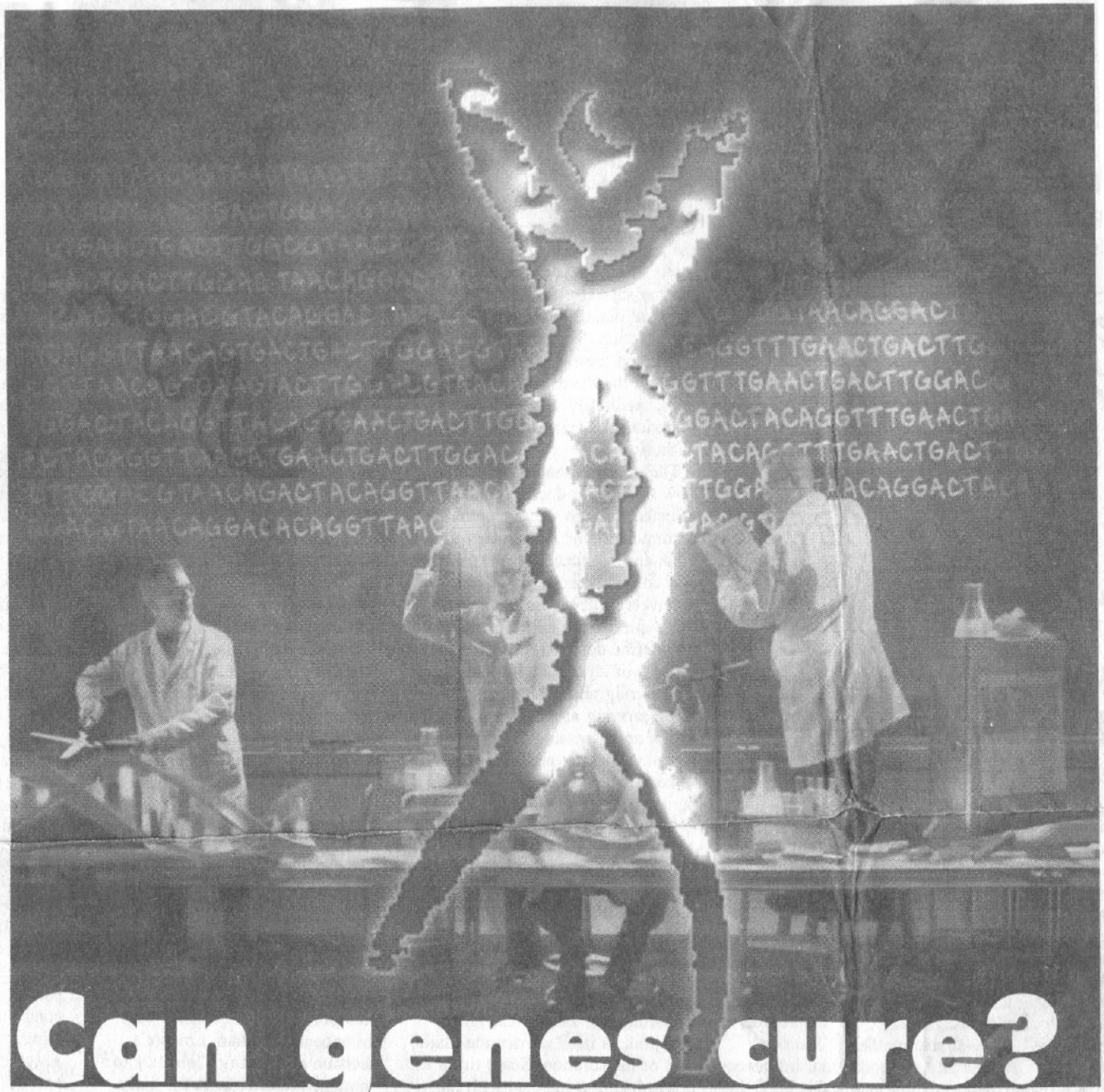

Can genes cure?

DR. MUHAMMAD ASGHAR dilates upon various issues of genetic therapy and says that cautious approach should be applied to create a sense of awareness among the masses to deal with the genetic issues as they arise

The Nation 30-12-02

It is only logical to consider "Gene Therapy" as the most successful example and ultimate achievement of Genetic Engineering. Gene therapy is the process by which DNA sequences encoding specific genes are delivered to cells with the goal of treating or curing disease. As the genetic and molecular basis for a multiplicity of diseases is elucidated, the promise of gene therapy continues to grow. By appropriate and extremely precise manipulations of a defective disease causing gene it can be replaced with a normal healthy counterpart and thus correct the defect. With this new technology of tinkering with the genes of reproductive cells and developing embryos it is now possible to internee directly to correct genetic errors underlying a number of human hereditary diseases.

Gene delivery systems

The initial efforts in gene therapy is although focused on delivering a normal copy of a missing or defective gene, current programmes are applying gene delivery [illegible] cross a broader spectrum of disease conditions.

Gene delivery is now being used to:

– Replace missing or defective genes

– Deliver genes that catalyse the destruction of cancer cells or cause cancer cells to revert back to normal tissue.

– Deliver viral or bacterial genes as a form of vaccination.

promote the growth of new tissue or stimulate regeneration of damaged tissue.

rapidly. Varieties [illegible]

tion of damaged tissue.

Therapeutic genes can be introduced into target cells in a variety of ways. The gene delivery systems include:

Viral vectors

Viral vectors take advantage of a virus ability to enter cells and deliver genetic material to the nucleus. Different viral vectors have both advantages and disadvantages related to the biology of the virus.

I. Retro-viruses

Most RNA viruses are unsuitable for gene therapy mainly because RNA, which cannot integrate into the DNA of human cells, is degraded rapidly. Varieties known as retro-viruses are an exception. They convert their RNA to DNA in infected cells and insinuate the DNA into the cells' genome. The integrated DNA then directs the synthesis of viral proteins. Retro-viruses can also infect a broad spectrum of species and cell types. For these reasons, disabled retro-viruses are the most promising gene delivery vectors studied to date.

ii. Adeno Viruses (AV)

Adeno-viruses can be preferred to retro-viruses because they dispatch their genes into the nucleus, but outside the chromosome. They are much less likely to disrupt the cell's genome. Their biggest failing is that patients develop anti-adeno-virus antibodies that may destroy the second dose of this vector given to patients.

iii. Adeno-Associated Viruses (AVV)

AAV is a non-pathogenic virus that requires co-infection with a "helper" adeno-virus for propagation. AAV seems to be custom ordered for gene transfer it stably integrates into chromosome 19, making long term gene expression possible, but it does not cause ill effects. However, it is very difficult to make large quantities of AAV, probably because it needs a "helper" virus to replicate".

Non-viral vectors

The therapeutic genes can be placed into liposomes (synthetic vectors) which are microscopic fat capsules. Liposomes can fuse with the cell membrane and slip DNA into the cell's nucleus. Although liposomes pose fewer problems than virus vectors but they are not very efficient at transferring genes into the nucleus of cells.

Gene expression systems

In addition to choosing a relevant therapeutic gene and the appropriate gene delivery system, the ability to express (turn on) the delivered gene is a key factor in the development of successful gene therapies. Current approaches utilise a variety of promoters, DNA sequences that act as on/off switches for gene expression. Some promoters are active only in specific cell types, and are used to target gene activity to specific cells. Other promoters are expressed in a wide variety of cell types, and may be used when cell specific expression is not required. Incredible promoter systems, which can be turned on or off in response to certain drugs or

compounds, also are being investigated, as are self-regulating expression systems that provide very high levels of expression.

A primary benefit of gene therapy is the ability to correct the underlying cause of genetic diseases. To date, the majority of therapeutics available for diseases such as cystic fibrosis, haemophilia and Gaucher's disease only palliate disease symptoms. The delivery of functional copies of the genes involved in these diseases provides a mechanism through which the disease may be corrected at the molecular level. Gene therapy holds the potential to provide patient friendly treatment regimens for a variety of diseases. Today, patients with haemophilia, diabetes and other diseases that are treated by the administration of therapeutic proteins must take daily or weekly injections in order to manage their disease. This is because proteins exist in the blood stream for a limited period of time before they are degraded or eliminated. Dosing regimens for gene therapy products are likely to require treatment every few weeks or every few months. As DNA is more stable and functions inside the cells, the delivery of therapeutic genes may result in longer-term expression of therapeutic proteins.

Gene therapy is likely to have the greatest success with diseases that are caused by single gene defects. Gene therapy had been approved for use on such diseases as severe combined immune deficiency, familial hypercholesterolelflia, cystic fibrosis and Gaucher's disease. Most protocols to date are aimed towards the enable patients to maintain a better quality of life during treatment than do chemotherapeutic agents or radiation therapy.

Gene therapy for AIDS

Genetic manipulation of somatic cells may have therapeutic value in a variety of infectious diseases, particularly in human immuno-deficiency virus (HIV) infection. The T-cells in human immune system becomes the targets for destruction by virus. The infected T-cells were modified to inhibit replication of virus. These altered T-cells were tagged and transfused back into the patient. The cells survived in the body four to five times longer than the subject's untreated T-cells. Researchers hope that prolonging the lives of patient's T-cells will translate into longer lives for AIDS patients.

Future prospects

How much impact will gene therapy have on medical practice in the future? It is far too early to tell. Investigations currently discourage any attempts on germ line therapy. Though it holds great promise for if a genetic cell defect is corrected in a zygote, cells from the zygote should contain the "normal" gene and the resulting phenotype should be normal. Zygote therapy is, however, a very complex issue and will not be attempted in the near future. One aspect to gene therapy that cries out for improvement is the delivery system-the vectors (viral and non viral) that carry foreign genes into cells. It is clear that gene therapy will fulfil its promise only which gene delivery systems are developed that can safely and efficiently be introduced into patients wide variety of diseases is likely to grow.

Ethical Issues

Fascinating as gene therapy is but it has raised several ethical questions for scientists, religious leaders and the general public. Should therapy be applied to simply improve one's offspring and not only to prevent an inherited disease? Who would be empowered to decide? Is society willing to risk introducing changes into the gene pool that may ultimately prove detrimental to species? Do we have the right to tamper with human evolution? These and many other questions need to be answered to clear the doubts. In studying the ethics of gene therapy, one should make a distinction between therapy on the somatic (non reproductive) cells and the germ (reproductive) cells of an individual. Only the germ cells carry the genes that will be passed on to - the next generation. Many people who voice concerns about somatic cell gene therapy use a "Slippery slope" argument against it. They wonder whether it is possible to distinguish between "Good" and "Bad" uses of the gene modification techniques, and whether the potential for harmful abuse of the technology should keep us from developing more techniques. Some commentators on gene therapy have objected to any form of genetic manipulation, no matter how well intentioned. One of the major sources of the complexity is the fact that it is exceedingly difficult, and almost impossible, to predict

therapy had been approved for use on such diseases as severe combined immune deficiency, familial hyper-fibrosis and Gaueher's disease. Most protocols to date are aimed towards the treatment of cancer; a few are also targeted toward AIDS. Numerous disorders are discussed as candidates for gene therapy including Parkinson's and Alzheimer's diseases, arthritis, and heart disease.

Gene therapy for Cancer

In the area of cancer therapeutics, gene therapy has the potential to eliminate cancer cells without damaging normal, healthy tissue. In some experiments, scientists seek to stop cancer by activating the body's own tumour suppresser genes. Cancer gene therapies may

the vectors (viral and non viral) that carry foreign genes into cells. It is clear that gene therapy will fulfil its promise only when gene delivery systems are developed that can safely and efficiently be introduced into patients. Vectors need to be engineered that will target specific cell types, insert their genetic information into a safe site in the genome, be regulated by normal physiological signals and be coaxed to work throughout the life of the patient. But until recently, the scientists have lacked the technical skills to tinker with individual genes in germ cells or to assign genes to unborn generations. As the genomics revolution identifies new genes and as gene delivery technologies continue to evolve, the role of gene therapy in the treatment of

form of genetic manipulation, no matter how well intentioned. One of the major sources of the complexity is the fact that it is exceedingly difficult, and almost impossible, to predict the pace at which new breakthroughs will occur. The cautious approach, therefore, is to create a sense of awareness and preparedness to deal with issues as they arise. Since every society finds answers within the framework of moral values that it practices, it is indeed important for the Muslim world to examine the question within the existing framework. ■

–The author is working as Assistant Professor of Biochemistry, in Department of Chemistry , University of