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Information
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underwriter

apropos

Genetic engineering

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Introduction

As early as 1865, during crossing experiments involving the pea plant, the Augustinian monk Gregor Mendel discovered that the plant's characteristics were determined by a number of mutually independent elements. Mendel used the results of these experiments as the basis for formulating his three fundamental laws of inheritance (Mendel's Laws). These are the origins of genetics. In 1944, the U.S. geneticist O.T. Avery was the first to recognise the role of DNA as the carrier of genetic information, thus founding molecular genetics. DNA stands for deoxyribonucleic acid. In 1953, J.D. Watson and F. Crick proposed their now famous model (based largely on X-ray crystallographic studies of DNA) which showed DNA to be composed of two spirally wound (helical) chains. Then, in 1970, scientists succeeded in isolating enzymes capable of cutting or cleaving DNA at specific sites. Two years later, DNA was recombined for the first time. It was thus now possible to manipulate the genetic systems of a variety of organisms.

The first production plant for genetically engineered human insulin was set up in the USA in 1982. The product was authorised as a drug by the US Food and Drug Administration. This was followed in 1985 by the development of "genetic fingerprinting", which opened up a whole new range of possibilities in the field of forensic medicine. The treatment of human beings with genetically modified cells was first authorised in the USA in 1989. In Europe, initial experiments in gene therapy took place in 1992.

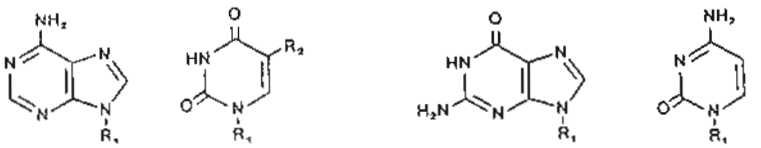
The rapid development of genetic engineering as a form of science called for the introduction of laws aimed at regulating its use. On 1 July 1990, West Germany introduced the Genetic Engineering Act (Gentechnikgesetz), subsequently amended in 1993.

Definition of terms
Genomes and DNA

The smallest element within most living creatures is the cell, the structure of which is fundamentally the same in all organisms. The cell's core, which performs a sort of central management function, contains DNA molecules in which information on the structure and functions of the cell is stored. These long, threadlike DNA molecules - known as chromosomes - contain the building plans for all the proteins of a cell and are, therefore, the carriers of genetic information. It is according to these 'blueprints' that the proteins, which themselves play many important roles, are produced. For instance, some proteins (called enzymes) act as catalysts to regulate the rate of specific biochemical reactions in cells, while others are responsible for transporting nutrients and waste material, and passing on information from the inside of the cell to its environment.

Sequential fragments of one of these DNA strands or chromosomes are known as genes. Each gene contains the blueprint for a certain protein. The cell is able to read this blueprint and thus produce the appropriate protein. A single DNA strand of a chromosome consists of thousands of genes. The chemical and physical (molecular) structure of DNA was first explained in 1953. It comprises two separate chains wound together spirally to form a double helix similar in appearance to a twisted ladder. The sides of the ladder are made up of deoxyribose molecules chained together by phosphate bonds, while the rungs consist of so-called paired bases held together by nitrogenous linkages.
Four different base pairs (= nucleotides) can occur:

- Adenine-Thymine A-T
- Thymine-Adenine T-A
- Guanine-Cytosine G-C
- Cytosine-Guanine C-G



Adenine Thymine Guanine Cytosine

Three such nucleotides are required to form an information unit (= codon) for any one of the 20 different amino acids naturally occurring in proteins. For example, if a certain protein consists of 100 amino acids, the coding part of the corresponding DNA fragment will need to be at least 300 nucleotides long in order for the cell to produce this protein. The way in which the codons are assigned to specific amino acids is known as the 'genetic code' and is valid for all life forms. The number of chromosomes and, thus, the sum of all genes together is known as the genome and varies from species to species. In higher life forms, genetic information is spread across several chromosomes. Human beings have 22 pairs of chromosomes (autosomes) together with the two pairs of sex chromosomes (XX or XY) comprising around 3×10^9 base pairs. If one were to transcript the human genetic code using the letters A, T, C and G and writing 3,000 letters on each page, one would end up with 1,000 books each with 1,000 pages. Compared with this, the genome of a virus with just 3,000 letters (one page) is relatively simple. The information for the genetic code of humans in the form of DNA strands weighs around 3 billionths of a gram and is contained once in every cell. For this reason, only minute quantities of cell material are required for analytical purposes.

To date, around 10 % of the human genome has been decoded, though scientists have a good idea of a further 50 %. It is estimated that the entire human genetic code will have been decoded by the year 2010.

Mutation

Mutation refers to the alteration of the genetic material of a cell. This change can be transmitted to the cell's offspring. We distinguish between

- Genome mutations
- Chromosome mutations, and
- Point mutations

Genome mutations include changes in the number of chromosomes present in a cell. An example of a genome mutation is trisomy 21 in humans, where chromosome 21 occurs three times. This anomaly is the cause of the serious human genetic disorder Down Syndrome.

Chromosome mutations occur when parts of a chromosome are lost, duplicated, reversed, or translocated to other chromosomes. Most cases of chronic leukaemia are the result of a chromosome mutation.

Point mutations affect a specific base pair or a few neighbouring base pairs of a gene. Mutations occur naturally in all life forms and are the result of accidents in the replication of the DNA. They are the natural basis for the emergence and evolution of species. In the human genome, for instance, it has been estimated that every millionth nucleotide is modified through mutation during DNA replication. This is the reason why e.g. even identical twins do not have exactly the same DNA. The natural rate of mutation can increase dramatically as a result of environmental agents such as radiation and toxic chemicals.

Clones, cloning

Cloning refers to the process whereby genetically identical organisms, cells or nucleic-acid molecules are derived from a single precursor. Clones occur naturally through asexual reproduction, e.g. when a plant divides its cells to produce shoots.

The term 'cloning' is open to different interpretation. In conventional genetics, it simply means producing clones. In molecular genetics, the sense has been broadened to include the recombination and multiplication of DNA fragments 'in vitro', i.e. outside the organism in a test tube or Petri dish.

Methods
Cloning and recombining DNA

In order to clone DNA fragments, the DNA that is packaged tightly in the core of the cell first has to be released from this environment and then separated from any interfering cellular components such as lipids and proteins. What is known as a restriction enzyme is then used to cleave the DNA at certain points, splicing it into different-sized fragments. With the help of a different enzyme called a DNA ligase, the fragments can then be recombined with another DNA (plasmid) cleaved using the same restriction enzymes. In this way, it is possible to relocate genes precisely and selectively.

DNA sequencing

A prerequisite for selective genetic engineering is precise knowledge of the relevant DNA sequences. To obtain such information, pieces of DNA are spliced to form fragments of different lengths. The fragments are then arranged in order of size by a process known as gel electrophoresis, thus enabling the nucleotide sequence to be determined. Nowadays this procedure is automated and the results can be analysed by computer.

Fields of application
Diagnoses at DNA level

The ability to diagnose DNA has now made it possible to detect the presence of disease-causing agents directly. The direct method reduces the time needed for diagnosis from the several days required for the old method via the formation of antibodies to just a few hours. The new method is particularly useful for diseases like HIV, hepatitis B, tuberculosis, and pneumonia, which were previously difficult to diagnose using the antibody procedure.

Genetic diagnostics is also used in forensic medicine and environmental analysis. It has also opened the door to new possibilities for detecting hereditary diseases or illnesses that are the result of a genetic disorder. Several hundred inborn diseases, including sickle-cell anaemia (chromosome 11), Lesch-Nyhan syndrome (purine metabolism, X chromosome), haemophilia A (X chromosome) and Alzheimer's disease (chromosomes 21, 14 and others), can now be diagnosed in this way. To some extent, the new test methods can even help forecast a patient's future health, thus opening the door to a highly individual form of risk assessment.

Production of drugs

The first genetically manufactured drug was human insulin. The previous practice of extracting the insulin needed to treat diabetes from cows or pigs had two problems: first, there was always a danger that the patient would begin to produce antibodies against the animal product. Second, the substance was in short supply, for the amount of insulin that could be extracted from a single pig amounted to just a day's supply for the average diabetic. By means of genetic engineering, the human insulin gene was inserted into bacteria capable of producing large amounts of ultrapure human insulin. Numerous genetically engineered drugs are now available on the market, in particular for use in vaccinations. They can be manufactured more cheaply and to a higher level of purity than using the former methods.

There are currently around 20 genetically engineered drugs on the market in Germany. An additional 150 products are undergoing clinical tests and a far greater number are in the development phase.

Somatic cell genetics

Somatic cell genetics is a new approach to treating hereditary disease, whereby the disorder is healed by repairing the underlying genetic defect. This form of genetic engineering involves modifying somatic cells by removing and cultivating them. The defect is ultimately repaired via a process of cloning and recombination. The cells containing the intact gene are then implanted into the patient. Procedures such as these are still in the basic research stage and are unlikely to become common practice for at least another ten years or so.

Production of transgenic plants and animals

Agricultural products, and animals and plants represent a broad field of application for genetic engineering. Objectives include enhancing a product's characteristics, accelerating breeding/cross-breeding projects, and using animals to manufacture pharmaceutical substances (known as pharming).

This particular topic is dealt with further in the following apropos brochure on "Genetic engineering in the food sector".

Acceptance

The degree to which genetic engineering is accepted by the public depends largely on its ultimate use. Where genetic engineering is used for medical (vaccinations, drugs) or environmental (microorganisms breaking down harmful agents) purposes, the response is positive. However, the genetic modification of plants and foodstuffs has met with a poor response, even slight rejection in some cases. The use of this form of science in connection with animals is rejected per se. Furthermore, acceptance in Europe varies from country to country: while acceptance in Spain, Portugal, Italy, Ireland and Greece tends to be above average, Great Britain, Belgium and France represent the European mean. A sceptical attitude towards genetic engineering is prevalent in Luxembourg, the Netherlands, Denmark, Norway, Austria and Germany. Only Germany and Norway adopt a negative stance overall, i.e. they generally dismiss the idea of genetic engineering.

Opportunities and risks

The greatest opportunities offered by genetic engineering are in the field of medicine. The ability to perform diagnoses at DNA level now means that diseases caused by genetic defects can be detected at an early stage, while gene therapy makes it possible to treat them. Genetically manufactured drugs or vaccines are not only purer, but are cheaper and simpler to produce in large quantities. In the food sector, the use of genetic engineering enables quality and yields to be improved in a way that is friendly to the environment (see the following apropos brochure on "Genetic engineering in the food sector").

Compared with conventional methods, genetic engineering poses relatively little risk in terms of the specific product or field of application, as the precision techniques employed reduce the likelihood of unintentional side effects or unexpected concomitant phenomena.

It is primarily in the development stage where genetic engineering poses a risk. The WHO distinguishes four risk categories for genetic engineering projects, the hazard being greatest when the subject of the research falls under the highest of the four categories (which includes e.g. the smallpox virus). A safety programme is required for work involving genetically modified organisms in this category.

The negative attitude towards genetic engineering on the part of the general public is founded on a fear of its being misused. It is here that legislators are called upon to introduce appropriate laws (e.g. the Genetic Engineering Act in Germany) aimed at making this sphere of activity safe and secure.

Tips for the underwriter

The risks involved in genetic engineering stem mainly from the respective field of application and the product manufactured, rather than from the technique per se.

It is, primarily, liability insurers who may be confronted by the risks of genetic engineering:

- Commercial TPL insurance/Environmental impairment liability insurance

The main hazard in this context is the risk posed by genetic engineering to human health and the environment. The potential scale of the loss would depend largely on the WHO risk category in question and on the state of the art. Loss scenarios might include the spread of disease or epidemics following the failure of safety systems in a genetics laboratory or production plant.

- Product liability

The risk here is from harmful properties of a product that were not recognised prior to its release, or from the effects of unexpected or unforeseeable changes to a product. That said, the loss potential is likely to be slight compared with conventional techniques. In the pharmaceuticals industry, this applies especially to the risk of side effects coming to light later on. For example, a coagulant manufactured from human serum was responsible for infecting 1,000 haemophiliacs with the Aids virus. The risk of this occurring would have been zero had the product in question been genetically engineered.

Property and Life/Health insurers too should take the genetic engineering factor into account when assessing a risk:

- Property insurance/Business interruption insurance

Failure of sophisticated plant and equipment can lead to a considerable loss of earnings. In addition, official directives might well hinder the reconstruction of plant or delay the resumption of production. Sabotage of production facilities or destruction of crops by opponents of genetic engineering is also a possibility.

- Life/Health insurance

Genetic engineering techniques may well reduce treatment costs in the medium to long term, supporting as they do a more precise and selective approach to healing.

The use of genome analyses in connection with applications for life insurance is problematical on ethical grounds. However, were such a practice admissible, it would make medical underwriting easier.

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