes for these two different subunits were cloned into two separate equalize population and the two populations produce the two different subunits.

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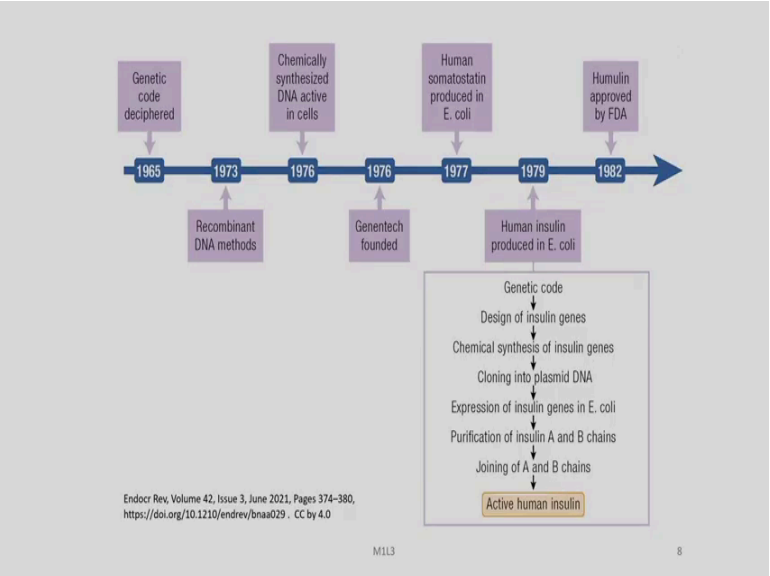

So, this is a brief history of the development of insulin artificial insulin and some of the important discoveries which contributed directly to its development. Starting with the deciphering of the genetic code followed by the development of recombinant DNA methods and then the chemical synthesis of DNA active in cells. And the inception of this company Genentech in 1976 is also a milestone in this case, because Genentech was the leading company who developed these therapeutic molecules.

In 1977 prior to the development of insulin human somatostatin was produced in *E. coli*. And, this is considered as a very important step which led to the development of confidence in building up human insulin 2 years later. Then finally, in 1982 the human humulin which is the human recommended insulin was approved by FDA and the rest is history. Let us focus on the production of human insulin production in *E. coli*.

So, this started with deciphering of the genetic code, then design of insulin genes, then chemical synthesis of insulin genes cloning into plasmid DNA followed by expression of insulin genes in *E. coli*, then purification of the two subunits insulin A and insulin B separately and then finally, joining both the subunits A and B together to generate active human insulin.

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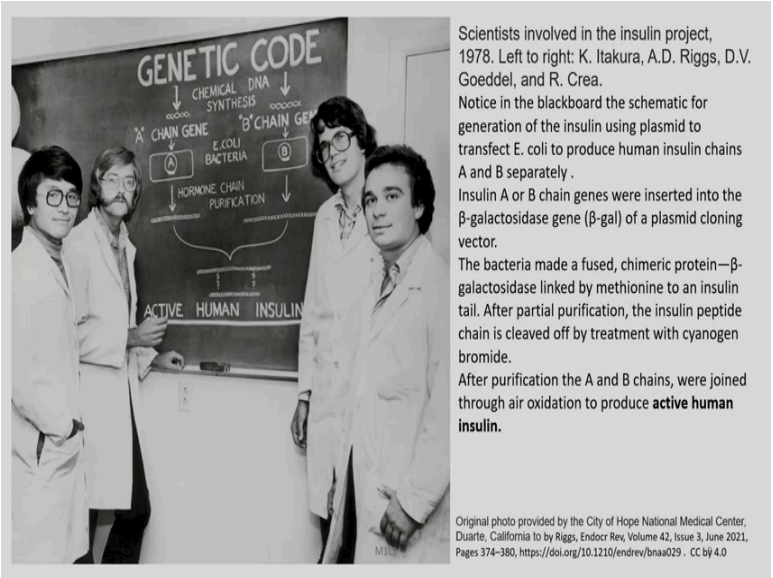

We will discuss a little bit more on this later. This is a very very historical photograph. You can see here the scientists involved in the insulin project in 1978 from left to right you can see Itakura, Riggs, Goeddel and Crea. And in this blackboard in the center you can see the schematic for generation of the insulin using plasmid to transfect *E. coli* to produce human insulin chains A and B separately.

This is the scheme which I have discussed in the earlier slide. And this is the same scheme which you can see in the center where after deciphering of the genetic code in chemical DNA synthesis, the A chain is cloned into a population of *E. coli* B chain is cloned into another population of *E. coli*. They are expressed and then they are purified. And then after purification, they cross linked to form the human insulin and you can see here the cross-linking schematics. The insulin A or B chains were inserted into the beta galactosidase gene of a plasmid cloning vector. The bacteria made a fused chimeric protein which contain beta galactosidase linked by methionine to an insulin tail. So, this product has chain A which was linked to beta galactosidase.

And this chain has link to it galactosidase, this chain B has linked with it the beta galactosidase as well. So, after partial purification, the insulin peptide chain is cleaved by treatment with cyanogen bromide to release the beta galactosidase from this fuse protein. And then it is purified to produce the pure A and B chains which are joined through oxidation to produce the human active human insulin.

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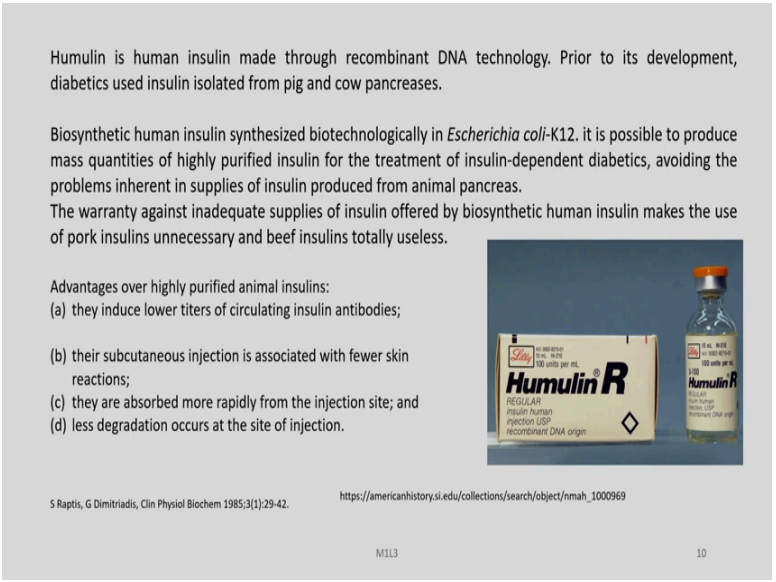

Humulin is human insulin made through recombinant DNA technology. Prior to its development, diabetics were treated with insulin isolated from animals like pig and cow pancreases. The advent of biosynthetic human insulin which was produced biotechnologically in *E. coli* strain K12 made it possible to produce mass quantities of highly purified insulin for the treatment of insulin dependent diabetics, while avoiding the problems inherent in supplies of insulin produced from animal pancreas.

The warranty against inadequate supplies of insulin offered by biosynthetic human insulin makes the use of pork insulins unnecessary and beef insulins totally useless. What are the advantages of humulin over highly purified animal insulins? (a) they produce lower titers of circulating insulin antibodies; because the insulins isolated from animal sources where like foreign proteins to some extent in the human body, they used to elicit antibody production; while humulin is a synthetic construct based on the human sequence, it produces low titers of antibodies.

The subcutaneous injection of humulin is associated with fewer skin reactions compared to those with animal insulins. They are absorbed more rapidly from the injection site unlike the animal insulins. And there is less degradation at the site of injection. So, overall humulin offered a big advantage over the purified animal insulins. You can see here, the humulin are which is regular insulin human injection and you can see here in the level this is of recombinant DNA origin. Now, let us focus on the statistics of the incidence of diabetes.

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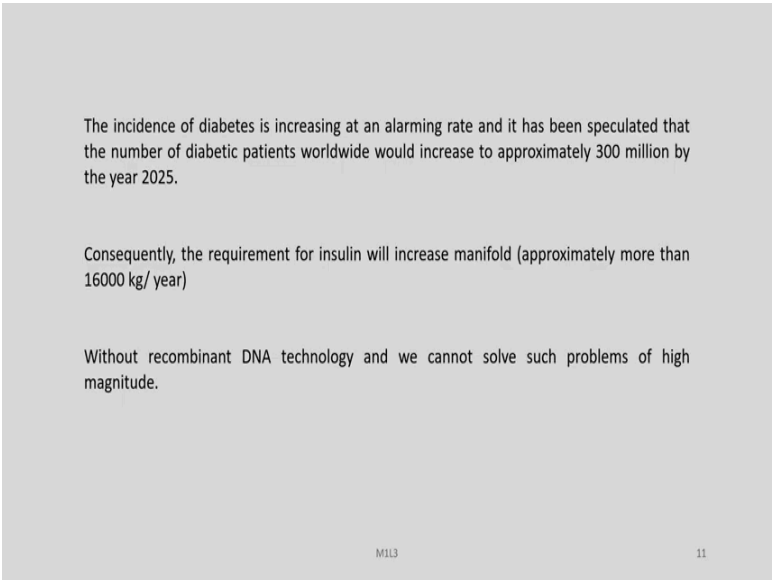

The incidence of diabetes is increasing at an alarming rate and it has been speculated that the number of diabetic patients worldwide will increase to approximately 300 million by the year 2025. Consequently, the requirement for insulin will increase many fold approximately more than 16000 kg per year which is a very very big quantity.

If this quantity was to be extracted from animal source, porcine or kettle, imagine the number of animals we would have required to produce these and the extent of land that would have been required to produce the food and feed for raising those animals, not to calculate the additional space required to shelter them.

And also the number of slaughterhouses the amount of energy the transportation that would have been required to produce this massive amount of insulin by the conventional process, but recombinant DNA technology is a blessing to us. Today we do not require that extensive space to produce the similar amount of recombinant humulin or human insulin. It can be done in a very small space. We do not require the land to grow the food and fodder for the raising of those elements.

We do not also need the space for their sheltering and the slaughterhouses; neither do we need a big transportation of bringing the animals to those slaughterhouses. So, thereby this has direct impact on the environment in terms of carbon footprint, water budgeting and so on. So, without recombinant DNA technology, we cannot solve such problems of high

magnitude. Now, insulin is just one of the recombinant therapeutic products. There are many other products which are now extensively being used and produced.

So, if you would have followed the conventional path of producing them, the art would soon become devoid of its resources whether it is land, water and other resources and it would act to the current crisis of climate change. So, recombinant DNA technology is a blessing for us that can be evident from one case study the production of recombinant humulin or human insulin. Another important area is the hepatitis.

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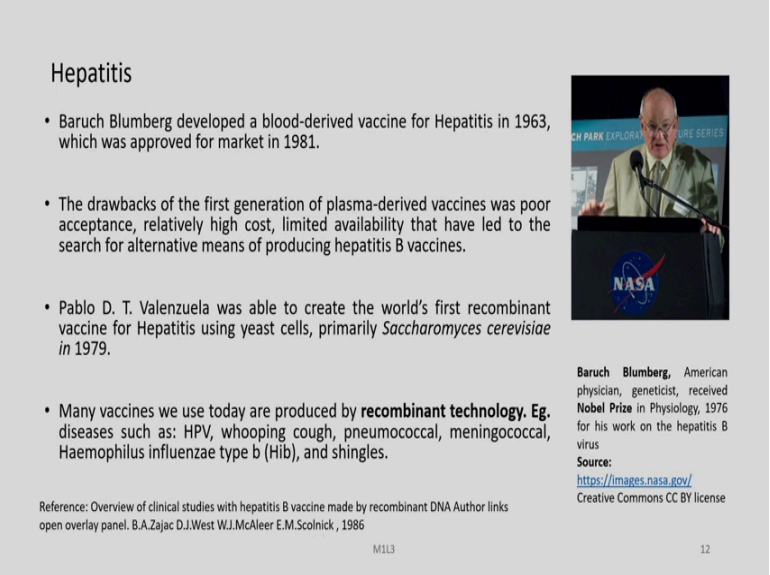

So, Baruch Blumberg developed a blood-derived vaccine for hepatitis in 1963, which was approved for a market by 1981. The drawback of these first generation of plasma-derived vaccine was poor acceptance, relatively high cost, limited availability that have led to the search for alternative means of producing hepatitis B vaccines. Pablo D. T. Valenzuela was able to create the world's first recombinant vaccine for hepatitis using yeast cells, primarily *Saccharomyces cerevisiae* in 1979.

Many vaccines we use today are produced by recombinant technology as I have told you a little bit earlier. For example, for diseases like HPV, whooping cough, pneumococcal, meningococcal, *Haemophilus influenzae* type b (Hib) and shingles, etc. So, in this picture you can see Baruch Blumberg who was an American physician and geneticist who received the Nobel Prize in Physiology in 1976 for his work on the hepatitis B virus.

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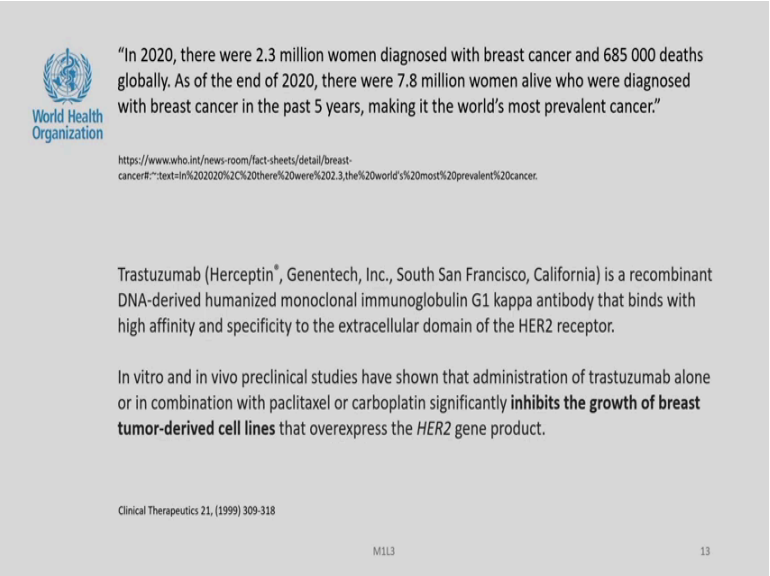

This is a report by the World Health Organization regarding the status of breast cancer. In 2020, there were 2.3 million women diagnosed with breast cancer and 6,85,000 deaths globally. At the end of 2020, there were 7.8 million women alive who were diagnosed with breast cancer in the past 5 years, making it the world's most prevalent cancer.

Now, there is a therapy for breast cancer called Trastuzumab which is basically also known as Herceptin produced by Genentech. And this is a recombinant DNA derived humanized monoclonal immunoglobulin G1 kappa antibody which binds with high affinity and specificity to the extracellular domain of the HER2 receptor. And thereby, elicits a therapeutic outcome.

In vitro and *in vivo* preclinical studies have shown that administration of trastuzumab alone or in combination with other drugs like paclitaxel or carboplatin significantly inhibits the growth of breast tumor derived cell lines they will over express the HER2 gene product. Now, there is an interesting story behind the development of trastuzumab or Herceptin.

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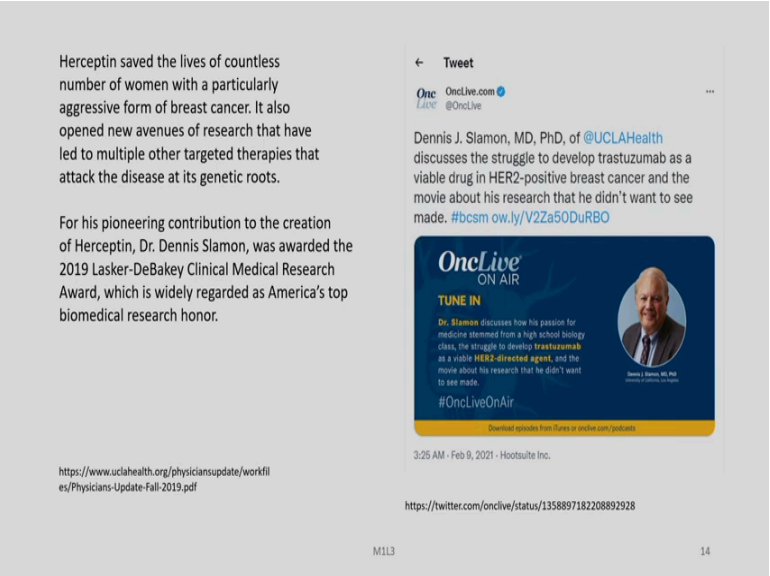

This Herceptin saved the lives of countless number of women with a particularly aggressive form of breast cancer. It also opened new avenues for research that have led to multiple other targeted therapies that attack the disease at its genetic roots. For his pioneering contribution to the creation of herceptin Dr. Dennis Slamon was awarded the 2019 Lasker-DeBakey Clinical Medical Research Award, which is widely regarded as America's top biomedical research honor.

So, in this tweet you can see an advertisement of an interaction with Dennis Slamon who was discussing the struggle to develop trastuzumab as a viable drug in hard to positive breast cancer. And the movie about his research that he did not want to see made. So, there is a very interesting book on the development of Herceptin the book is known as HER2 written by Robert Bazell those who are interested can read that book.

And a beautiful movie has been made out of that book known as Living Proof where this entire struggle in making these trastuzumab is being portrayed. It needs to be mentioned here that this drug acts only in her two positive breast cancer patients which means, this particular marker has to be present in the tumor cells otherwise this therapy is not going to work as efficiently.

Let us now discuss the application of recombinant DNA technology in another area the development of agricultural crops.

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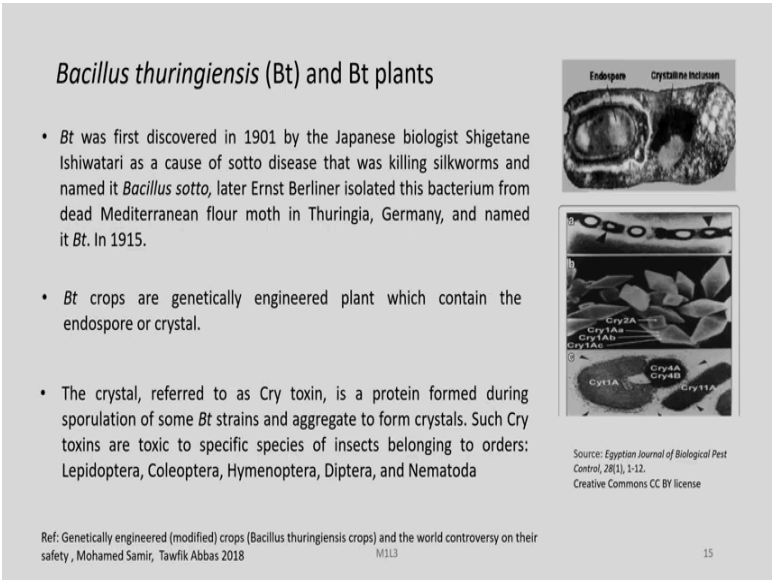

Bacillus thuringiensis and Bt plants. Bt was first discovered in 1901 by a Japanese biologist Shigetane Ishiwatari as a cause of sotto disease which was killing mulberry silkworms and he named it as *Bacillus sotto*, later Ernst Berliner isolated this bacterium from dead Mediterranean flour moth in Thuringia, Germany and named it as *Bacillus thuringiensis* in 1915.

This was later used to produce bio pesticides. So, initially the technology was to grow *Bacillus thuringiensis* in large vessels and then use the culture directly as a spray on crops to protect them from attack from insects. Later on, to cut down on the cost the gene that produces this toxic effect was transferred to plants directly to produce genetically engineered Bt crops.

So, these Bt toxicity is due to a crystal which is referred to as the Cry toxin and this is a protein which is formed during sporulation of some Bt strains and it aggregates to form crystals which you can see in the left side over here. Such Cry toxins are toxic to specific species of insects belonging to orders like Lepidoptera, Coleoptera, Hymenoptera, Diptera and also Nematoda.

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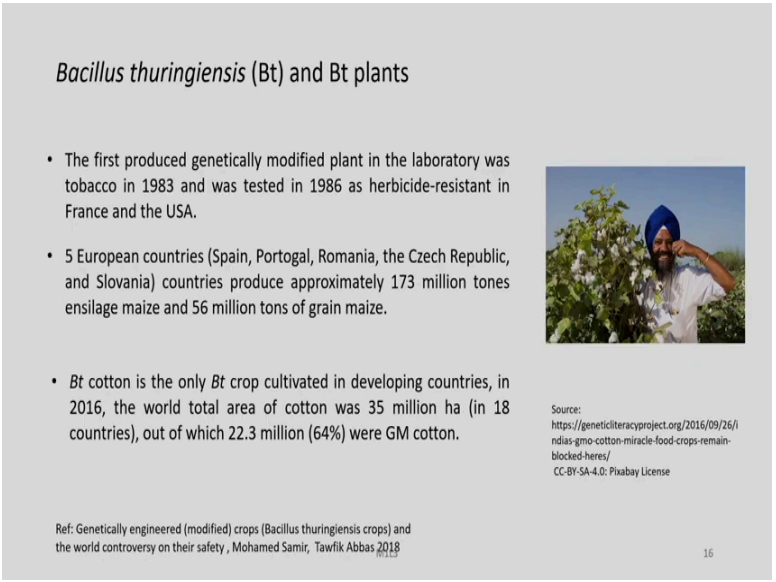

The first genetically modified plant in the laboratory was tobacco in the year 1983 and was tested in 1986 as herbicide-resistant in France and the USA. 5 European countries like Spain, Portugal, Romania, Czech Republic and Slovania produce approximately 173 million tons of ensilage maize and 56 million tons of grain maize.

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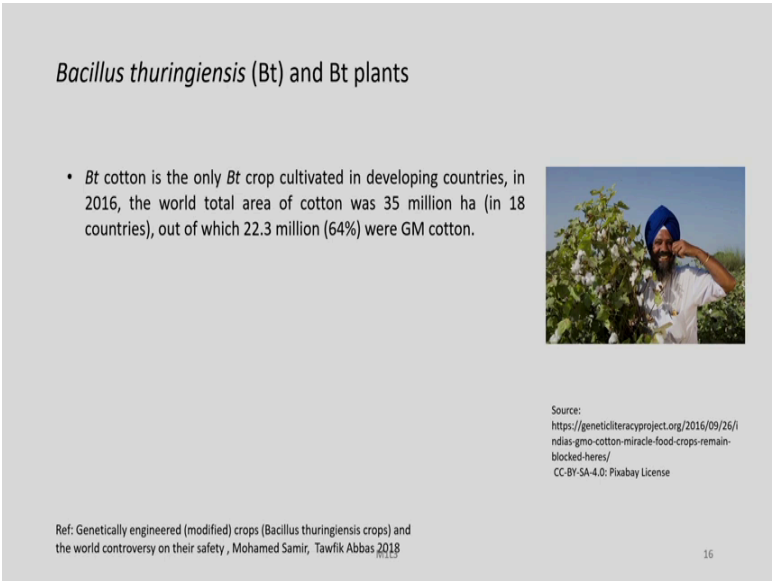

Bt cotton is the only Bt crop cultivated in developing countries, in 2016, the total world area of Bt cotton was 23.3 million which was 64 percent of the total area of 35 million hectares across 18 different countries grown globally.

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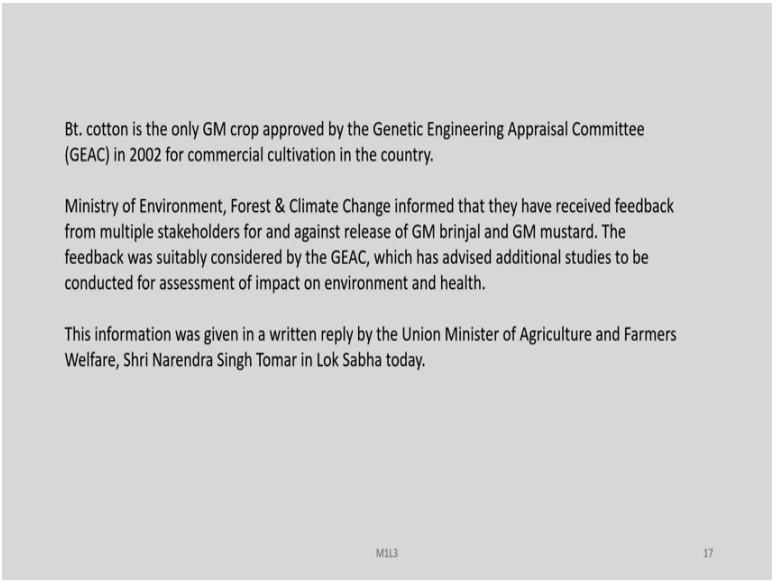

Bt cotton is the only GM crop approved by the Genetic Engineering Appraisal Committee GEAC in 2002 for commercial cultivation in India. The Ministry of Environment Forest and Climate Change have informed that they have received feedback from multiple stakeholders for and against release of GM brinjal and mustard which are other two crops having the Bt gene.

The feedback was suitably considered by the GEAC which has advised additional studies to be conducted for assessment of impact on environment and health. This information was given in a written reply to the Lok Sabha by the Union Minister for Agriculture and Farmers Welfare.

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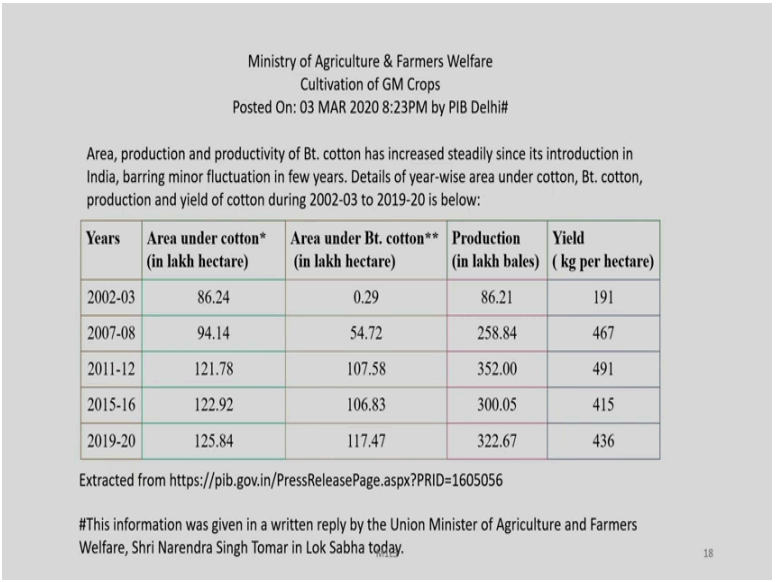

Ministry of Agriculture & Farmers Welfare
Cultivation of GM Crops
Posted On: 03 MAR 2020 8:23PM by PIB Delhi#

Area, production and productivity of Bt. cotton has increased steadily since its introduction in India, barring minor fluctuation in few years. Details of year-wise area under cotton, Bt. cotton, production and yield of cotton during 2002-03 to 2019-20 is below:

Years	Area under cotton* (in lakh hectare)	Area under Bt. cotton** (in lakh hectare)	Production (in lakh bales)	Yield (kg per hectare)
2002-03	86.24	0.29	86.21	191
2007-08	94.14	54.72	258.84	467
2011-12	121.78	107.58	352.00	491
2015-16	122.92	106.83	300.05	415
2019-20	125.84	117.47	322.67	436

Extracted from https://pib.gov.in/PressReleasePage.aspx?PRID=1605056

#This information was given in a written reply by the Union Minister of Agriculture and Farmers Welfare, Shri Narendra Singh Tomar in Lok Sabha today.

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Now, this is the data provided by the Ministry of Agriculture and Farmers Welfare on the cultivation of GM crops posted on 3rd March 2020 by PIB. It tells us about the area and production and productivity of Bt cotton which has increased steadily since its introduction in India in 2002, 2003.

Barring minor fluctuations in certain years the details of year wise area under cotton Bt cotton, production and yield of cotton during 2002 to 2003 to 2019 to 2020 is available in the original document. Here we have taken data at a 5 years interval between 2002-03 to 2007-08, 11-12 15-16 and finally, 2019 and 20.

And as we can see since 2002, the area under cotton total area under cotton has increased from 86.24 lakh hectares to 125.84 hectares which is not much in a way, but if you look into the area under Bt cotton there is a large increase. Say, the area under Bt cotton in 2002 and 3 when it was introduced was 0.29, but over the years in the very next year is jump to 54.72 and the next 5 years it doubled to 107.

And then, it has been hovering around that number 106 in 2015-16 and 2019-20 the area increased to 117. Now, if you look into the production statistics, the production of cotton has increased from 86.21 lakh bales to 322.67. So, if you look into the yield kg per hectare there is a huge increase which is twice in 2002-03 the yield kg per hectare was 191.

But by the year 2019 and 20, it has more than doubled and become 436. So, this is a comparison between the area under conventional cotton as well as the area under Bt cotton.

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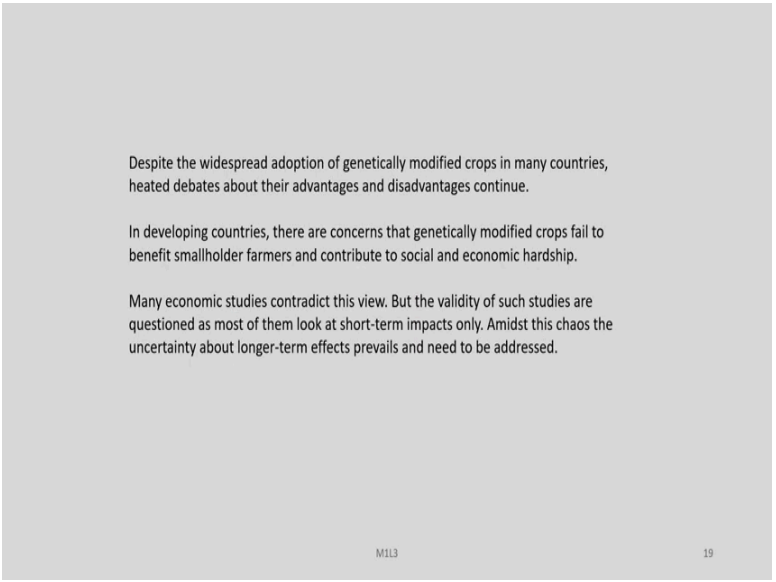

So, despite the widespread adoption of genetically modified crops in many countries, heated debates about their advantages and disadvantages continue. In developing countries there are concerns that genetically modified crops fail to benefit smallholder farmers and contribute to social and economic hardship. Many economic studies; however, contradict this view, but the validity of such studies is questioned by many as most of them look at short term impacts only.

Amidst this chaos the uncertainty about long term effects prevails and these need to be addressed.

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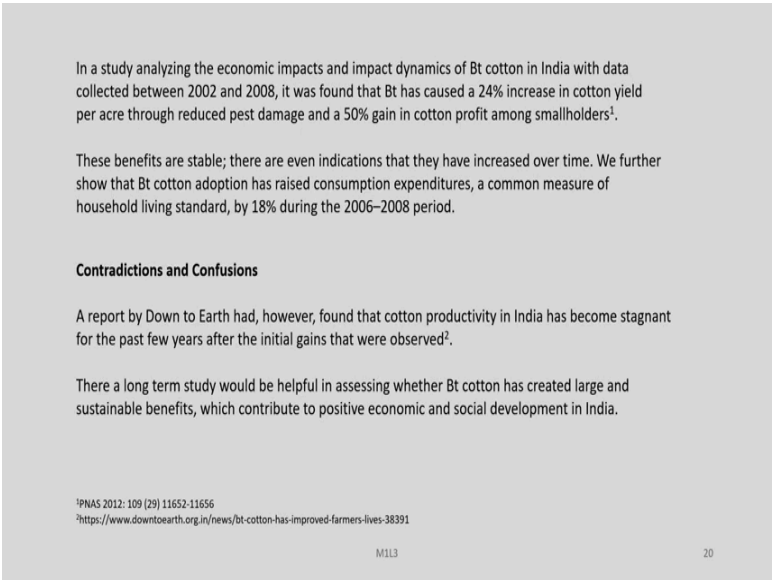

In a study analyzing the economic impacts and impact dynamics of Bt cotton in India with data collected between 2002 and 2008, it was found that Bt has caused a 24 percent increase in cotton yield per acre through reduced pest damage and 50 percent gain in cotton profits among small holders.

These benefits are stable; there are even indications that they have increased over time it was further shown that Bt cotton adoption has raised consumption expenditures, a common measure of household living standards by 18 percent during the study period between 2006 and 2008. However, there are lot of contradictions and confusions. A report by Down to Earth, a periodical found that cotton productivity in India has become stagnant for the past few years after the initial gains that were observed.

Therefore, a long-term study would be helpful in assessing whether Bt cotton has created large and sustainable benefits which contribute to positive economic and social development in India.

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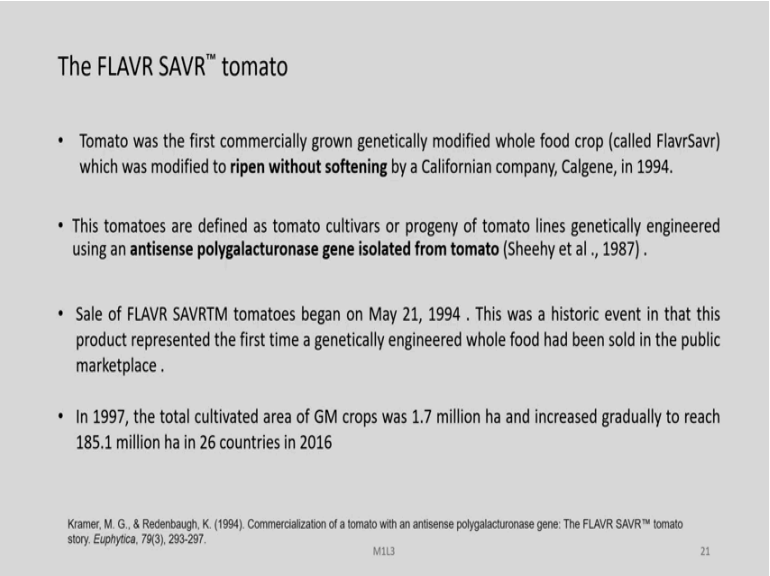

Let us discuss about another agro product which is produced by genetic engineering the FLAVR SAVR^{TM} tomato. The tomato was the first commercially grown genetically modified whole food crop which was modified to ripen without softening by a Californian company, Calgene in 1994.

The problem with tomato marketing was its short shelf-life due to softening there used to be huge loss in the marketing channel and this problem was solved by delayed ripening of the FLAVR SAVR^{TM} tomato. So, these tomatoes were produced by genetically engineering antisense polygalacturonase genes. The sale of the FLAVR SAVR^{TM} tomato began in May 21, 1994, this was a historic event in that.

This product represented the first genetically engineered whole food to be sold in public marketplace. By 1997, the total cultivated area of GM crop was 1.7 million hectare and this increased gradually to reach 185.1 million hectares in 26 countries by the year 2016.

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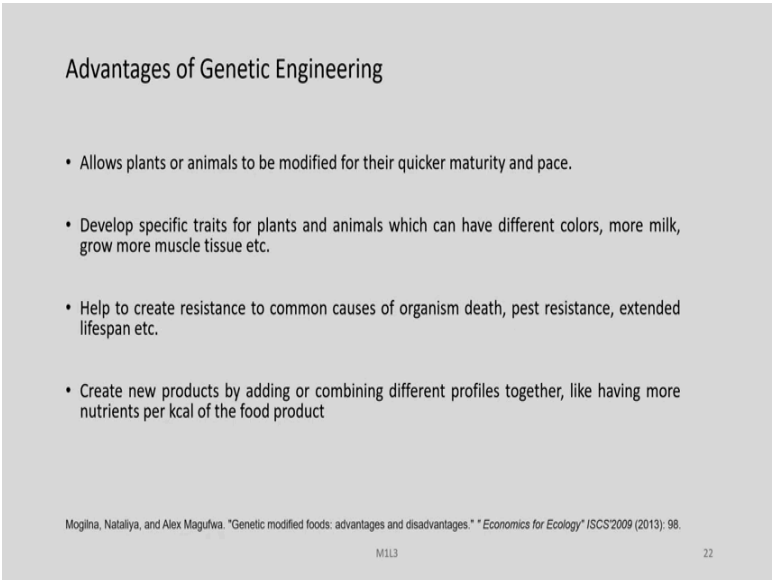

What are the various advantages of genetic engineering? Genetic engineering allows plants or animals to be modified for their quicker maturity and pace. It develops specific traits for plants and animals which can have different colors, more milk, grow more muscle tissue, etcetera. It helps to create resistance to common cause of organism death pest resistance, extended lifespan, etcetera.

It also creates new products by adding or combining different profiles together like having more nutrients per kilo calorie of the food product.

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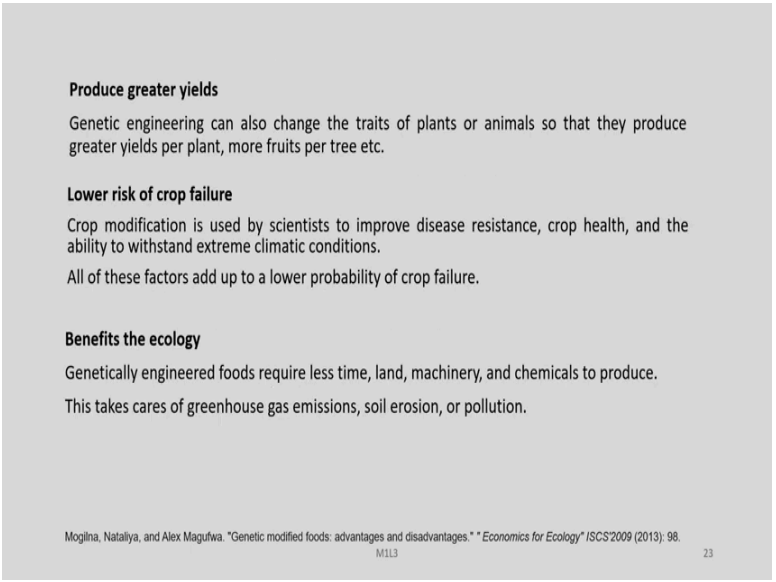

It gives us greater yields. Genetic engineering can change the traits of plants or animals so they produce greater yields per plant, more fruits per tree. It lowers the risk of crop failure. By crop modification. The scientists could improve disease resistance crop health and the ability to withstand extreme weather or climate conditions. All of these factors add up to a lower probability of crop failure. It benefits the ecology.

Genetically engineered foods require less time, land, machinery and chemicals to produce. This takes cares of greenhouse gas emissions, soil erosion or pollution.

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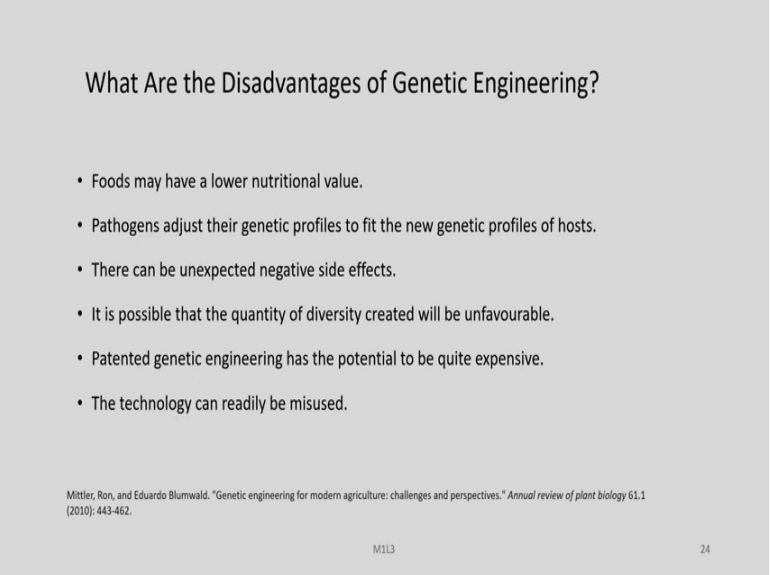

But it has also certain disadvantages what are the disadvantages of genetic engineering? It is often alleged that the foods produced by genetic engineering method may have lower nutritional value; however, we do not have sufficient data for or against it. The pathogens adjust the genetic profiles to fit the new genetic profiles of the host, thereby it develops resistance. There can be unexpected negative side effects and it is possible that the quantity of diversity created will be unfavourable.

Patented genetic engineering has the potential to be quite expensive and the technology can be readily misused.

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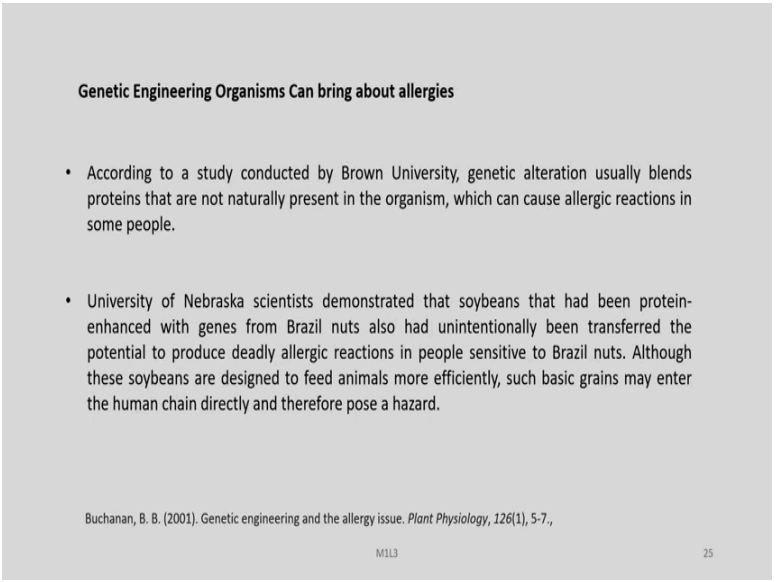

It is also many times discussed that the genetic engineering organisms can cause allergies. According to a study conducted by Brown University genetic alteration usually blends proteins that are not naturally present in the organism and this can cause allergic reactions in some people.

University of Nebraska demonstrated that soybeans, that they had been they have enhanced with protein genes from Brazil nuts also had unintentionally been transferred the potential to produce deadly allergic reactions in people sensitive to Brazil nuts. Although, these soybeans are designed to feed animals more efficiently such basic grains may enter the human chain directly and therefore, pose a hazard.

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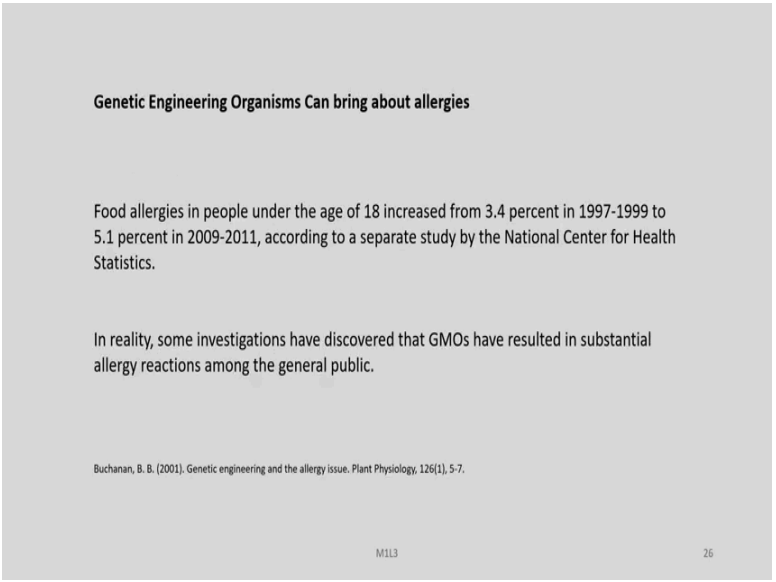

Food allergies in people under the age of 18 increase from 3.4 percent in 1997-1999 to 5.1 percent in 2009 and 2011, according to an independent study by the National Center for Health Statistics. In reality, some investigations have discovered that GMOs have resulted in substantial allergy reactions among the general public.

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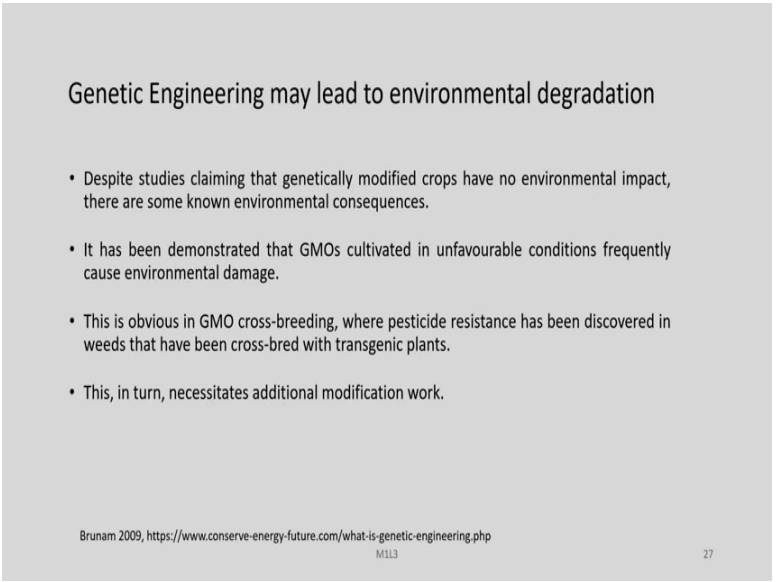

Genetic engineering also may lead to environmental degradation. Despite studies claiming that genetically modified crops have no environmental impact, there are some known

consequences as well. It has been demonstrated that GMOs cultivated in unfavourable conditions frequently cause environmental damage.

For example, certain GMO crops are very very water hungry. If these crops are grown in water scarce areas, there will be competition between this crop and other crops and this may lead to environmental imbalances. This is obvious in GMO crossbreeding where pesticide resistance has been discovered in weeds that have been crossbred with the transgenic plants. This in turn necessitates additional modification work to make the technology safer.

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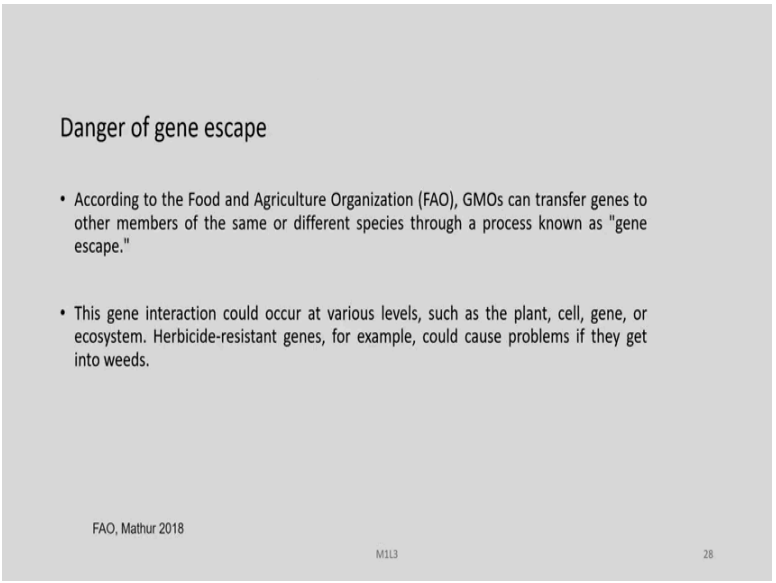

Now, there is an associated danger of gene escape. According to the food and agriculture organizations GMOs can transfer genes to other members of the same or different species through a process known as gene escape. This gene interaction could occur at various levels such as the plant cell gene or ecosystem level. Herbicide-resistant for example, could cause problem if they get into the weeds.

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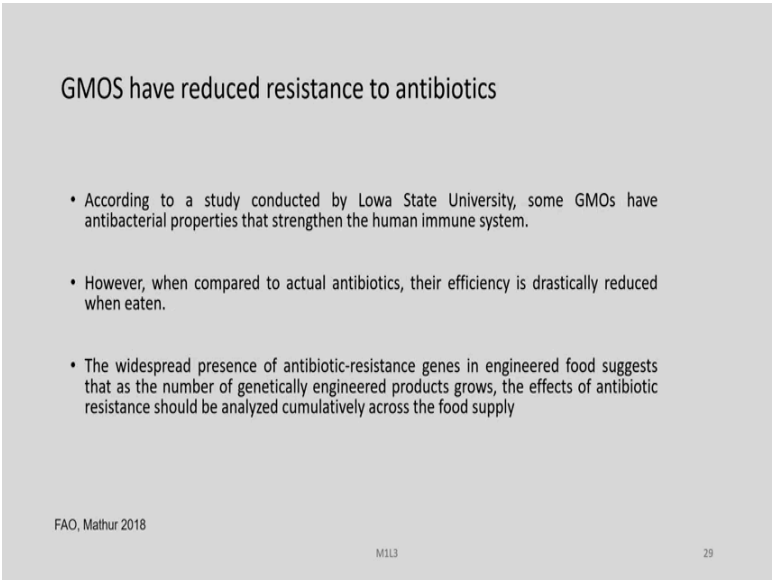

GMOs have reduced resistance to antibiotics: According to a study conducted by Lowa State University some GMOs have antibacterial properties that strengthen the human immune system. However, when compared to actual antibiotics their efficiency is drastically reduced when eaten. The widespread presence of antibiotic resistant genes in engineered foods suggest that as the number of genetically engineered products grow the effects of antibiotic resistance could be analyzed cumutitively cumulatively across the food supply.

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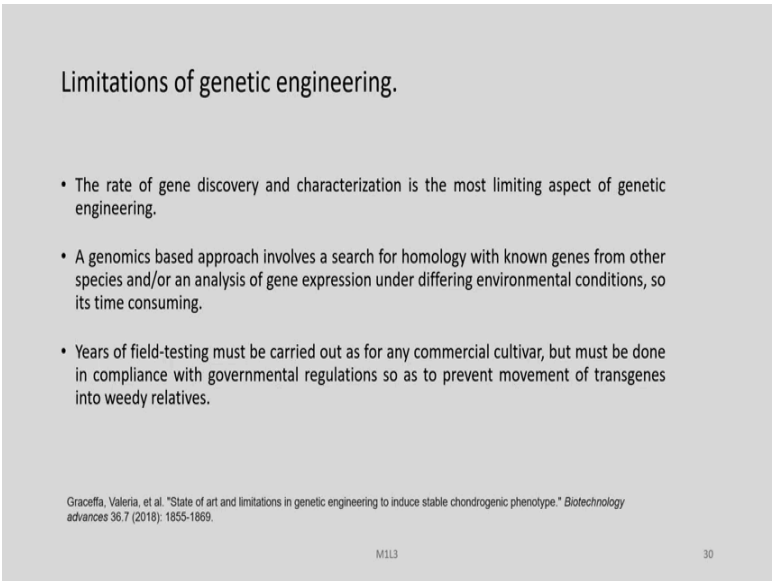

The rate of gene discovery and characterization is the most limiting aspect of genetic engineering. A genomics-based approach involves a search for homology with known genes from other species and or analysis of gene expression under differing environmental conditions which is time consuming. Years of field testing must be carried out as for any commercial cultivar, but must be done in compliance with governmental regulations so as to prevent movement of transgenes into weedy relatives.

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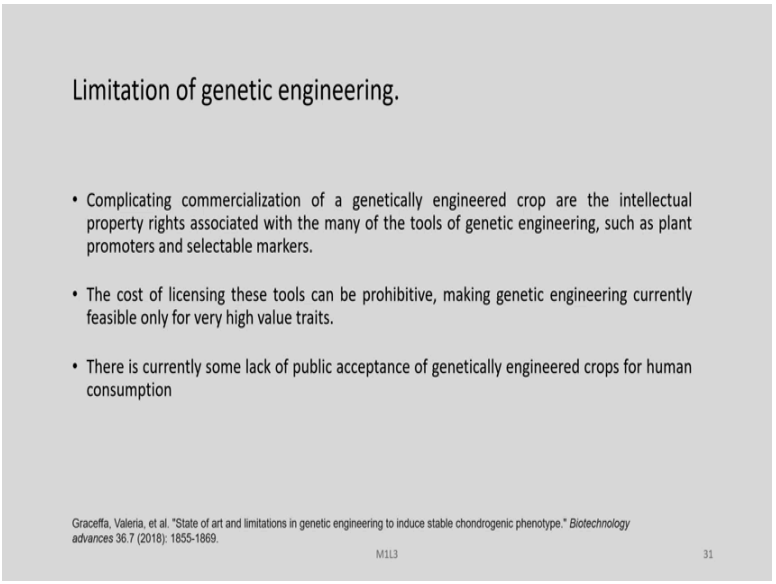

The other limitations of genetic engineering include complicating commercialization of a genetically engineered crop are the intellectual property rights associated with the many of the tools of genetic engineering such as plant promoters and selectable markers. The cost of licensing these tools can be prohibitive, making genetic engineering currently feasible only for very high value trades.

There is currently some lack of public acceptance of genetic engineered crops for human consumption in many countries across the globe.

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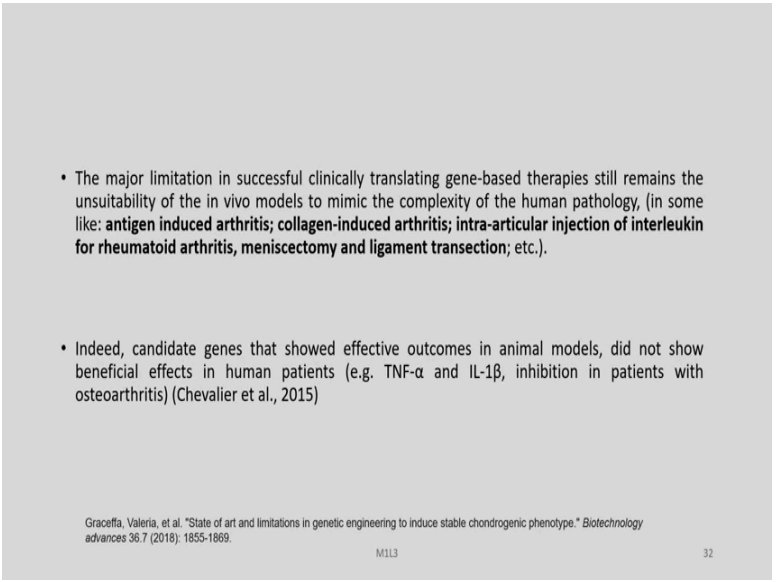

The major limitation in successful clinically translating gene-based therapies still remains the unsuitability of the in vivo models to mimic the complexity of the human pathology. The indeed candidate genes that showed effective outcomes in animal models did not show beneficial effects in human patients.

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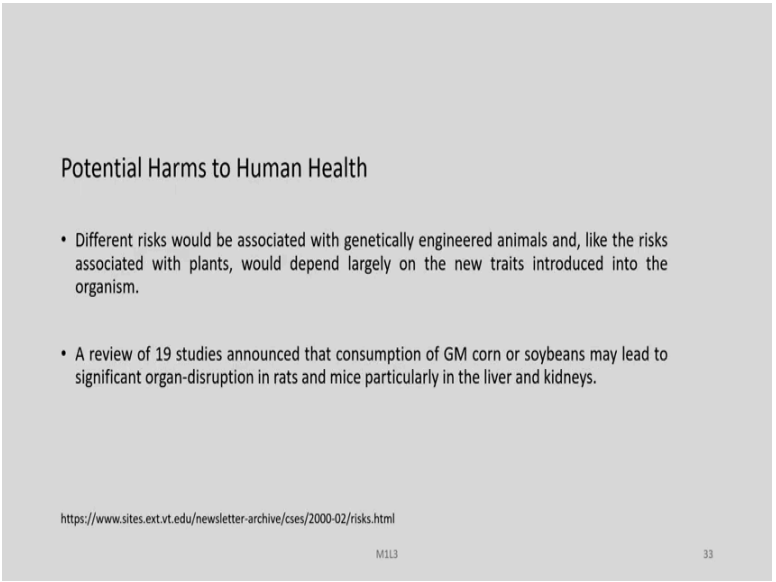

These are some of the other limitations. Genetic engineering may cause potential harm to human health different risks would be associated with genetically engineered animals and like the risk associated with plants this would depend largely on the nutrients introduced into

the organism. A review of 19 studies announced that consumption of GM corn or soybeans may lead to significant organ-disruption in rats and mice particularly in the liver and kidneys.

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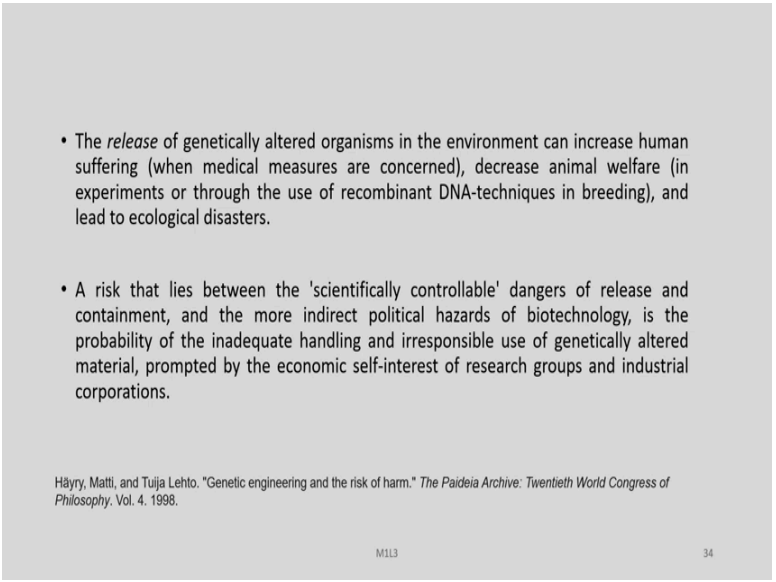

The release of genetically altered organisms in the environment can increase human suffering, decrease animal welfare and lead to ecological disasters. A risk that lies between the scientifically controllable dangers of release and containment and the more indirect political hazards of biotechnology, is the probability of the inadequate handling and irresponsible use of genetically altered material, prompted by the economic self-interest of research groups and industrial corporations.

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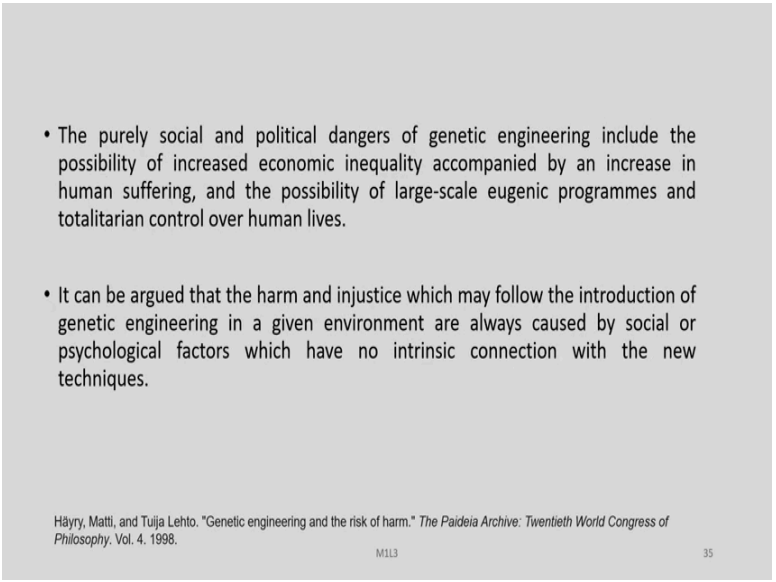

The purely social and political dangers of genetic engineering include the possibility of increased economic, inequality accompanied by an increase in human suffering and the possibility of large-scale eugenic programs and totalitarian control over human lives. It can be argued that the harm and injustice which may follow the introduction of genetic engineering in a given environment are always caused by social or psychological factors which have no intrinsic connection with the new techniques.

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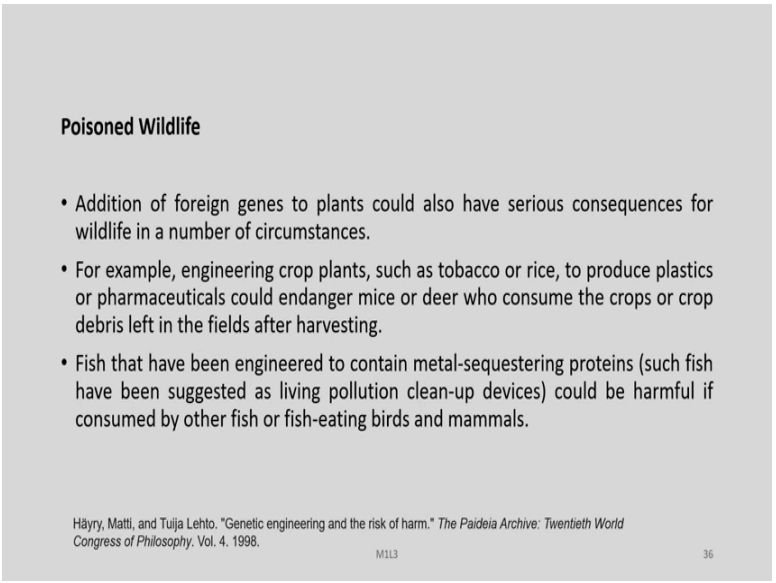

Another disadvantage is the fear of poisoned wildlife. Addition of foreign genes to plants could also have serious consequences for wildlife in a number of circumstances. For example, engineering crop plants such as tobacco or rice, to produce plastics or pharmaceuticals could endanger mice or deer who consume the crops or crop debris left in the field after harvesting. Fish that have been engineered to contain metal-sequestering proteins could be harmful if consumed by other fish or fish-eating birds and mammals.

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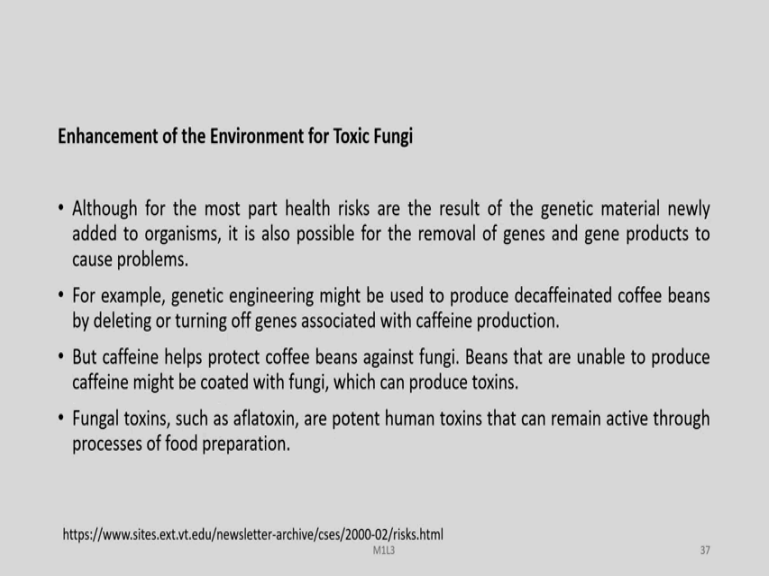

The enhancement of environment for toxic fungi is another concern although for the most part health risks are the result of the genetic material newly added to organisms. It is also possible for the removal of genes and gene products to cause problems. For example, genetic engineering might be used to produce decaffeinated coffee beans by deleting or turning of genes associated with caffeine production.

But caffeine helps protect coffee beans against fungi. Beans that are unable to produce caffeine might be coated with fungi, which can produce toxins. Fungal toxins, such as aflatoxin, are potent human toxins that can remain active through processes of food preparations.

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Another concern is regarding the super soldiers. This is of course, a fictional idea which is which has popularized the concept of super soldiers, but with the recent technological advancements it may be a possibility in the future. In the US, the Pentagon earmarks considerable resources for human enhancement research that could create enhanced soldiers as reported by many.

Overall, the safe genes program is creating a layered, modular and adaptable solution set to protect war fighters and the homeland against intentional or accidental misuse of genome editing technologies; prevent and reverse unwanted genetic changes in a given biological system and facilitate the development of safe, precise and effective medical treatments that use genome editing.

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One of the main concerns of recombinant DNA technology and its misuse is the genetically engineered bio weapons which are considered as a new breed of weapons for modern welfare. So, you see these biological weapons conventions which is an international initiative to stop the spread of bio weapons.

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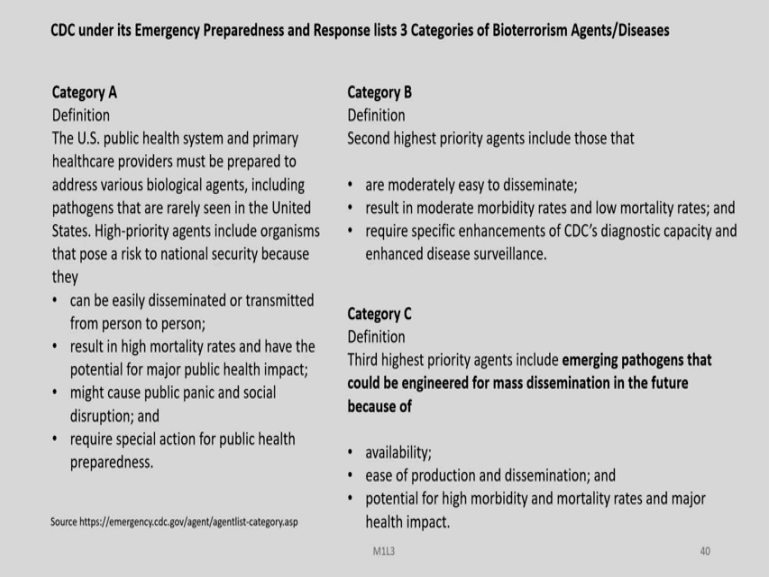

So, CDC under its emergency preparedness and response list 3 categories of bioterrorism agents or diseases which are category A, B and C. Category A: it is defined that the US public health system and primary health care providers must be prepared to address various

biological agents, including pathogens that are rarely seen in the United States. High priority agents include organisms that pose a risk to national security because they can be easily disseminated or transmitted from person to person.

Result in high mortality rates and have the potential for major public health impact, might cause public panic and social disruption and require special action for public health preparedness. The category B are the second highest priority agents and it includes those that are moderately easy to disseminate, result in moderate morbidity rates and low mortality rates and require specific enhancement of CDC diagnostic capacity and enhanced disease surveillance.

Category C defines the third highest priority agents which includes emerging pathogens that could be engineered for mass dissemination in the future because of availability, ease of production dissemination and potential for high morbidity and mortality rates and major health impacts. So, recombinant DNA technology can produce many of these categories of bioterrorism agents especially category C, the emerging pathogens which can be engineered for mass dissemination.

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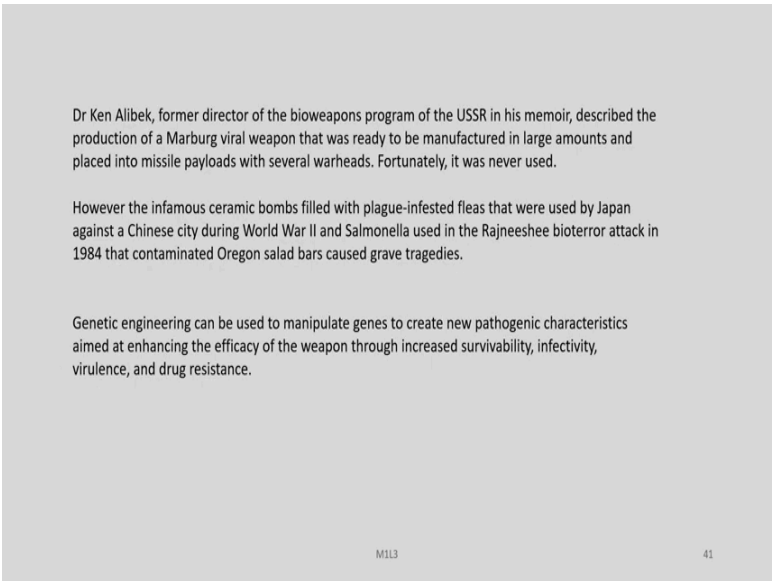

Dr. Ken Alibek a former director of the bio weapons program of the USSR in his memoir, described the production of Marburg viral weapon that was ready to be manufactured in large amounts and placed into missile payloads with several warheads. Fortunately, it was never

used. So, bio weapons and bioterrorism is not a fiction many countries has been working on it since many decades.

You have the infamous ceramic bombs filled with plague-infested fleas that were used by Japan against Chinese city during World War II and *Salmonella* used in the Rajneeshee bioterror attack in 1984 that contaminated Oregon salad bars and caused grave tragedies. Genetic engineering can be used to manipulate genes to create new pathogenic characteristics aimed at enhancing the efficiency of the weapon through increased survivability, infectivity virulence and drug resistance.

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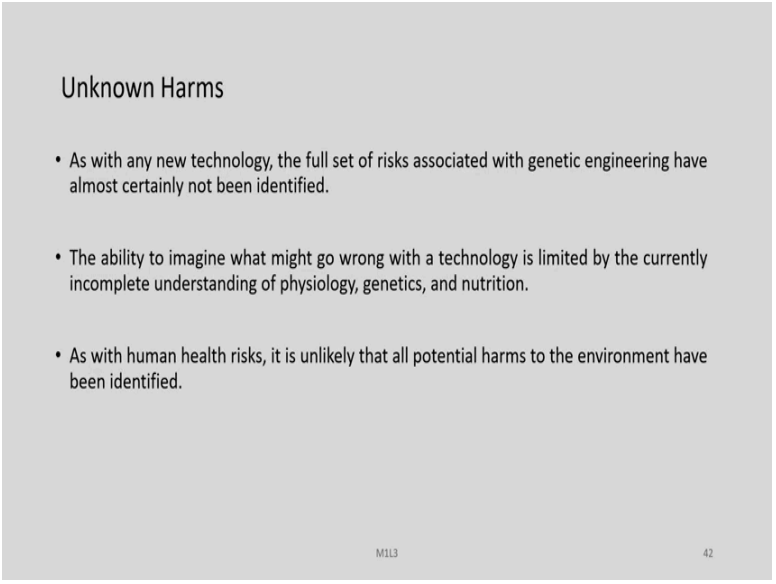

There are also many other unknown harms: as with any new technology, the full set of risks associated with genetic engineering have almost certainly not been identified. The ability to imagine what might go wrong with a technology is limited by the currently incomplete understanding of physiology, genetics and nutrition. As with human health risks it is unlikely that all potential harms to the environment have been identified.

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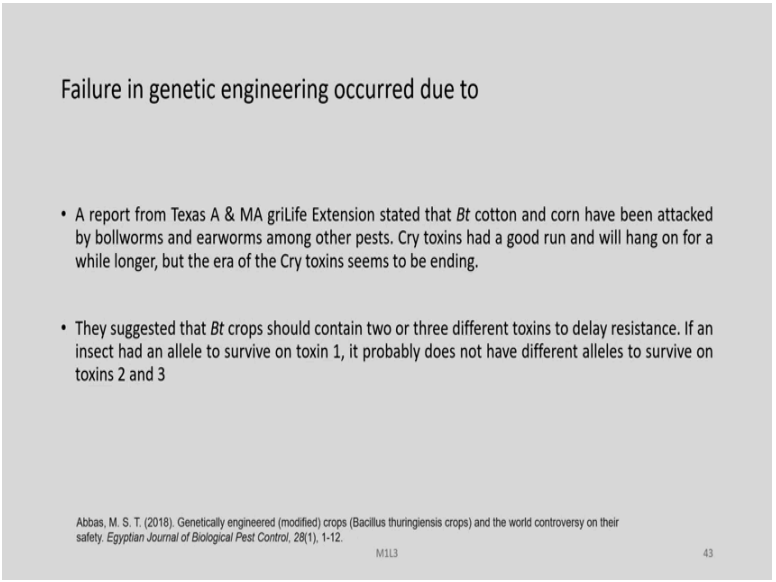

Many failures have been encountered in genetic engineering due to various reasons: A report from Texas A and M AgriLife Extension stated that Bt cotton and corn have been attacked by bollworms and earworms among other pests. Cry toxins had a good run and will hang on for a while longer, but the era of the Cry toxins seems to be ending. They suggested that Bt crops should contain two or three different toxins to delay resistance.

If an insect had an allele to survive on toxin 1, it probably does not have different alleles to survive on toxin 2 and 3 and these strategies can be very very helpful in the future.

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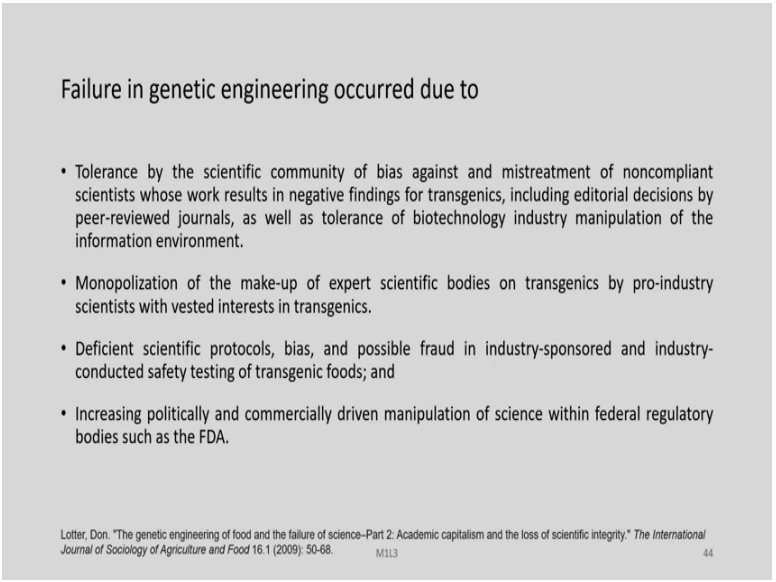

Tolerance by the scientific community of bias against the mistreatment of noncompliant scientist whose work results in negative findings for transgenics, including editorial decisions by peer-reviewed journals, as well as tolerance of biotechnology industry manipulating the information environment is also very very critical.

Monopolization of the make-up of expert scientific bodies on transgenics by pro-industry scientists with vested interest in transgenic is equally dangerous. The deficient scientific protocols, bias and possible fraud in industry sponsored and industry conductive safety testing of transgenic foods; and the increasing politically and commercially driven manipulation of science within federal regulatory bodies such as the FDA also needs to be understood.

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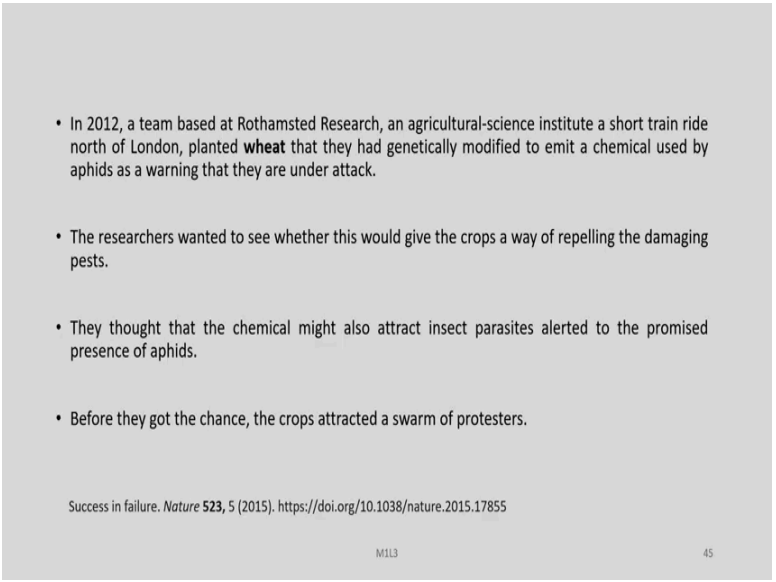

In 2012, a team based at Rothamsted Research, an agriculture-science institute a short train ride north of London, planted wheat that they had genetically modified to emit a chemical used by aphids as a warning that they were under attack. The researchers wanted to see whether this would give the crops a way of repelling the damaging pests. They thought that the chemical might also attract in parasites alerted to the promised presence of aphids. Before they got the chance, the crops attracted; however, a swarm of protestors.

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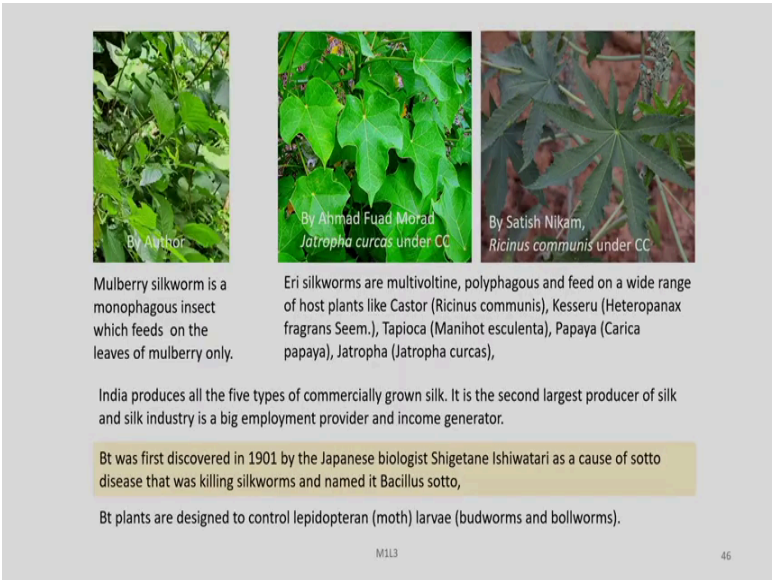

Let us now shift our attention to another area which is the Seri culture area. Mulberry silkworm is a monophagous insect which feeds on the leaves of a single plant the mulberry; however, there are other breeds of silkworm like the Eri silkworm which are multivoltine and polyphagus and feed into wide range of host plants like Castor, *Ricinus communis*, then Kesseru, *Tapioca*, Papaya, Jatropha, etcetera.

So, Eri silkworms has a better sense of survival because it can feed into various kinds of host plants. It needs mentioning here that India produces all the five types of commercially grown silk the mulberry silk, the tussar silk, the Eri silk and the Muga silk. Tussar has two varieties one is the temperate or the cold tussar. India is the second largest producer of silk and silk industry is a big employment provider and income generator.

We need to go back to our earlier discussion about the discovery of *Bacillus thuringiensis*. Hope you remember that Bt was discovered in 1901 by the Japanese biologist Ishiwatari as a cause of sotto disease that was killing silkworm and who named it as *Bacillus sotto* and later which was named as *Bacillus thuringiensis*. So, if we design a Bt plant which is a host to silkworm, the silkworm is going to die.

So, Bt plants designed to control lepidopteran moth and larvae and these can be harmful to polyphagous insects.

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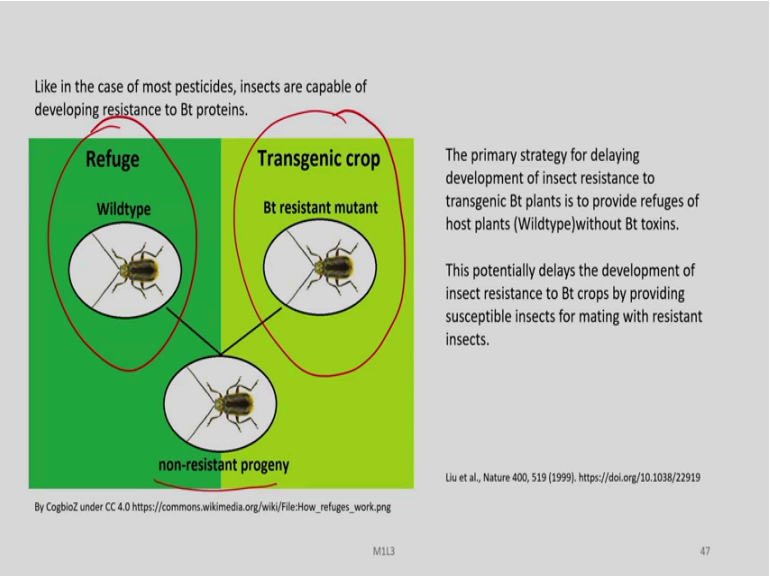

And in case there is some kind of escape of the gene to some of these plants, it can cause havoc in this sector, but that is most unlikely. But, there is a competition of biodiesel production and we know that castor already produces castor oil and the jatropha is being targeted to produce biodiesel and there have been many efforts to produce Bt resistant jatropha and Bt resistant *Ricinus communis*.

So, here we need to exercise some kind of a restraint because this can be very very harmful to one of our important economic sectors which provides lot of employment in the rural economy. Like in the case of most pesticides the insects are capable of developing resistant to Bt proteins as well. The primary strategy for delaying development of insect resistance to transient Bt plants is to provide refused to host plants without the Bt toxin.

So, this is the refuse which do not have any plants with Bt gene or where no any transgenic plants are grown. So, the wild type insect will be surviving in this area; however, in the transgenic area we plant the Bt resistant or the Bt crop and here some kind of Bt resistance may develop along with time. Now, if this Bt resistant mutant is allowed to breed with the wild type which is not resistant, the progeny most likely would be non-resistant progeny.

Because the Bt resistance is probably a not dominant character. So, this potentially delays the development of insect resistance to Bt crops by providing susceptible insects for meeting with the resistant insects.

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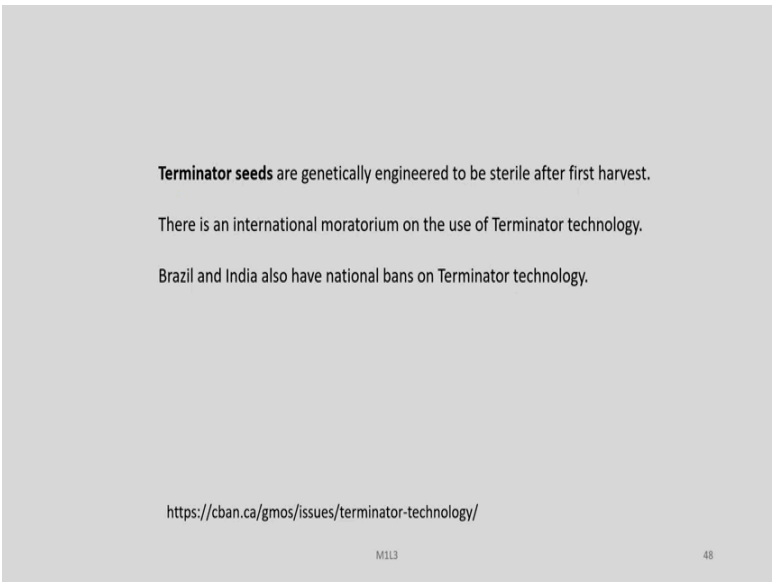

Another very dangerous technology was the advent of terminator seeds which are genetically engineered to be sterile after the first harvest. So, there is currently an international moratorium on the use of these terminator technology and countries like India and Brazil have banned it for long.

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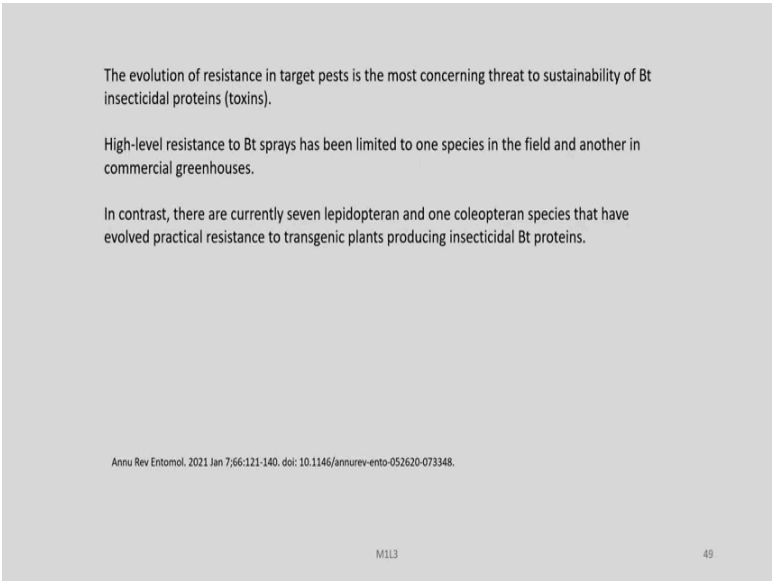

The evolution of resistance in target pest is the most concerning threat to sustainability of Bt insecticidal proteins. High level resistance to Bt sprays has been limited to one species in the field and another in commercial greenhouses. In contrast, there are currently seven

lepidopteran and one coleopteran species that have evolved practical resistance to transgenic plants producing insecticidal Bt proteins.

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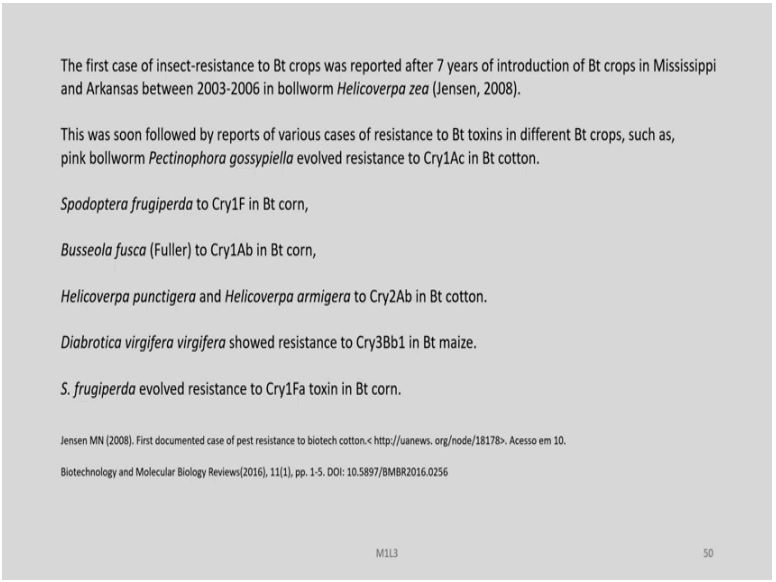

The first case of insect resistance to Bt crops was reported after 7 years of introduction of the Bt groups in Mississippi and Arkansas between 2003 and 2006 in bollworm *Helicoverpa zea* and reported by Jensen. This was soon followed by reports of various cases of resistance to Bt toxins in different Bt crops such as pink bollworm which evolve resistance to Cry1Ac in Bt cotton and others like *Spodoptera*, *Busseola*, *Helicoverpa punctigera* and *Helicoverpa armigera*.

They developed the Bt resistance to various kind of constructs like Cry2Ab, Cry21Ab and so on. And finally, these *S. frugiperda* evolved resistance to Cry1Fa toxin in the Bt cotton.

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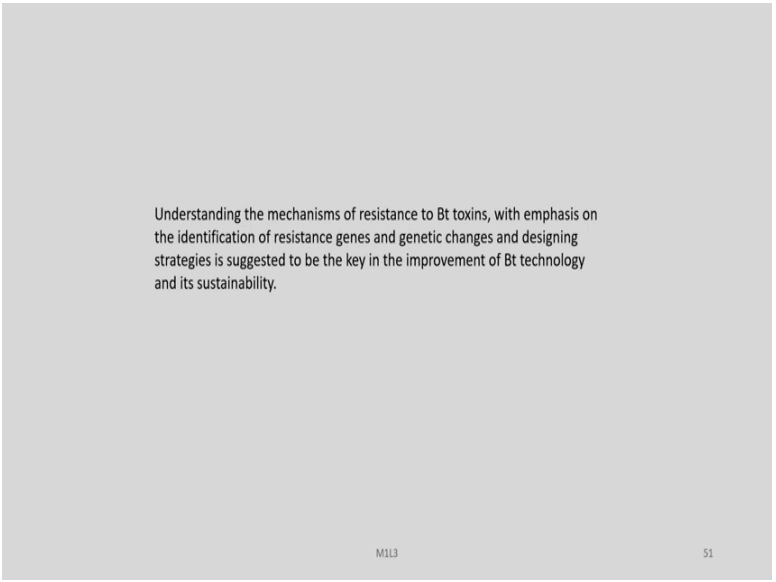

Therefore, understanding the mechanisms of resistance to Bt toxins, with emphasis on the identification of resistance genes and genetic changes and designing strategies is suggested to be the key in improvement of Bt technology and its long-term sustainability.

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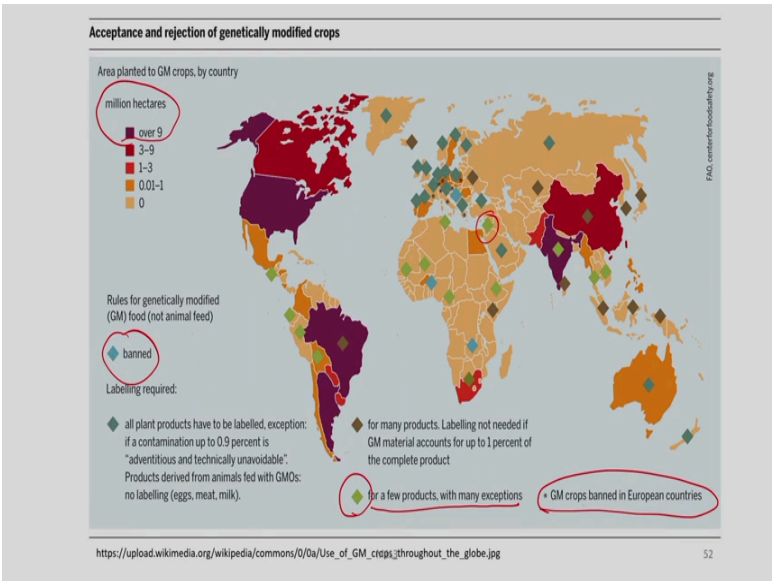

Now, this is a global map which shows the exception and rejection of genetically modified crop. So, you can also see here the area planted under GM crops by country. So, this is the color which indicates over 9 million hectares of land and India falls in that category along

with USA and Brazil, then in certain countries genetically modified plants are banned. So, these are the countries where or geographies where it is being banned.

Then, you have certain countries where all plant products have to be labeled exception if a contamination up to 0.9 percent is advantageous and technically unavoidable. So, labeling is very very important. So, the food products should be labelled that this is a GM product. And there are some countries with this green symbol, this is for few products with many exceptions and you can see that GM crops are mostly banned in European countries as per this map.

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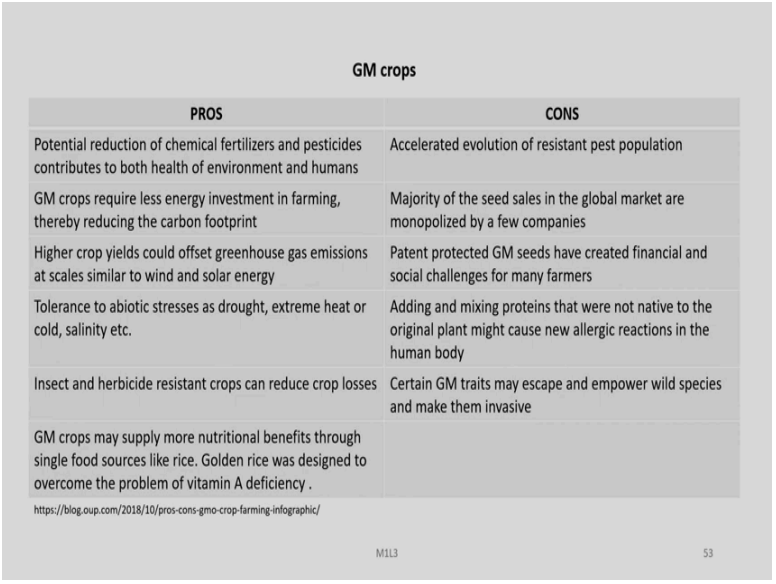

Now, let us conclude with this comparison regarding the genetically modified crops what are the pros and cons some of those we have already discussed. So, the pros regarding the GM crops is that potential reduction of chemical fertilizers and pesticides contribute to both health of environment and humans. The GM crops require less energy investment in farming thereby reducing the carbon footprint. Higher crop yields could offset greenhouse gas emissions at scales similar to wind and solar energy.

Tolerance to abiotic stress as drought, extreme heat or cold, salinity, etcetera. Insect and herbicide resistant crops can reduce crop loss. The GM crops may supply more nutritional benefits through single food sources like rice for example, golden rice was designed to overcome the problem of vitamin A deficiency; however, there are some allegations that GM crops may not be nutritionally as good as the normal crop.

Now, what are the cons? The cons include the accelerated evolution of resistant pest population which we have discussed at length prior to this slide. Majority of the seed sales in the global market are monopolized by a few companies. Patents protected GM seeds have created financial and social challenges for many farmers and this can be reasons for distress and other social problems.

Adding and mixing proteins that were not native to the original plant might cause new allergic reactions in the human body. Certain GM traits may escape and empower wild species and make them invasive.

Thank you.