**Genetic Engineering: Utopian Dream or Eugenic Nightmare?**

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Almost daily we read or hear in the media about tremendous advances being made in the area of genetics.  Generally, the hope for new treatments of human diseases aroused by these advances is accompanied by fears about the dangers which may accompany them.

In the quality newspapers, we read headlines such as “Scientist ordered to axe deadly virus…. Safety inspectors fear engineered cancer germ could escape from lab….”

When we reach a middle ground newspaper, we have headlines such as “Are genetic researchers menders or meddlers?” followed by a very interesting sentence which says... “They are a group who revel in obscurity.”

Personally I have never revelled in obscurity and certainly many of my colleagues have done as much as they can to describe the advances being made in lay terms and to present the ethical and other issues involved.

This, of course, is not a new issue.  JBS Haldane, former Professor of Genetics at UCL, writing in 1927 says:

***“I think, however, that the public has a right to know what is going on in laboratories, for some of which it pays.”***

In this lecture, I will consider the issues which are raised by genetic engineering, examining particularly gene therapy, in which genes are used to produce therapeutic benefit in human disease.  In the first part of the lecture, I will consider so called somatic gene therapy, in which the gene is used to produce a therapeutic benefit in a particular organ or organs of the patient, but that benefit will be limited to the patient themselves.  When the patient dies (either from the disease or from some other cause), the therapeutic benefit will end and will not be transferred to the individual’s children.  I will argue that this procedure arises from others which are generally accepted by the public and does not pose any significant ethical problems.  I will then consider several methods by which somatic gene therapy could be achieved.

In the last  part of the lecture, I will consider germline gene therapy, in which by contrast with somatic gene therapy, the gene would be delivered in such a way that it would not only benefit the individual, but would be passed on to their children in order to benefit them as well.  This form of potential therapy poses many more ethical issues which I will discuss.

The central dogma of Molecular Biology is that the genetic information in the DNA is converted into RNA and then into proteins then producing specific functional biological effects.  Hence, if an individual has an error (mutation) in the DNA, then this will be transferred to the RNA and may produce a protein which is non-functional. In this situation, the individual will have a genetic disease caused by the absence of functional protein.

For many years, in several diseases, it has been possible to treat the patient by supplying a functional version of their defective protein obtained from an animal.  For example, individuals with Diabetes, caused by a lack of functional insulin, can be treated by injecting insulin prepared from the pancreas of an animal such as a cow or a pig.    This is a form of treatment which is generally accepted and does not raise significant ethical issues.

A problem which arises with this approach, however, is that in many cases the animal protein, whilst working perfectly well in the animal, does not work in the human situation, due to the millions of years of evolution which separate us from animals.  An example of this is a growth hormone, which has an essential role in producing normal body growth.  Deficiencies in this hormone cannot be treated simply by supplying animal growth hormone, since this does not work in humans.  Instead, such patients were treated with human growth hormone, prepared from the pituitary glands of dead individuals with large numbers of pituitaries being pooled to produce sufficient growth hormone.  Although this allowed growth to normal stature, it also resulted in several treated individuals developing Creutzfeldt-Jakob Syndrome, the human equivalent of Bovine Mad Cow Disease.  This was due to the growth hormone samples being contaminated with the causative agent of this disease which must have been present in one or more of the individuals contributing pituitaries to the pool.  Similarly, haemophiliac patients treated with Factor VIII purified from blood donations were contaminated with the HIV virus present in the blood of some donors, and developed AIDS.  Hence, human products are highly dangerous and should be avoided if at all possible.

A solution to this, conceived in the early days of genetic engineering, was to take the piece of DNA containing the human gene and to link it to another piece of DNA known as a plasmid and then introduce this into bacteria.  The bacteria would copy the human DNA within the plasmid and would convert it into RNA and then into protein, producing a source of human protein.

It may seem paradoxical that when an animal cannot make a growth hormone protein which is functional in humans, this should be possible in the much simpler bacteria.  However, the bacteria have been given the information to make human growth hormone in the human DNA sequence and are simply converting it into RNA and protein.  An analogy for this would be that if a computer disc containing the Times newspaper editorial were to be taken to the offices of the Sun newspaper, and placed in one of their computers, a Times editorial would emerge, even though the computer had previously only had to print out the possibly more simple language used in the normal Sun editorial.  Hence, this is simply an exercise in information transfer.

This is not a new development and this technique has been in use for many years.  Indeed, it is now over twenty-five years since human insulin was first produced in this way and both insulin and growth hormone produced in bacteria were first marketed for therapeutic use in the 1980s.  A very large number of different proteins are now produced in this way, including, for example Factor VIII, which was mentioned above.

Interestingly, however, if one examines a list of these substances, one observes that they are all factors which normally circulate around the body, for example, in the blood.  There is a very good reason for this since such substances normally act by binding to receptors on the surface of cells and then triggering a signal which enters the cell.  Evidently, if a normal copy of this protein is supplied to the body to replace the non-functional protein, it will similarly circulate in the blood and bind to the appropriate cell receptors, thereby relieving the problem caused by the absence of the functional protein.  However, if a protein normally acts within the cell to achieve its function, then it cannot be replaced simply by injecting the protein into the patient’s bloodstream, since the protein will not cross the cell membrane and will therefore not reach the appropriate point to achieve its action.

This can be overcome, however, by supplying the functional DNA encoding the protein and getting this to cross the cell membrane into the interior of the cell.  Once it has done so, the cell’s normal machinery will convert it to RNA and then into functional protein, allowing it to achieve its effects.  Evidently, this machinery for converting DNA into RNA and protein will be intact in the patient’s cells, since otherwise he or she would not be able to make any proteins and would not have survived embryonic development.  The problem is that the patient has an error in a particular DNA sequence, which causes them to make a non-functional protein.

This is the principle on which somatic gene therapy is based, namely using DNA to get the patient’s own cells to make the protein which they require.  This procedure clearly builds on a series of other procedures which are in routine use and pose no ethical problems.  Indeed, one could argue that gene therapy should be more efficient since it cuts out the middle man of the bacteria.  Thus, in making recombinant human proteins, the human gene is put into bacteria, protein is then made by the bacteria and isolated, with this protein then being injected into the patient.  Evidently, a much more simple procedure would be just to deliver the functional DNA to the patient and allow them to make the corresponding protein from it.

I believe that it is clear, therefore, that somatic gene therapy of this type emerges from other forms of therapy and does not present any significant ethical problems.  Indeed, the scope of this therapy goes beyond its use simply to provide a functional protein to replace the inactive protein in genetic disease.  Thus, gene therapy can also be used to provide symptomatic therapy in diseases which do not have a genetic component, or where the gene involved has not been identified.  Thus, for example, if an individual has an accident and suffers a spinal injury leading to paralysis, this is clearly not a genetic disease.  However, such an individual could potentially be treated by supplying genes encoding factors, which promote the growth of the damaged nerves across the break, so restoring the functional connection of the nerve with the appropriate muscle.

The central question with somatic gene therapy is not, therefore, whether it should be undertaken but how it can be achieved.  Essentially, this is a problem of delivering the gene with high efficiency to the appropriate cells within the patient’s body.  One method of doing this would be to place the human DNA within a similar plasmid to that which was used to express such genes in bacteria.  Unfortunately, however such delivery of plasmid DNA to the patient’s body is of extremely low efficiency, even when the DNA is coated with fat particles, known as liposomes, to improve efficiency.

Very many groups, therefore, have attempted to use viruses to deliver DNA more efficiently.   This is based on the fact that over millions of years of evolution viruses have evolved to deliver their DNA into our cells.  Thus, viruses, unlike bacteria, are obligate intracellular parasites.  They cannot convert their DNA into RNA or protein on their own, but must enter the cell and use the cell’s machinery to convert their DNA into the corresponding RNA and then protein.  Hence, viruses must by their very nature have a high efficiency gene delivery system for ensuring that their DNA enters our cells.

Different laboratories have used many viruses as potential means of such delivery, including adenovirus, adeno-associated virus, retroviruses (including lentiviruses) and Herpes Simplex virus. All of these have their own particular advantages and disadvantages. I want to focus on the work of our laboratory utilizing Herpes Simplex virus (HSV). This virus causes recurrent cold sores in approximately forty per cent of the population, which is hardly a good start for a potential treatment of human disease.

Following the initial infection of skin cells with HSV, the virus makes its way up the nerve processes, innervating the site of infection and hides away in nerve cell bodies in what is called a latent infection. The virus can repeatedly emerge from these nerve cell bodies, come back down their processes and reinfect skin cells, producing the classic pattern of recurrence due to a cold or stress, which is experienced by those suffering from infection with the virus. For our purposes, it is of particular importance that the latent infections established in nerve cells by the virus are entirely asymptomatic and do not, in any way, affect the functioning of the nerve cell. Hence, if this aspect of the virus can be utilized without having its damaging effects, a human gene could be delivered to nerve cells and produce a therapeutic effect without damaging them.

Moreover, the virus also has other advantages as a gene delivery vehicle. Firstly, it can be grown in large amounts in culture. This is essential if the virus is ever to be used therapeutically since sufficient amounts must be made to treat large numbers of patents. Secondly, as indicated in the table below, the virus has a much larger DNA genome than any of the other viruses proposed for gene therapy.

**Genome Size of potential virus vectors for the nervous system**

*Adeno-associated virus          8,500 base pairs*

*Adenovirus                           35,000 base pairs*

*Herpes Simplex virus         150,000 base pairs*

*Lentivirus                             10,000 base pairs*

This is important, because the virus can only deliver with high efficiency the amount of DNA which it normally packages into its viral particle. Hence, even if parts of the virus DNA are replaced with the human gene of interest, a virus with a small genome will not be able to carry a large human gene or the multiple different genes which may be necessary to treat very complex human diseases.

Despite these advantages, however, the problem remains of preventing HSV performing its normal function of producing cold sores. Indeed, the problem is worse than this since direct injection of HSV into the brain (such as would be required if it is to be used to deliver genes in neurological diseases) would result in the virus replicating in the brain and producing encephalitis, leading to the rapid death of the patient.

Hence, with HSV, as with other virus vectors, the challenge is to disable the virus sufficiently to make it safe for human use without inactivating it completely so that it cannot be grown or deliver the gene of interest. Two basic methods are available for this. In the first method, the HSV is inactivated by removing a gene encoding a protein which is essential for it to replicate in all cell types. Although this will prevent the virus having damaging effects when infected into the patient, it also leaves the problem that such replication of the virus is necessary for it to grow in culture, which would be required to produce it. It is therefore necessary to provide a functional copy of the deleted viral gene within the cells on which the virus is grown in culture. This allows the virus to grow in these cells, but when injected into the brain, it obviously does not have the additional gene and therefore cannot replicate or cause disease. One potential problem with this approach, however, is that the virus is under strong selective pressure to pick up the missing gene from the cultured cells, thereby restoring the virus to a fully functional, disease-causing state.

A second method which avoids these problems is to delete from the virus a gene which is not required for growth in dividing cells in culture, but is required for the virus to grow in non-dividing cells. In this case, therefore, the virus will be able to be grown in dividing cells in culture to produce sufficient amounts, but when injected into the brain will not cause disease because it cannot replicate in non-dividing nerve cells.

A gene of this type is the viral gene encoding ICP 34.5. Viruses lacking this gene can grow in dividing cells, but not in non-dividing cells. Indeed, a company which we founded on the basis of patents developed by my laboratory (BioVex Ltd.) is now using this to develop therapies for cancer patients involving the virus replicating in their dividing tumor cells and killing them whilst not affecting normal non-dividing cells. This treatment is now in Phase I clinical trials in a number of different tumors.

From the point of view of gene therapy for brain diseases, however, viruses lacking ICP 34.5 are also relevant since such viruses do not replicate when they are introduced into the brain, and therefore do not cause encephalitis. We therefore introduced the gene encoding b-galactosidase into a virus lacking ICP 34.5. This gene was chosen since its protein product can stain cells blue, allowing us to readily visualize gene delivery. Unfortunately, however, when this virus was injected into the brain of an animal, it produced only a very small number of blue cells, indicating that gene delivery was highly inefficient.

To take this further, we decided to combine the deletion of ICP 34.5 with the deletion of the gene encoding ICP 27, which is a gene whose protein product is required for growth in all cell types. Although the ICP 27 gene would then have to be supplied in the cultured cells used to grow the virus (as described above), this would have the advantage that even if the virus took back the ICP 27 gene to replace the deleted gene, we would still have the deletion of ICP 34.5, preventing the production of a disease-causing virus. Hence, this virus would be much safer in having two deleted genes than viruses lacking either ICP 34.5 or ICP 27 alone.

Very surprisingly, however, we also found that such a virus was able to deliver the b-galactosidase gene to approximately one-hundred-fold more cells in the brain than was observed with the virus lacking ICP 34.5. This is probably because the virus lacking ICP 34.5 alone is recognised as damaging by the nerve cell which then dies and does not express the gene, whereas the doubly disabled virus does not trigger such cell death, allowing the gene to be expressed. In any case, this somewhat surprising result, in which a safer virus was also more effective, was much appreciated by our patent agents, who prefer results which are not easily explainable, and therefore cannot be criticised on the grounds of being obvious.

Based on this doubly disabled virus, it has now proved possible to construct further viruses, which are more disabled, and therefore safer, but still produce effective delivery to the nervous system.

Before discussing the potential use of such viruses in gene therapy for neurological diseases, I also want to mention that such viruses can be used to probe gene function in the intact animal. Thus, whilst it is fairly simple to do this in cultured cells, it is often difficult to extend such conclusions to the intact animal. For example, in the case of Brn-3a, a transcription factor, which is studied in our laboratory, we were able to show that over expression of this factor in cultured neurons was able to protect them from stimuli which would otherwise induce cell death. By making an HSV virus expressing Brn-3a, we were able to extend this, and show that this protective effect of Brn-3a is also observed in the intact animal.

Similarly, in the case of the heat shock protein hsp27, we had obtained data showing that this protein was protective in cultured cells and also in the intact animal by using a transgenic approach, in which the gene is injected into a fertilised mouse egg and is therefore present in all the cells of the animal. Although the transgenic animal technique is of great value, it does not indicate whether the gene would be protective when delivered to the adult organism, as would be required in the treatment of human diseases. However, once again, by constructing an HSV vector with the hsp27 gene within it, we were able to demonstrate a protective effect when this virus was introduced into the intact adult animal.

These cases, therefore, illustrate the use of our viruses to prove that a particular gene has a beneficial effect in a particular situation. Evidently, they could be extended by constructing viruses which could be used to deliver the Brn-3a or hsp27 gene to patients suffering from excess nerve cell death, in a gene therapy procedure. However, the proof of principle that these genes are important could also be used to develop pharmacological therapies, which would upregulate the patient’s own copy of the Brn-3a or hsp27 gene, thereby producing a therapeutic benefit.

Evidently, therefore, this work has established Brn-3a and hsp27 as potential therapeutic tools in diseases such as Alzheimer’s and Parkinson’s Diseases, which involve the loss of specific nerve cells in the brain. However, in the case of Parkinson’s Disease it is also possible to conceive of other more specific approaches to gene therapy of this disease, which involves the loss of dopamine-producing neurons. This could involve delivery of the gene encoding tyrosine hydroxylase, which catalyses the rate-limiting step in the synthesis of dopamine, or alternatively delivering the gene encoding the neurotrophic factor GDNF, which enhances the survival of dopamine-producing neurons.

This is evidently, therefore, an example of where gene therapy may benefit from the ability of a large virus such as HSV to deliver two different genes which stimulate different processes for therapeutic benefit. We have produced viruses carrying the tyrosine hydroxylase or GDNF genes, and have used these to show therapeutic improvement in behaviour in a rat model of Parkinson’s Disease. It is likely that such gene therapy approaches will ultimately be used to treat patients with Parkinson’s Disease.

In other situations, gene therapy is already being used clinically. For example, at the Institute of Child Health, where I was Dean, I was able to work closely with Great Ormond Street Hospital to develop appropriate facilities for clinical trials involving gene therapy for children with severe combined immuno-deficiency disease. These patients, who have a non-functional gene encoding the gamma c receptor, were successfully treated with a virus containing a functional copy of this gene by a team led by Professor Adrian Thrasher and Professor Christine Kinnon. Although side effects of this treatment have been observed in a similar trial in Paris, there is no doubt that these studies represent an important step forward for gene therapy, and that ultimately such somatic gene therapy will be widely used in a range of genetic and non-genetic diseases.

Interestingly, however, such somatic gene therapy does not take advantage of the full power of DNA. Thus, in somatic gene therapy, the DNA is used to treat a particular cell system for the patient’s benefit, but is not passed on to their offspring. Clearly, however, DNA as the genetic material, has the capacity not only to act within an individual, but also to be inherited by their descendants. Indeed, in 1944, the original demonstration that DNA was the genetic material by Avery and colleagues involved precisely such an experiment in which DNA but not other material such as lipid or protein was able to alter the genetic characteristics of bacteria with such a modification being inherited by all their descendants.

Similarly, large numbers of laboratories now routinely make transgenic mice (as noted above for hsp 27), in which an extra gene has been introduced into an animal and is inherited by all its descendants. The question, therefore, is whether such germline gene therapy should be attempted in humans by trying to introduce the therapeutic gene in such a manner that it would be inherited by the individual’s descendants, thereby correcting not only the genetic deficiency of the patient, but that of all their offspring. In considering this question it is helpful to think of it in terms of three questions: Is it safe? Is it worthwhile? Is it ethical?

In terms of safety, it is clear that such procedures would not yet be safe. Thus, when a gene is introduced to make a transgenic animal, it does not replace the equivalent gene already present in the animal. Rather, it can enter the DNA at any point and may therefore disrupt another gene, producing undesirable side effects. Clearly, this would not be acceptable in humans, where it would be necessary to develop targeting procedures, so that the introduced gene would replace the damaged gene. Such procedures have, however, already been developed in mice, and therefore, although we could not attempt germline gene therapy at present, in terms of safety it may not be far off.

In terms of whether it is worthwhile, it has been argued that this is not the case. This argument suggests that if two individuals are both carriers of a particular genetic disease and this has already been identified by their having a child with the disease, then they can simply be offered *in vitro* fertilisation, followed by embryo-sorting. This would identify an embryo which contained two functional copies of the gene (one from each parent) and would eliminate not only an embryo with two defective copies (who would, therefore, develop the disease), but also those with one functional copy and one defective copy, who would be carriers like their parents.

Apart from the ethical problems of this for those who do not wish to destroy unwanted embryos, there will also be the situation where both partners carry two defective copies of the gene and have the genetic disease themselves. Indeed, they may have met at the somatic gene therapy clinic and been successfully treated, so allowing them to have children! In this case, sorting of embryos could be continued indefinitely, but would never yield an embryo with even one functional gene, since neither parent has such a functional gene. In this case, therefore, germline gene therapy, rather than treatment of every generation, may be the optimum solution.

Assuming, therefore, that the technique is safe and may be worthwhile in some cases, is it ethical to carry it out? In this situation, my ideas are no more relevant than anyone else’s, and the important thing is to provoke a debate. It is important to indicate, however, that this has no connection with the debate about cloning produced by the creation of Dolly the cloned sheep and numerous other cloned animals, as well as claims of cloned humans. Thus, cloning does not even require one to know that DNA is the genetic material, so long as one knows that the information for creating an individual is contained in the nucleus and that, therefore, putting this into an egg will result in a cloned individual, if embryonic development is successful. The advances in this area are thus really ‘advanced gardening’, being about improvements in culturing eggs and embryos to ensure the potential for development of the cloned organism. In contrast, in our case, we are dealing with defined pieces of DNA, expressing a particular gene product, which are being used for therapeutic benefit.

This situation is obviously connected to that of eugenics, involving improvement of the race, which was propounded by Francis Galton, another Professor of Genetics at UCL. He said:

***“It would be quite practical to produce a highly gifted race of men by judicious marriages during several consecutive generations.” (18*69**)

Indeed, he proposed a national eugenic competition, involving all eighteen-year olds, who would be graded on looks, intelligence etc with the winners being married in Westminster Abbey, and being encouraged to have as many children as possible.

The snag of this, of course, is that the losers should be encouraged to have as few children as possible. Although this eugenic idea reached its pinnacle with the Nazis, it went wrong well before that. Thus, by 1931, seventeen US states had compulsory sterilization laws, allowing the sterilization of mentally handicapped individuals without their consent. Moreover, this law was used, with 9,931 compulsory sterilizations being carried out in California alone by 1935.

In a famous judgement, the liberal jurist, Oliver Wendell Holmes said:

***“The principle that sustains compulsory vaccination is broad enough to cover the Fallopian Tubes. Three generations of imbeciles is enough.”* (1927)**

He allowed the compulsory sterilization of a mentally handicapped girl who was said to be sexually promiscuous.

Given this sorry history, one may ask why we should open the eugenic debate now. The answer comes in another quotation from JBS Haldane, writing in 1941:

“In man there is good evidence that arteriosclerosis and some other senile diseases are largely genetically determined […] If this is so, the indefinite prolongation of human life demands not merely the abolition of war and infection and a vast reduction of accidents, but the abolition of these genes.”

Notice that Haldane does not write abolition of these people, but rather abolition of these genes. We are now in a situation where it is possible to contemplate using genes to improve the inheritance which a particular individual passes on to their children, rather than, as in the past, determining that this inheritance is somehow unsatisfactory for society and sterilizing or ultimately killing the individual.

Clearly, therefore, we need a debate on these issues and I can do no better than to quote Thomas Jefferson, the third President of the United States of America, who said:

**“I know of no safe depository of the ultimate powers of society but the people themselves, and if we think them not enlightened enough to exercise that control with a wholesome discretion, the remedy is not to take it from them, but to inform their discretion.”**

Unfortunately, however, many of those in the media who act as the intermediaries between science and the public are not sufficiently briefed on scientific issues to fulfil their key role in this debate.

I was once invited to appear on a television programme, and before appearing was asked what I thought about the donkey that talked. Having never heard of this, I asked the reporter to send me the appropriate press cutting. This indicated that a donkey had been given the vocal chords of a road accident victim, and now talked. However, because the road accident victim was a Glaswegian, the donkey spoke with a thick Glaswegian accent, and no one could understand what it was talking about! The date of the story in The Scotsman newspaper was 1 April, and it was clearly intended as an April Fool's joke. However, the real joke is that a science journalist considered it to be a real story!

In concluding, I can do no better than to give one final quote:

“**The inquiring spirit of the age has loudly demanded that the door of science should be thrown open, and that its mysteries should be revealed to all mankind.”**

This quotation is clearly as relevant today as when it was said over 180 years ago, in February 1824, by our founder, George Birkbeck, in giving the inaugural lecture of the Mechanics Institute, which ultimately became Birkbeck College.

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