search news

press releases

background

act!

links

archive

Respect natural Complexity!

We must understand biological complexity at many levels when we try to evaluate the effects of genetic engineering.

highlights:

Live Webcast Replay

Click on the image to launch a replay of the webcast which gives an overview of the issues raised regarding biological complexity and GE.

Windows Media Player required

Summary | Levels | Assessing the Effects | Remote Causation | X

The information in these pages has been assembled by Peter R Wills,
University of Auckland, New Zealand.
Page construction and navigation graphics by Ken Richardson.

Biological Complexity

Biological systems display extraordinary dynamic complexity. They are integrated both within and across multiple levels in time and space. The highest level where intricate dynamic complexity is evident is the domain of global evolution. Entire species continually appear and disappear in a pattern extending over billions of years. The lowest level of dynamic complexity in biology is the domain of elementary biochemical and molecular genetic processes. These processes occur in microscopic cells, and take times as short as a millionth of a second to reach completion.

The authorities who assess the environmental and ecological impacts of genetically engineered organisms usually ignore the complex patterns of causation that are characteristic of biology. This is because no-one has sufficient scientific understanding of biological processes to analyse adequately or predict accurately change in complete systems of any size: cells, organisms, ecosystems or our planetary biosphere. As a result of this ignorance, releasing the products of genetic engineering into the environment puts the world of nature at risk of harm that we don't yet know about.

Biological systems are characteristically hierarchical and there is a constant interplay between events at different levels. This interplay extends from the events that happen very slowly on a global scale right down to the most rapid events observed on a microscopic scale. A unique molecular event, like a mutation occurring in particularly fortuitous circumstances, can be amplified to the extent that it changes the course of evolution. On the other hand, the global environment, now moulded by aeons of biological activity, has been very influential in determining things that happen far more rapidly and on a scale smaller than we can perceive: the biochemical transformations of ordinary cellular metabolism.

To assess the effects of genetic engineering we must understand how biological networks operate. However, we must also keep in mind the fundamental limitations placed on our ideas and pictures of complex biological systems and their dynamic behaviour.

Some of the networks of interaction that we find at different levels of biological organization are, from the top down:

1. the evolutionary tree of life
2. ecological networks
3. the genetic control networks of organisms
4. the protein interaction network in cells
5. the metabolic network in cells

Levels of Complexity

Complex networks are found at every level of biological organization. They range across all scales of both time and space, from the global to the molecular.

1. the evolutionary tree of life
   time-scale: billions of years
   length scale: thousands of kilometres

2. ecological networks

3. the genetic control networks of organisms

4. the protein interaction network in cells

5. the metabolic network in cells
   time-scale: millionths of a second
   length scale: billionths of a metre

Assessing the Effects of GE

When we do genetic engineering we manipulate organisms at the most basic level - the information required for their construction and maintenance. This information, usually held in the form of DNA sequences, is replicated as new cells are formed in each generation. In the normal course of events a new cell receives a copy of the information from its parent cell, or in the case of sexual reproduction, information from both parent cells.

Everything we observe in biology depends on which particular DNA sequences are found in particular cells. This is true at all levels, from the history of evolutionary change down to the elementary events of cellular metabolism. Some effects of genetic change can be seen straight away, but the final effect of any genetic change is very hard to predict because of the complexity of biological networks.

Any genetic change can have an effect many levels. Most immediately a genetic change affects the molecular events inside a cell. This may show up as altered cellular metabolism or altered development of the embryo. The change may produce an organism with altered characteristics. It may respond differently with its environment. It may interact differently with members of other species. Ultimately, the course of evolution can be affected by an apparently small genetic change.

Genetic engineering is the art of changing a cell's DNA sequences in ways that would not occur in the normal course of events. The effects of genetic engineering can show up at any level of biological complexity, sometimes quite unexpectedly. Assessment of these effects requires both experimentation and informed speculation.

The most immediate effects of genetic engineering are often assessed by using an experimental *trial and error* method: first make the genetic change and then try to detect any effects.

The most remote effects of genetic engineering can only be assessed by using a speculative *best guess* method: look at all of the relevant information and evidence from similar cases and then try to estimate the likelihood of every possibility.

The complexity of biological networks restricts enormously our ability to assess the effects of genetic engineering. We can understand these restrictions by looking at different levels of biological complexity:

1. effects of GE on the evolutionary tree of life
2. effects of GE on ecological networks
3. effects of GE on the genetic control networks of organisms
4. effects of GE on the protein interaction network in cells
5. effects of GE on the metabolic network in cells

Wisdom dictates: until we are much better able to assess the effects of manipulating the world of biology by using genetic engineering, we should:

exercise the utmost precaution,
isolate all the products of our experiments,
use the most stringent containment facilities, &
refrain from creating some possible organisms.

Remote Causation in Biology

Causative links in ecological networks are often unseen and hard to trace, because their effects are very indirect. Changes in the behaviour or abundance of one species can have far-reaching effects on apparently unrelated species, affecting even their ability to survive.

Indirect effects are typical in biology, but very often they are not so specific and not so easily discernible as in the rabbit-butterfly example. It is usually quite difficult to attribute change, like the extinction of a species in an ecosystem, to such a simple localised change at some point in the system. Rather, the change may appear to be a "whole system property" of the network of interacting species. This applies to most irreversible changes in large, densely-connected networks.

Fundamental Limitations

We can create a partial sketch of the complexity that characterises life on earth by examining the natural hierarchy of biological networks. However, we must continually remind ourselves that none of these networks is really an isolated entity.

A picture of a biological network shows what a cell, organism or ecosystem looks like from just one aspect. The networks we describe are only parts of systems that we have artificially abstracted from the whole. Pictures of biological networks are designed to help us build a description of cells, organisms and ecosystems that we can fit into a framework of elementary ideas.

Our pictures of biological networks fail to represent their dynamic aspect. Biological networks are continually changing and developing, sometimes in a repetitive pattern, sometimes quite chaotically, sometimes reversibly and sometimes irreversibly.

Of equal importance: biological networks extend across space, from the microscopic scale of intra-cellular organization to the global scale of planetary ecology. Spatial organization can be observed everywhere in biology, but we have a very poor understanding of its effect or significance at any level. Our pictures of networks give no real hint of this aspect of biological organization.

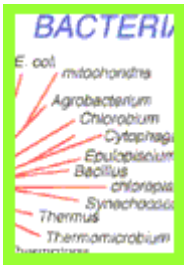
For more than half a century theoretical biologists have been developing ideas about biological networks and hierarchies and applying them to our knowledge of molecular genetics. However, science does not yet provide the conceptual tools needed to make confident predictions or even to present clear analyses of the behaviour of densely connected networks comprised of interacting modules of different varieties (molecules, organisms, species or ecosystems).

Link To: "Assessing the Effects (Index)"

Evolution and Genetics

(I) Evolutionary relationships.

(ii) Diversity of a protein.



(iii) Genetic diversity of organisms.

Genetic change is the basis of biological evolution – an ever-developing pattern of species in interacting ecosystems distributed across the globe. The historical record of the genetic changes that have taken place during the last four billion years is rather like a web, especially because of occasional "horizontal gene transfer" between species, but it is often presented as a tree or star diagram.

The story of terrestrial evolution is about continual variation in the genetic make-up of species and the ecological effects of those variations. Looking over very long times, we see evolution as the continual appearance and disappearance of species and whole families of species. Constellations of genes are held together in species and inherited from one generation to the next, continually varying.

Genetic variation inevitably gives rise to novelty in individual organisms. Novelty may survive and be inherited by later offspring. This process is called *natural selection*. Survival of biological novelty as a result of natural selection depends on all of the factors that go into determining the life history of a reproducing organism.

Natural selection can be thought of as irreversible ecological change. It poses a barrier to survival for biological novelty generated by genetic change.

Natural selection is understood extremely poorly by thinking in terms of genes “encoding” characteristics of individual organisms. This is because most of the factors that determine the survival of organisms are external to them and continually changing. What appears to be an individual’s genetic advantage in one ecological context may be a disadvantage in another context.

Natural selection is mediated by interactions in ecological and social networks. Those interactions often appear to have remote and obscure causes. The original genetic change in an individual organism is only a minor part of any event of natural selection. The ecological context of that original change, affected by all of the constellations of genes in other organisms and the way they interact, is probably more important.

During biological evolution, enduring genetic change in ecosystems has happened mainly as a result of three sets of processes:

(i) mutation and recombination;
(ii) horizontal (interspecies) gene transfer;
(ii) natural selection due to environmental and ecological pressures.

Selective breeding, practised by humans for millennia, is a manipulation of the first set of processes. Genetic engineering is a manipulation and extension of the second set of processes.

"Assessing the effect of genetic engineering (Evolution and Genetics)"

Summary Levels Assessing the Effects Remote Causation X

Complexity of Ecological Networks

The ecology within any geographical region consists of an ever-changing pattern in the distribution of different species. Any very detailed description of the ecology of a region should also show the different spatial scales relevant to the lives of different species and the niches they live in.

We can get some idea of the complexity of ecological networks by looking at food-chain relationships, ignoring how organisms of different species are distributed in space. Food-chain relationships are very important in ecology because they impose constraints on the flow of energy and the distribution of bio-mass among species inhabiting neighbouring and overlapping niches.

The best scientific analysis of ecological dynamics is achieved by writing equations that describe how the populations of different species change in time. Changes in the population of one species can affect the population of other species in many ways: consumption as food, disturbance of habitat, influence on reproductive behaviour or opportunities, etc.

Any system of equations that takes into account the inter-dependence of species population numbers in a complex ecological network demonstrates many modes of behaviour. The population of a species may remain relatively constant or vary up and down over a short or long period of time in a simple or complicated fashion. From year to year, the seasonal population of some species varies in an apparently chaotic manner and is very difficult to predict.

The dynamic behaviour of any ecological system depends on the environment as well as interactions between species. How organisms interact and the way they affect one another's populations reflect many characteristics of the various species living in the ecological system. All these characteristics depend on genes. Variations in the characteristics of one species influence how other species behave. No change in the characteristics (or genes) of an organism, regardless of how insignificant it may appear, can be considered in isolation from the network of ecological interactions between different species.

What happens in an ecosystem can also be sensitive to the initial population numbers of different species. Sometimes a threshold in population numbers is crossed beyond which there is no return. Phenomena of this sort have been encountered during attempts to reintroduce species into ecological systems from which they have been lost. Even when the apparent cause of the initial loss is no longer operating, reintroduction of the lost species often fails. The extinction of whole species is a special example of irreversible change in ecosystems.

"Assessing the effect of genetic engineering (Ecological Networks)"

Complexity of Genetic Control Networks in Organisms

Proteins are the biochemical products of gene expression. Throughout the life of an organism the production of different proteins is being switched on and off (induced or repressed). This regulation of gene expression is central to the constitution of any organism. It is needed for any cell's normal development and the maintenance of all biological functions, including responses to environmental change.

Many of the genes in the chromosomes of higher organisms encode proteins whose sole apparent function is to act as switches for the regulation of the production of other proteins. Bacterial genomes encode something like 1000 proteins and mammalian genomes encode some tens of thousands of proteins. The action of these proteins makes up a complex gene control network.

During the life of an organism the gene control networks of its cells switch between different states of activation at different locations in the organism's complete DNA sequence. The networks in different cells are connected through complicated signalling processes requiring the synthesis of special proteins at different times.

The fine control of gene expression in different cells at different locations is especially important during embryo development. The development of a complete organism from a single cell requires the expression of many genes to be switched on and off in perfect sequence.

Any sufficiently complicated dynamic network, like a cell's genetic network, has different operational states. These complex networks often switch between different dynamic states in response to external changes. Some networks have the ability both to "remember" and to "learn" about what changes have been imposed on them.

One feature of biological networks that is especially important in genetic networks is the distribution of control among several different mechanisms. This is known as *degeneracy*. It is the ability of elements that are structurally different to perform the same function or yield the same output. Degeneracy in genetic control networks makes them more resilient to change. However, it also makes it more difficult for us to be certain that we have identified all of the functions of any gene that are important to an organism.

Network interactions can have their effect at several stages in the expression of any gene (synthesis of a protein). The three main stages of gene expression are:

(i) transcription of the DNA gene (synthesis of messenger RNA);
(ii) translation of the messenger RNA (protein synthesis);
(iii) folding and modification of the protein (making it functional).

Each stage in the formation of one functional protein can be affected by other proteins. One protein can affect the transcription of the gene encoding another protein by binding to the cell's DNA close to the site of the gene. One protein can affect the translation of the messenger RNA encoding another protein by binding to the messenger. There are also ways that one protein can affect the folding and modification of another protein.

During translation, biomolecular machines called ribosomes use the genetic information in messenger RNA to construct a protein with the correct amino acid sequence. The unique amino acid sequence of a protein is a "translation" of the genetic sequence encoding it. The mechanism of translation is universal in terrestrial organisms. The rules for matching amino acid sequences to genetic sequences are called *the genetic code*. One triplet of nucleic acid bases in a genetic sequence (DNA or messenger RNA) corresponds to one amino acid in the sequence of the corresponding protein.

"Assessing the effect of genetic engineering (Genetic Control Networks in Organisms)"

Complexity of Protein Interaction Networks

There are thousands of different proteins active in a cell at any time. Many act as enzymes, catalysing the chemical reactions of metabolism. Others are components of cellular “machines”, like ribosomes that reads genetic information and synthesises proteins.

Many other proteins are involved in the regulation of gene expression (protein production) in some way. There are proteins that play specific roles in special cellular compartments and others move from one compartment to another, acting as "signals". By directly interacting with one another, proteins continually affect one another's functions.

Proteins are produced and degraded all of the time. The rates at which these processes occur depend on what proteins are already present, how they interact with one another and how they interact with genes (DNA or messenger RNA). Proteins that bind to DNA or RNA often have a direct effect on the production or degradation of other proteins. One protein can speed up or slow down the rate of production of another by binding to the DNA or RNA (the genetic information) that is needed to make it.

The chart represents protein-protein interactions as lines (edges) forming a network between points (nodes). It doesn’t show the functions of different proteins or the effect of the interactions. The relatively large number of red points in the chart demonstrates the fragility of cells. When a mutation causes the loss of one of these essential protein functions the cell dies. Correspondingly, the large number of green points in the chart demonstrates the robustness of organisms. The organism can survive loss of these proteins. Much of this robustness is due to “degeneracy” in the network – more than one protein, encoded in separate genes, serving the same or a closely similar function.

"Assessing the effect of genetic engineering (Protein Interaction Networks)"

Complexity of cellular metabolism

The metabolic processes that occur continually within cells form a complex network of chemical reactions. All of the basic substances needed for the construction and survival of a cell and its different components (except vitamins that have to be introduced from the outside) are synthesised from other substances. Almost all cellular reactions occur as a result of the catalytic action of protein enzymes.

Control of the chemical reaction network in cells is needed to maintain the proper regulation of energy consumption, production of molecular substances and intracellular signalling.

Each point (node) on the chart represents a chemical substance and each line (edge) represents a transformation of one substance into another. The spatial organization of the chart does not represent the spatial organization of chemical processes in different cellular compartments (like the cytoplasm, nucleus and mitochondria).

The chart represents only the complexity of the network of chemical transformations and their catalysis by enzymes. It does not show how some apparently unrelated chemical substances have an effect on the rate of transformation of others. Some molecules do this by interacting “allosterically” with the enzyme that catalyses a chemical reaction of other molecules.

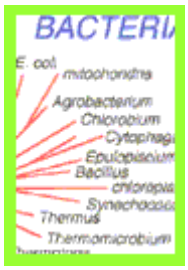
To imagine the chemical processes occurring in a cell you have to think about the rate at which each transformation ("flow" along a line in the diagram) takes place at any time. Cells have a multitude of ways for speeding up or slowing down in these flows in different parts of the network, all the time maintaining balanced regulation between different, sometimes remotely connected, parts of the network.

"Assessing the effects of genetic engineering (Cellular Metabolism)"

Assessing the Effects - Evolution and Genetics

(I) Evolutionary relationships.

(ii) Diversity of a protein.



(iii) Genetic diversity of organisms.

When we come to assess the effects of genetic engineering, we have to question whether the tree of life has build-in genetic regularities that we do not see when focus exclusively on the accidental, historical aspects of evolution.

Since the time of Darwin and Mendel biologists have developed elaborate mathematical theories to describe the processes of natural selection.

Can the tree of life survive and flourish without any particular structure of the sort we see in it now? Or can we modify genes and swap them around as much as we want, without having any significant effect, except to produce organisms more pleasing to some humans?

The genetic relationships between species, those that are now extinct as well as those still existing, can be traced through the many growing branches, occasional web-like crossings and hosts of dead outgrowths that make up the tree of life. The branches of the tree of life form a detailed record of multitudes of unrelated historical accidents, tracing out every genetic change that has survived the pressures of natural selection.

Genetic engineers assume that the tree of life has no intrinsic value – humans can graft a hotchpotch of cross-branches into it, presuming to have perceived what the consequences are. They assume that the tree of life will cope with whatever genetic change they impose on it and nothing of value will be lost.

We cannot start to describe accurately the character of the novelty that genetic engineering is generating in the biosphere. There is no knowledge available on which to base a sound assessment of such a sudden injection of novelty into such a complex system. We do not have the scientific tools we need, neither a body of observation nor a set of theoretical concepts, to understand global biological structure and dynamics.

Our understanding of ecological networks and their evolution is insufficient for any meaningful assessment of the impacts of artificial genetic change accomplished by using techniques of genetic engineering and its follow-on effects through natural processes of genetic change.

In evolutionary terms, the practice of genetic engineering represents a sudden, astronomically large increase in the rate of gene transfer between species whose genomes have been isolated from another for aeons. Genetic engineering opens up completely new pathways of gene transfer. Releasing genetically engineered organisms into the environment can be expected to generate new selective pressures that have never before operated during biological evolution.

There are many natural mechanisms that allow genes to cross between species but “horizontal gene transfer”, as it is called, occurs only infrequently on an evolutionary timescale. Bacteria exchange genes relatively simply, plants less so, and animals hardly at all. Horizontal gene transfer between species from different biological kingdoms also occurs naturally, but only rarely.

Geographical and ecological isolation of species plays an obvious role in limiting horizontal gene

transfer, but physical and biological barriers to gene transfer are even more important in preserving the integrity of species.

The main point of most genetic engineering is to circumvent natural barriers to horizontal gene transfer. Much genetic engineering consists of taking genetic information (DNA sequences) from one species and introducing it into the genome of a completely unrelated species.

Our 25 years of genetic engineering is practically infinitesimal in comparison with the billions of years of evolutionary history. However genetic engineering has outstripped all natural routes to become the most significant mechanism of horizontal gene transfer ever to occur.

The ultimate effects on the tree of life of releasing genetically engineered organisms into the wild cannot be assessed. There is no theory that gives a clear picture of the connection between genetic change and its overall evolutionary effects. Darwin's principle of natural selection allows interpretations to be made after the event, once the effect of a genetic change is evident, but it cannot be used to make the sort of predictions we need.

No adequate assessment of the overall effects of genetic engineering on the tree of life is currently possible. All the relevant arguments come down, in the end, to questions of value.

Examples

Genetic information has been artificially transferred between many species that have no natural hereditary relationship or realistic pathways for horizontal gene transfer:

a toad gene for the production of an antibiotic has been transferred to potatoes;
a fish gene for the production of an anti-freeze protein has been transferred to tomatoes and trees;
a gene for the production of a fluorescent protein has been transferred to many species, including rabbits;
a gene from soil bacteria for the production of a protein toxic to some insects has been transferred to crops (maize, potatoes).

Assessing the Effects - Ecological Networks

The task of assessing the environmental impact of a genetically engineered organism is to understand what effect, no matter how small, the genetic modification has had on every one of the characteristics relevant to the organism's interactions with members of other species (as well as the physical environment); and then to predict all of the resultant effects that may occur in the organism's ecological network.

With our current, very sketchy knowledge of how complex networks behave, it is impossible to carry out this task in a satisfactory way. We understand that networks are very robust against some types of perturbation and extremely sensitive to others, but we do not know how to predict the overall effect of imposing a particular change on a complex ecological system.

We can compare a genetically engineered organism with the range of variant individuals from the unaltered species. However the whole point of genetic engineering is to produce new organisms from outside of this range. Therefore, any assessment of a genetically engineered organism based on comparison with the wild-type is prone to error. There are many subtle mechanisms whereby novel characteristics may be created unexpectedly through the process of engineering.

Without knowledge of how important each detailed characteristic of an organism is and how it is influenced by all of the relevant genetic factors, assessing the effects of genetic engineering on an organism’s interaction with its ecological network remains a form of uncertain guesswork.

The task is even more difficult than we might think because natural selection operates over relatively short times within the populations of individuals occupying a space even as small as a single field. The individuals of any species show considerable variation, so traits of separate species become selected because they provide a mutual advantage for two or more species against environmental pressures. This phenomenon is generally more effective in an ecosystem with a greater diversity of species because of the greater scope for advantageous trait-matching.

At present, complicated effects like trait-matching are completely ignored by the various national and international regulatory authorities who consider proposals for the creation, cultivation or farming of genetically engineered organisms.

An applicant wanting to introduce a genetically engineered organism into the open environment usually attempts to satisfy authorities that there is no significant difference between the genetically engineered organism and the original “wild-type” organism, especially in terms of ecological interactions. This is true whether the application is for a "field trial" or all-out (commercial) release of the modified organism.

For their part, regulatory authorities ask about the direct effects, on other species, of any obviously changed characteristics of the genetically modified organism. Most often consideration is restricted to molecular biological arguments about the significance of new genes in the organism's chromosomes and altered protein in its cells.

Assessments of this sort ignore the network characteristics of ecological systems. The main factors influencing the ecological effects of genetic change are not taken into account, simply because not enough is known about them.

Example

A common soil bacterium was genetically engineered to make ethanol for industrial purposes. Soils containing the organism were found to kill wheat seedlings and certain fungi. Ecological networks could be severely disrupted by the introduction or escape of such organisms into the wild, depending on their ability to survive and multiply in different environments.

Assessing the Effects - Genetic Control Networks

Inserting a new gene into an organism's chromosomes can affect the organism's genetic regulatory network in a number of ways. However, such effects are not given much consideration in assessments of genetically engineered organisms. It is usually assumed that any problems of this sort have been overcome or eliminated during the “development” phase of the genetically engineered organism.

Scientists and authorities generally assume that any significant alteration in the genetic network of an engineered organism will have shown up as an easily observable change in some obvious characteristic of the organism. However, very important changes in the organism could remain hidden, perhaps until triggered by some environmental or physiological event. Such possibilities abound in biology because of the feature of degeneracy in genetic control networks.

The protein(s) produced by expression of newly inserted or modified genes can have undetected, unintended effects on the genetic regulatory network of a cell. One effect is the possible disruption of a gene (or genes) encoding a regulatory protein (or proteins). The path of development of the organism from a single cell to an adult may be affected.

If insertion of the new gene(s) occurs in the middle of the gene encoding a regulatory protein then that regulatory protein will not be produced, or a truncated (or elongated) version with different regulatory functions may be made. Other regulatory proteins may function to compensate for the change under most observed circumstances, but under other circumstances the change may prove to be fatal.

On the other hand, if insertion of the new genetic sequence takes place in a DNA region needed for the induction or repression of a regulatory protein, the protein may not be produced at all, or produced continually in an uncontrolled manner. Although not immediately evident, these effects may represent a heritable weakening of the genetically engineered organism relative to the natural "wild-type". As a result of normal reproduction, such genetic weakness can cross into offspring of other members of sexually-reproducing species, acting as a sort of newly-propagating genetic disease.

A protein produced as a result of genetic engineering may also have some new regulatory effect on the organism's genetic network. The most likely way that such an unintended effect could occur would be through the protein-protein interaction network; we say "most likely" because there is a greater chance of detecting a direct effect on the genetic regulatory network (such as specific binding of the protein to DNA or RNA regulatory sequences).

Examples

One of the main techniques used by plant genetic engineers is to insert DNA sequences that include a "promoter" of protein production taken from a virus. The most commonly used promoter in genetically engineered plants comes from the cauliflower mosaic virus (CaMV). The function of the viral promoter is to circumvent the normal control mechanisms of the organism's genetic control network so that the genes associated with it are expressed preferentially, leading to production of the desired foreign protein in the genetically engineered plant. By inserting the CaMV promoter element along with the other genes, engineers are able to create plants that are incapable of regulating production of the foreign protein(s) that give the plants new characteristics; they may be resistant to some proprietary herbicide, poisonous to selected insects or immunologically active when consumed by some animal.

Assessing the Effects - Protein Interaction Networks

It is to be expected that when a new protein is introduced into a cell it will have some direct physical effect on a number of other proteins. These new interactions may cause some change in the function and action of the other proteins. Such effects could be felt right across the protein interaction network, most often becoming less significant as the remoteness of the new protein from the new protein increases.

It is also possible that cells genetically engineered to produce a new protein will display completely new patterns of protein network interactions. This may not be evident until the cells find themselves in some unusual circumstances. They may then respond in a way very different from wild-type cells. Although the genetically engineered cells may appear to behave just like wild-type cells, this cannot be guaranteed under all circumstances.

The techniques currently available for inserting new DNA into the chromosomes of cells are unable to control the point of insertion in the organism's existing genome. In fact, it is customary to produce millions of cells with the new DNA inserted at essentially random positions. Screening is then conducted to find those cells which have survived the engineering process and also express the newly inserted gene. These survivors are then subjected to further screening to find those that seem to behave most like the wild-type, except for having the new, desired, engineered properties.

Regulatory authorities impose no requirement on genetic engineers to study, within their engineered cells, the effect of a new protein on the protein interaction network existing in the wild-type. The presentation of such information is not required, nor are such considerations judged to be important.

It is generally assumed that any harm to an organism as a result of inserting a new gene will be observed as a change in gross characteristics of the organism. Then, apart from the production of the new protein, the new genetically engineered and "wild-type" varieties of the organism are considered to be equivalent. Any unintended differences are treated as completely insignificant, especially differences that are undetected.

Normal logic runs like this: since the genetically engineered organism has survived and appears otherwise normal, any disruption in production of one or more of the organism's normal proteins caused by insertion of the new gene is of no consequence.

On the basis of this logic, regulatory authorities do not require it to be demonstrated that genetic engineering has not significantly altered patterns of cellular protein production and other normal functions of the "wild-type" organism. They ignore the possibility that in some untested environment disruption or change in the protein interaction pattern in cells may prove to be vitally significant in relation to the safety of the organism or its behaviour toward other organisms.

Example

There is a natural harmful process that propagates in a replicative fashion purely on the basis of protein-protein interactions – prion disease. When wrongly-folded "foreign" forms of the protein PrP get into mammalian brain cells they interact with "wild-type" PrP molecules produced by the cells and convert the normal PrP into the wrongly folded form, which is then infectious. In this manner, transmission of the wrongly folded form of PrP from organism to organism causes the diseases we know as spongiform encephalopathies - BSE in cattle and CJD in humans.

The possibility that a foreign protein introduced into the cells of an organism by using genetic engineering could cause a phenomenon similar to prion disease in genetically engineered animals is considered by regulatory authorities to be so improbable that the hazard can by ignored entirely.

In yeast and fungi, prions serve as protein-only heritable agents that can switch cells from one stable form to another. Genetic engineering has been used to create new prions in yeast and it has been proposed that prion tinkering is broadly applicable to the engineering of organisms.

Assessing the Effects - Cellular Metabolism

The aim of genetic engineering is often to create an organism whose cells contain a foreign enzyme that catalyses a reaction not occurring in the wild-type species that is found in nature. This amounts to adding a new metabolic pathway, corresponding to a new line or lines in the cell's chemical reaction network, and probably a new point (or more than one). In some cases the engineered cells contain a whole new set of enzymes corresponding to an entire new metabolic pathway of chemical transformations.

Adding new metabolic pathways has the inevitable effect of changing the flow of matter down existing pathways. The change can be quite significant, causing an imbalance in the metabolic flows inside the cells of genetically engineered organisms. This can cause the creation of new toxicities in organisms, or their derivatives, that are consumed as food.

The artificial transfer of genes between organisms that have no natural hereditary relationships is especially problematic. In such cases experience through breeding provides no information of the toxicities and other difficulties that may arise from the genetic cross.

A first assessment of cells genetically engineered to produce a new enzyme is made by considering what reactions the enzyme catalyses and what new substances may be produced. However, the operation and control of cells' chemical reaction networks is very complex. Changing the flow of matter and energy through one part of the network can affect some other part. The effects of this "remote action" may not show up as a change in any obvious property of the cells.

Genetic engineers are forced to use a trial and error approach when they try to assess the overall effect of what they do to cells' metabolic networks. Even rigorous testing in an very wide range of environments cannot be guaranteed to reveal all significant effects. Because of this, the satisfactory evaluation of the safety of genetically engineered organisms and their products as food, food supplements or medicines is virtually impossible.

Examples

A highly toxic component in preparations of L-tryptophan derived from genetically engineered bacteria caused about 40 prompt deaths and an epidemic of neurological disease affecting thousands of other individuals. The toxin is suspected of having been produced because the metabolism of the bacteria was forced down an unusual pathway (gross over-production of the sought-after L-tryptophan).