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Gene Therapy

Definition:

"At the most basic level, gene therapy can be defined or described as the intracellular delivery of genetic material to generate a therapeutic effect by correcting an existing abnormality or providing cells with a new function."

OR

"Gene therapy is the insertion of genes into an individual's cells and tissues to treat a disease and hereditary diseases in which a defective mutant allele is replaced with a functional one."

OR

"Gene therapy involved transferring genes into cells for therapeutic purposes."

OR

Gene therapy is an experimental treatment that involves introducing genetic materials (DNA or RNA) into a person's cells to fight disease."

Purpose of gene therapy:

The purpose of gene therapy is to correct the nonfunctioning of malfunctioning of a single gene or multiple genes in either a monogenic disease or a polygenic (multi-factorial) disorder on permanent basis.

History:

There are currently thought to be about 5'000 different genetic disorders that affect humans. To date, the mutations responsible for about 400 of these have been identified. For the rest, the search continues.

This usually entails transfer of chosen cDNA (or genomic DNA), under the control of an appropriate promoter, into host cells. Once inside the cell, the host's transcriptional and transcriptional apparatus effects production of the desired protein.

The first clinical trial of gene therapy was approved in 1989; it involved the transfer of human cDNA encoding adenosine deaminase to a patient with severe combined immune deficiency (SCID).

Although the technology is still in its infancy, it has been used with some success. Antisense therapy is not strictly a form of gene therapy, but is a genetically-mediated therapy and is often considered together with other methods.

Goals of gene therapy:

The ultimate goal of gene therapy is the amelioration of disease upon a single administration of an appropriate therapeutic gene. The genetic materials considered for use are intended to replace a defective or missing gene, augment the functions of the gene present and instill a specified sensitivity to a normally inert prodrug or to interfere with the life cycle of infectious disease.

The fully functional and expressible gene is introduced into a target cell, resulting permanent correction of a specific genetic disease when the target is a tissue or organ within an organism.

Most suitable target organ or tissue for gene therapy:

Liver is an organ, which contains a large number of potential cells to be more suitable tissue for gene therapy.

Strategy for identifying disease genes:

The strategy for identifying disease genes depends on available resources and on how much is known about the biochemistry and physiology of the disease process. These strategies aim initially to identify a number of candidate genes, based either on their chromosomal location or their functional relevance to disease phenotype.

Once candidate disease genes have been identified they have to be tested individually to determine the likelihood that they are associated with the disease. Identifying mutations in multiple affected individuals strongly suggests that the correct gene has been identified but formal proof requires additional evidence. This could involve demonstrating the restoration of the normal phenotype in vitro or the production of a mouse model of disease. The field of DNA-based diagnosis of genetic disease has progressed very rapidly over the last few years.

How much information the DNA tests can give depends on the state of knowledge about the gene(s) involved.

Direct testing involves the DNA from an individual to see whether or not it carries a known mutation associated with the the suspected disease. This is almost always done using PCR because it is quick and requires only a small sample.

Indirect testing (gene tracking) uses closely linked molecular markers in family studies to discover whether or not an individual inherited the disease-carrying chromosome from a parent.

DNA-based diagnosis has many advantages:

It can be used to identify individuals with progressive genetic disorders before the onset of symptoms, even before birth.

This is of particular importance if treatment is available that can minimize symptoms.

It is also possible to identify symptomless carriers of potentially harmful recessive disorders.

Types of gene therapy:

1. Somatic gene therapy
2. Germ line gene therapy

1.Somatic gene therapy

Human somatic cell gene therapy is a form of medical treatment that is being developed as a genetic approach to disease management. It is to correct the nonfunctioning or malfunctioning of a single gene is either a monogenic disease or a multi-factorial disorder and therapy that will affect the patient only.

(This means that there is no interference with or crossover into germ line). Also consider enhancement that will affect the patient only.

Advantages:

- Insertion of genes into diploid cells of an individual (use of only body cells so that the individual's disorder is corrected.
- Effects of gene therapy are not passed to progeny.
- Currently, this (somatic gene therapy) is allowed.

Disadantages and Limitations:

- Polygenic and multifactorial diseases are not good candidate.

- Sometimes the single time treatment is not sufficient.

Strategies/ Techniques or Methods:

Three basic gene therapy strategies/ techniques or methods have been investigated:

1. **In-vivo gene therapy:**

In vivo gene therapy vectors often viruses or liposomes (fatty particles) are used to deliver the desired gene to cells in the patient's body. This form of gene therapy is called in vivo, because the gene is transferred to body cells systemically (IV).
In vivo gene therapy is done by targeting the gene delivery system to the desired cell type in the patient using either physical means such as tissue injection (brain tumor) or biolistics (dermal DNA vaccination), or potentially in the future, using systemic infusion of cell specific receptor-mediated DNA carriers (reconstructed liposomes or viruses).

Advantage:

- It is potentially the most useful as it can be administered like conventional parenteral medication.

Disadvantage:

- Administration of material systemically is probably the lease advanced strategy at present (The main reason for this, is the insufficient targeting of the vectors to the correct tissue sites).
- It does not achieve the required therapeutic effects (The liver also rapidly clears adenoviral vectors together with lipid/DNA complexes after administration).
- All of the viral vectors used todate stimulate strong immune responses upon repeated doses.
- Current retroviral vectors activate complement resulting in their neutralization.

2. **Ex-vivo gene therapy:**

In this technique genetic material is delivered after explantation, cultivation and manipulation in vitro, followed by subsequent re-implantation. Cells from the patient's blood or bone marrow are removed and grown in the laboratory. The cells are exposed to the vector (virus) that is carrying the desired gene. The virus enters the cells and inserts the desired gene into the cell's DNA. The cells are cultured to multiply to a sufficient number and they are then returned to the patient by infusion or transplantation. This type of gene therapy is called ex-vivo because the cells are grown outside the body. The gene is transferred into the patient's body.
If the patient's own cells (autologous cells) are used, rejection does not occur.
The biggest technical hurdle for ex-vivo gene therapy is the transplantation of transfected cells.
For Example: Non-viral approach called transkaryotic therapy. An individual's cells are obtained through a skin biopsy, and the gene of interest is inserted into them. Transformed cells are cultured in vitro to increase the number of cells expressing the desired protein and are then injected under the person's skin, where the therapeutic protein is synthesized. The protein is circulated throughout the body.

Two types of ex-vivo gene therapies under development are those directed at fibroblasts and hematopoietic stem cells.

Advantage:

- Vectors are only introduced to the target cells not into the body or ciculatory system (as in case of In vivo gene therapy).
- Individual's immune system is not in direct contact with the vectors.

Disdvantage:

- It is time consuming.
- At present and very expensive method of treatment.

3. In situ delivery:

In this method, the material is directly administered to the desired tissue is currently major area of clinical interest, as many of the current delivery systems lack effective targeting. One disease that has shown some success with this strategy has been cystic fibrosis (CF), which shows 20-30% correction. This form of delivery also used in the treatment of cancer. A study in rodent model used direct administration of a retroviral vector expression the suicide gene herpes simplex virus thymidine kinase (HSVTK) directly into small intra-cereberalgliomas. Upon treatment with the prodrugganciclover, 75% of the tumor showed regression. However, low efficiency of transduction is a continuing problem. This is a particular important consideration in cancer therapy, as a single malignant cell remaining would re-establish tumor.

2.Germ line gene therapy:

In this type of gene therapy the human eggs or sperms are genetically altered, the reproductive cells that pass gene onto future generation. Because reproductive cells are also called germ cells, this type of gene therapy is referred to as germ-line gene therapy. Although both germ line gene therapy and genetic enhancement have the potential to produce benefits, possible problems with these procedures worry many scientists. Germ line gene therapy would forever change the genetic makeup of an individual's descendants. Thus, the human gene pool would be permanently affected. In many countries, human germ line gene therapy is considered unethical or even illegal.

It is currently considered to be ethically unacceptable, even though it has the potential to erdicate many hereditary disorders.

The technology is relatively simple and requires no targeting as genetic abnormalities can be corrected by direct manipulation.

It is sophisticated technique being developed in the field of transgenic animals

Vectors used in gene therapy:

- Viral vectors
- Non viral vectors

Viral Vectors:

Viral vectors are the tool commonly used by the molecular biologist to deliver genetic material into cells. This process can be performed inside a living organism (in vivo) or in cell culture (in vitro). Viruses have evolved specialized molecular mechanisms to efficiently transport their genome inside the cells they infect. Delivery of genes by a virus is termed transduction and the

infected cells are described as transduced. Molecular biologist first harnessed this machinery in the 1970s. Paul Berg used a modified SV 40 Virus containing DNA from the bacteriophage lambda to infect monkey kidney cells maintained in culture.

Key properties of viral vector:

Viral vectors are tailored to their specific applications but generally share a few key properties.

Safety:

Although viral vectors are occasionally created from pathogenic viruses, they are modified in such a way as to minimize the risk of handling them. This usually involves deletion of a part of viral genome critical for viral replication. Such a virus can efficiently infect cells but, once the infection has taken place, requires a helper virus to provide the missing protein for production of new virions.

Low toxicity:

The viral vector should have minimal effect on the physiology of the cell it infects.

Stability:

Some viruses are genetically unstable and can rapidly rearrange their genomes. This is detrimental to the predictability and reproducibility of the work conducting using a viral vector & is avoided in their design.

Cell type specificity:

Most viral vectors are engineered to infect a wide range of cell types as possible. However, sometimes the opposite is preferred. The viral receptor can be modified to target the virus to a specific kind of cell.

Examples of viral vectors are:

Retrovirus
Adenovirus
Adeno-associated virus(AAV)
Vaccinia virus
Sendai virus
Polio virus **(Detail is at the end of this chapter)**

Non-viral vectors:

Non-viral vectors principally comprise cationic liposomes which can effectively cationic lipid bi-layers capable of enveloping (anionic) plasmid DNA. These polycationic liposomes with negatively charged nucleic acids form a naometric complex. Liposomes can incorporate into cell membranes liberating their DNA contents into the cytoplasm.

Advantages:

- Liposomes have found favor in many quarters because
- They are relatively easy to produce and administer.
- They do not carry the theoretical risk of oncogenesis or superinfection that may accompany the use of some viruses.
- Biologically inert, and thus amenable to repeated administration without inducing inflammatory or immune responses, although this position has been challenged recently.

A major limitation of liposome vector:

Vast majority of nucleic acid carried into cells is directed into, and degraded by, endosomes before reaching the nucleus.

Limitations:

Nucleic acid enters the cell and is destroyed by the endosomes before reaching the nucleus. The all proportion of the DNA reaching the nucleus is usually only transiently and weakly expressed.

In the context of the lungs, affective disposal of the liposomes throughout the bronchial tree is difficult practically.

In contrast, viral vector make use of the sophisticated machinery employed by viruses specifically to deliver DNA to the host nuclei.

	Retrovirus	Adenovirus	AAV	Naked DNA	Liposome mediated
Genome transfer	RNA	DNA	DNA	DNA	DNA or RNA
Virus titers	10^6-10^9/ml	10^{11}-10^{12}/ml	10^{10}/ml	n.a.	n.a.
purification	Difficult	Yes	Yes	Yes	Yes
Max.size recombinant gene	8 kb	7.5 kb	5 kb	At least 50 kb	At least 50 kb
In vivo use	No	Yes	Yes	Yes	Yes
Integration	Yes	No	Yes	Low	Low
Efficiency	High	Very high	Moderate	Moderate	Low
Safety issue	Insertional Mutagenesis	Immune Reactions	No Known	No Known	No known
Non-divided cells	No	Yes	Yes	Probably	Probably
Limitation	Cell division needed	Transient correction	Production is difficult	Efficiency is low	Efficiency is low

Viral systems:

Many viral vector systems now exist for use in gene delivery studies. The most widely studied include retrovirus, adenovirus (type 2 and 5, adeno-associated virus and herpesvirus. Common to all viral vectors is the fact that their genomes have been modified, deleting areas which render them replication incompetent. This has the effect of limiting the virus particle to only a single infectious cycle, so improving the safety of their use.

1- Retroviral vectors:

Retroviruses have been extensively used for gene therapy. With a few relatively nonpathogenic. Retroviral vectors have the ability of infecting a wide variety of cell types and have the potential

of integration into host genomes. Murine leukemia virus (MuLV) has been the most widely used, with several systems developed for generation of infectious replication incompetent particles. In essence, all of the viral genes have been removed, creating approximately 8kb of space for transgene incorporation. Integration of the genetic material can only be accomplished in dividing cells using MuLV vectors. However, newer vector systems incorporating HIV sequences are being developed with the ability to integrate into nondividing cells. Human spumaviruses are also being examined as potential gene delivery vehicles. These are nonpathogenic human retro-viruses that have the ability to integrate into quiescent cells.

The problem with current retroviral systems include inability to produce high titers; immunogenic problems and complement inactivation in the case of MuLV. In the latter, systems are being developed to overcome this hurdle. Active research is presently being performed to address the issues that hamper retroviral vector production and use. Retroviruses are the most widely used delivery vehicle in clinical trials to date accounting for approximately 40% of studies.

2- Adenoviral vectors:

The most common DNA virus systems used for gene therapy applications are adenovirus (type 2 and 5). The serotypes used have not been implicated in serious illness. As an added safety measure several essential genes have been deleted so that viral replication can only occur under controlled conditions. Adenovirus-delivered genes are episomally maintained and lost due to genetic instability. Hence repeated doses are necessary to maintain expression of the transgene. Most adenoviral vector systems have a transgene capacity of approximately 7kb. However, more recently systems have been developed in which essentially all of the viral genome has been deleted resulting in sufficient space for 35kb of transgene sequence – the so called 'gutless' or 'pseudo' adenoviruses.

The advantage of the adenoviral system is the ability to produce high numbers of purified particles, their ability to infect a wide range of tissues and, more importantly, their tropism for the lung. This has made them particularly attractive to CF gene therapists. However, the particles are highly immunogenic which limits the number of repeated applications. Cancer gene therapists have used this to their advantage, where enhanced cell death due to immune recognition is desirable.

3- Adeno-associated viral vectors:

Another DNA virus-based vector system utilizes adeno-associated virus (AAV). AAV has no known pathogenic effects and its genome preferentially integrate at a specific site on chromosome 19 with no noticeable effects. The AAV vectors have been shown to be weak immunogens upon delivery to some tissues. Unfortunately recombinant AAV vectors have a much reduced propensity for site-directed integration and studies are underway to boost their desired function. The major drawbacks of these vector systems include the complicated process of vector production (most systems necessitates the use of adenovirus to supply helper functions) and the limited transgene capacity of the particles ($\leq$4.8kb). Whereas little can be

done to extend the packaging constraint of the particles, research is ongoing to modify and improve recombinant virus production.

4- Herpes simplex viral vectors:

One of the most recent viruses to emerge as a candidate for vector generation is herpes simplex virus (HSV). HSV based systems include the development of so called disabled Infectious single copy (DISC) virus which compromises a glycoprotein H defective mutant HSV genome. When propagated in complementing cells viral particles are generated which can infect subsequent cells, replicate their own genomes but will not produce further infectious particles. Another intriguing system involves the packaging of a minimal HSV amplicon devoid of almost all HSV sequences that would have the potential to package in excess of 150kb of transgene sequences.

Major hurdles still exist to the widespread use of viral vectors and research is underway to address these. Some of the more important drawbacks are immunogenicity of the particles, packaging constraints, long term maintenance of the genetic material and, in the case of retroviruses, random integration. Another major obstacle is the specific targeting of the genetic material to the correct cells. Two avenues of research are now being extensively pursued namely transduction targeting, which concentrates upon manipulation of the viral vector to obtain delivery to specific cells, and transcriptional targeting in which the transgene expression is controlled by tissue specific transcriptional elements.

In the following chapters, the problems regarding the use of these vectors and current thoughts for their modification will be discussed.

Non-viral systems:

An alternative to the viral strategies has been the application of chemically synthesized vehicles such as liposomes or the use of naked plasmid DNA. This has been of particular interest in the emerging field of DNA vaccination technology.

1- Lipid-mediated delivery:

Over the past decade, extensive research has led to the development of chemically based delivery systems. For several reasons, cationic lipids are the preferred choice, not least due to their highly efficient nature at affording gene transfer but also the case with which the DNA/lipid complex is formed.

Cationic liposomes usually comprise a formulation of positively charged lipid and a co-lipid required for the stabilization of the liposome complex. A widely used formulation is N-[1-(2, 3-dioleyloyx) propyl]-N-N-N-trimethyl ammonia chloride (DOTMA) and dioleoyl phosphatidylethanolamine (DOPE). Interaction between negatively charged DNA and positively charged lipid results in the spontaneous formation of complexes. There are now many preparations, with different formulations affording a variety of properties, which are capable of delivering genetic material to cells. However, once again, problem exists regarding their use.

Most notably, gene transfer in vivo occurs at low efficiency, although some success has been achieved in delivering material to lung and liver.

2- Naked DNA:

Investigations have revealed that naked plasmid DNA can enter cells and express their genetic material, although the efficiency of uptake is poor. Plasmids ranging in size between 2 and 19kb have been successfully delivered but the mechanism by which this occurs is undetermined. Tissues exhibiting transgene expression following plasmid DNA injection include skin, thymus, cardiac muscles, and especially striated (skeletal) muscle. Long term expression has been observed in murine striated muscle following injection, for more than 19 months. Effectiveness of gene transfer into muscle by intra-muscular DNA injection is affected by variety of factors. Single injection yields transgene expression in less than 1% of the total myofibers of the muscle. However, this can be improved by multiple injections. Similarly, pre-treatment of the muscle with sucrose or by degenerating the muscle prior to plasmid injection improves the overall uptake and expression of the transgene. Age and species of the test subject can also influence the efficiency of uptake. Primate muscle has a lower efficiency of DNA uptake compared to murine muscle, and young mice demonstrate improved gene transfer efficiencies. This could be due in part to variations in the muscle composition. Striated muscle is currently under investigation for use as a platform for expression of secreted therapeutic polypeptides (e.g. in hyperlipidemia) following DNA injection.

The greatest advantage of intra-muscular DNA injection is its relative simplicity. However, lack of integration into the host genome, limited tissue types to which DNA can be delivered and a low efficiency of uptake of the genes following injection are just some of the disadvantages.

An alternative to injection of naked DNA is the use of biolistic or 'gene gun' methods of administration, a modification of a technique originally developed for gene transfer to plant cells. Gold or tungsten particles (1-3μm diameter) are coated with plasmid DNA and accelerate to high speeds by a variety of means including electronic and helium pressure discharge, enabling the coated particles to penetrate the target tissues. The technique has been used for genetic transfer to a variety of cell types, including muscle, liver and epidermis. Some in vivo investigations have been performed targeting surgically exposed tissue. The drawbacks of the technique include transient gene expression and cellular damage.

3- VP22

As mentioned earlier, the herpes simplex virus (HSV-I) tegument protein VP22 has the exciting property of spreading from the cytoplasm of the cell in which it is expressed to the nuclei of the surrounding cells. The mechanism by which this function occurs is currently unknown. However, this propensity remains when fusion molecules are generated between VP22 and a cargo partner, including reporter genes such as aequoria Victoria green fluorescent protein and genes currently under examination as therapeutic agents such as p53. As such it heralds the prospect of improving the numbers of cells receiving therapeutic molecules, even under condition whereby the transfer of genetic material is quite inefficient.

Despite of difficulties with the current delivery systems many diseases have reached the stage of clinical trial using these vehicles. It will be interesting to see how these fare in a clinical setting. This will give us an insight into the factors that need to be addressed to improve these vectors

Applications of the gene therapy:

Gene therapy is very useful advanced technique and is used for many purposes. It is not only used for the treatment purpose but also for the prevention and diagnosis of different life threatening disease. Different trials are done which shows that it will be the most beneficial technique for near future to cure many diseases accurately and permanently.

1. **For monogenic diseases:**

It is being used for many monogenic diseases (the diseases which are caused due to the mutation or defect of single gene)

Examples:

Adenosine deaminase deficiency
Cystic fibrosis
Familial kidney disease
Polycystic kidney disease
Hungtington's chorea
Hemophilia
Phenyketonuria

2. **For many polygenic/multigenic or multi-factorial diseases:**

(The diseases which are caused due to the mutation or defect of more than one gene)

Examples are:

Cancers (lung cancer, breast cancer, colorectal cancer, malignant lymphoma, myeloma, leukemias and ovarian cancer)
Diabetes mellitus
Atherosclerosis vascular disease

3. **For the treatment of mitochondrial disorders:**

These diseases, affecting many organ systems, are caused by mutations in mitochondrial DNA.

For the treatment of Chromosome disorders:

Sometimes complete chromosomes or large regions of a chromosome are missing, duplicated, or modified in some way. Example include Down Syndrome

4. **For different infectious diseases caused by bacteria or viruses:**

Examples are:

pneumonia
Tuberculosis
Herpes complex
Kaposi's sarcoma
AIDS

5. **To cure inherited diseases**

To cure immune disorders

6. **For prevention purpose**

DNA vaccines are made against various infectious diseases

7. **For diagnostic purposes:**

It is also used to identify disease at embryonic stages and also to know the progress of the disease. It is helpful tool to identify the disease condition at early stages.

8. **Other applications:**

It has potential to enhance human capabilities for examples improving memory and intelligence by genetic intervention.

Table shows the disease, target cells and transfected genes of different diseases.

Disease	Target cells	Transfected genes
Hemophilia A and B	Liver, muscles, bone marrow cells, fibroblast	Factor VIII and IX
Familial hypercholesterolaemia	Liver	Low density lipoprotein receptor
Severe combined immune-deficiency	Bone marrow cells and T cells	Adenosine deaminase (ADA)
Hemoglobinopathics	Red blood precursor cells	a-globin, b-globin
Cystic fibrosis	Lung airway cells	Cystic fibrosis gene (CFTR)
Gaucher's	Bone marrow cells, macrophages	Glucocerebrosidase
Cancer	Tumor cells	Rb, intrleukins, growth inhibitory genes, apoptosis genes.

For further knowledge (especially for viva voce)

Altered genes:

Each of us carries about half a dozen defective genes. We remain blissfully unaware of this fact unless we are one of our close relatives are amongst the many millions who suffer from a genetic disease. About 1 in 10 people has or will develop at some later stage an inherited genetic disorder and approximately 2800 specific conditions are known to be caused by defects (mutations in just one of the patient genes). Some single gene diseases are quite common-cystic fibrosis is found in 1 of every 2500.

Genes are located on chromosomes inside cells and are made of deoxyribonucleic acid (DNA), which is a type of biological molecule. Humans have between 30,000 and 40,000 genes. Genes carry the instructions that allow the cells to produce specific proteins. Such as enzyme single gene control the single factor.

To make a protein, a cell must copy the information stored in genes into another type of biological molecule called ribonucleic acid (RNA). The cells protein synthesizing machinery than decodes the information in the RNA to manufacture specific proteins. Only certain genes in a cell are active at any given moment. As cells mature many gens become permanently inactive. The pattern of inactive genes in a cell and the resulting protein composition determines what kind of cell it is and what it can and cannot do. Flaws in genes can result in disease.

Q. What risks are associated with current gene therapy?

Viruses can usually infect more than one type of cell. Thus when viral vectors are used to carry genes into the body, they might infect healthy cell as well as cancer cell. Another danger is that the new gene might be inserted in the wrong location in the DNA, possibly causing harmful mutation to the DNA or even cancer. In addition when viruses or liposome are used to deliver DNA to cells inside patient's body; there is a slight chance that this DNA could unintentially be introduced in to patients' reproductive cells. If this happens, it could produce changes that may be passed on if patients have children after treatment.

Q. What major problems must scientist overcome before gene therapy becomes a common technique for treating disease?

Scientist needs to identify more efficient ways to deliver genes to body. To treat cancer and other diseases effectively with gene therapy, researches must develop vectors that can be injected into the patient and specifically focus on the target cells located throughout the body. More work is also needed to ensure that the vectors will be successfully inserting the desired gene into each of these target cells. Researcher's also need to be able to deliver gene consistently to a precise location in the patient's DNA and ensure that transplanted genes are precisely controlled by the body's normal physiological signals. Although scientists are working hard on these problems, it is impossible to predict when they have effective solutions.

The first disease have approved for treatment with gene therapy was adenosine deaminase (ADA) deficiency.

What is this disease and why was it selected?

ADA deficiency is rare genetic disease. The normal ADA gene produces an enzyme called adenosine deaminase, which is essential to the body's immune system. Patients with ADA deficiency do not have normal ADA genes and do not produce functional ADA enzyme. ADA-deficient children are born with severe immune deficiency and are prone to repeated serious infections, which may be life threatening. Although ADA babies born in the western world and in total, diseased that can be traced on a single gene defects account for about 5% of all admissions to children's hospitals.

Disease of genetic origin:

Most of us do not suffer any harmful effects from our defective genes because we carry two copies of nearly all genes, one derived from our mother and the other from the father. Male have X and one Y chromosome the former from the mother and later from the father. The only exception to this rule is the genes found on the male sex chromosome. In the majority of cases, one normal gene is sufficient to avoid all the symptoms of disease. If the potentially harmful gene is recessive, than its normal counterpart will carry out the entire task assigned to both. Only if we inherit from our parent's two copies of recessive genes will develop a disease. On the other hand, if the gene is dominant, it can alone produce the disease, even if its counter-part is normal/clearly only the children of the parent with the disease can be affected. Huntington's chorea, a severe disease of nervous system, which becomes apparent only in adult hood, is an example of dominant genetic disease.

Finally there are the X chromosome linked genetic diseases. As males have only one copy of the genes from these chromosomes, there are no other available to fulfill the defective genes function. Examples of such diseases are Duchene muscular dystrophy and, perhaps most well known of all, hemophilia. Queen Victoria was a carrier of the defective gene responsible for

hemophilia, and through him it was transmitted to the royal families of Russia, Spain, and Russia. Minor cuts and bruises, which could do little harm to most people, can prove fatal to hemophilia's, who lack the protein (factor VIII and IX) involved in clotting of blood was contaminated with the AIDS virus, and has resulted in tragic consequence for many should be possible in near future to distinguish between defective gene and their normal counterparts, an important development. The human genome programmed in U.S will provide about $200 million each year to scientist to multidisciplinary research centers who are attempting to determine the makeup of all human genes. Together with similar programs in Europe, it is hoped that in 15 years time we shall be able to identify and treat all disease to which humans are susceptible. This will revolutionized modern medicines, and hopefully improve the quality of life of all me, women and children. Already the genes for Duchene muscular dystrophy, cystic fibrosis, and retinoblastoma have been identified, and more such information's immerging all the time.

What are genes?

Genes are the biological units of hereditary. Genes determine obvious traits, such as hair and eye color, as well as more suitable characteristics', such as physical strengths such as ability of blood to carry oxygen, complex characteristics', such as physical strength may be shaped by the interaction of a number of different genes along with environmental influences.