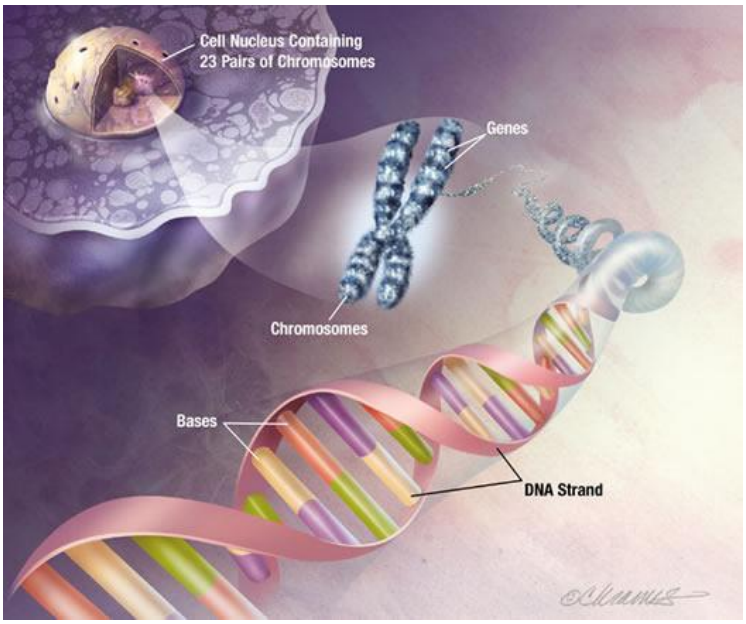

Genetic Engineering and Gene Therapy: Examining the Issues

D. John Doyle

Genetic engineering has been a reality for several decades now, as evidenced by such remarkable innovations as the invention of bacteria that produce human insulin (Figure 1) or the development of genetically engineered goats that produce human growth hormone in their milk [1].

Equally interesting, especially to environmentalists, is that scientists have successfully inserted a human gene into rice to enable it to digest toxins such as pesticides [2]. This gene, normally expressed only in liver tissue, produces an enzyme that goes by the cryptic name of CPY2B6 and breaks down various chemical toxins to help keep us healthy. The hope is that genes of this kind inserted into various crops might also help clean up contaminated soil.

There are an estimated 20,000 to 25,000 genes (3.1 billion base pairs) in the human genome, residing in 23 chromosome pairs [3]. As the human genome continues to be studied in detail, the role of these genes in health and disease will continue to be elucidated.

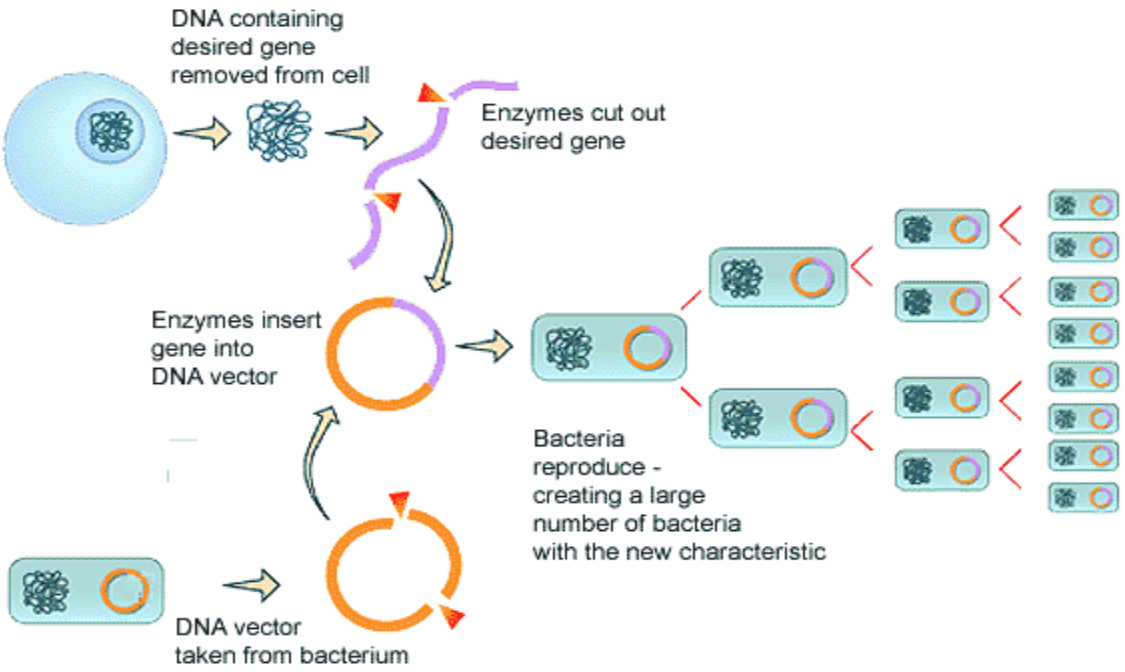

Figure 1:

Illustration showing how a bacterium's genetic composition can be enhanced by splicing a new gene into its DNA. Such a gene might code for insulin, growth hormone, somatostatin or countless other proteins. When a missing or defective gene is inserted into human cells in such a manner, the hope is that the newly programmed cells will produce the associated missing protein that was responsible for a particular affliction.

Image Source:

http://www.bbc.co.uk/schools/gcsebitesize/img/bigeneticeng.gif

Scientists have naturally been considering how they might use information about the human genome to develop various means to modify or repair it for clinical purposes, a process known as **gene therapy**. Given that genetic engineering methods might reasonably be expected to offer future humanity the means to treat or cure genetically-based ailments such as cystic fibrosis, sickle cell anemia, Tay-Sachs disease, or Gaucher's disease (Figure 2), numerous gene therapy programs around the world are fervently working towards this goal.

Gene therapy involves adding one or more genes to a person’s genome for some therapeutic purpose, such as ensuring that a missing enzyme is produced [4]. Viruses are usually used to transport the extra DNA into cells (Figure 2), a process that is still experimental and occasionally hazardous.

Additionally, scientists have given extensive thought to the potential benefits of adding human genes to various animals, as in creating animals with organs that would be suitable for transplantation into humans [5]. (Regrettably, past attempts at using animal organs for transplantation in humans have met with disaster in that organ rejection is

almost inevitable. This rejection occurs even when employing aggressive anti-rejection therapy and occurs as a direct result of immunological differences between animals and humans.)

A similar situation involves research programs which place human stem cells into the embryonic brains of mice or other animal embryos [6]. This is done since, as a rule, the more genetically human-like are the research animals, the better scientists will be able to study the progression of human diseases in animal models, as well as test new drugs for efficacy and toxicity.

At Stanford University's Institute of Cancer/Stem Cell Biology and Medicine in California, Professor Irv Weissman has created mice with brains that are about one percent human and plans to eventually produce mice have 100 percent human brains [7]. The process of producing these chimeras involves injecting human neurons into the brains of embryonic mice. With a view to understanding the process of neuronal development, before being born the mice are killed and dissected to determine if the neuronal architecture appropriate to a human brain has formed.

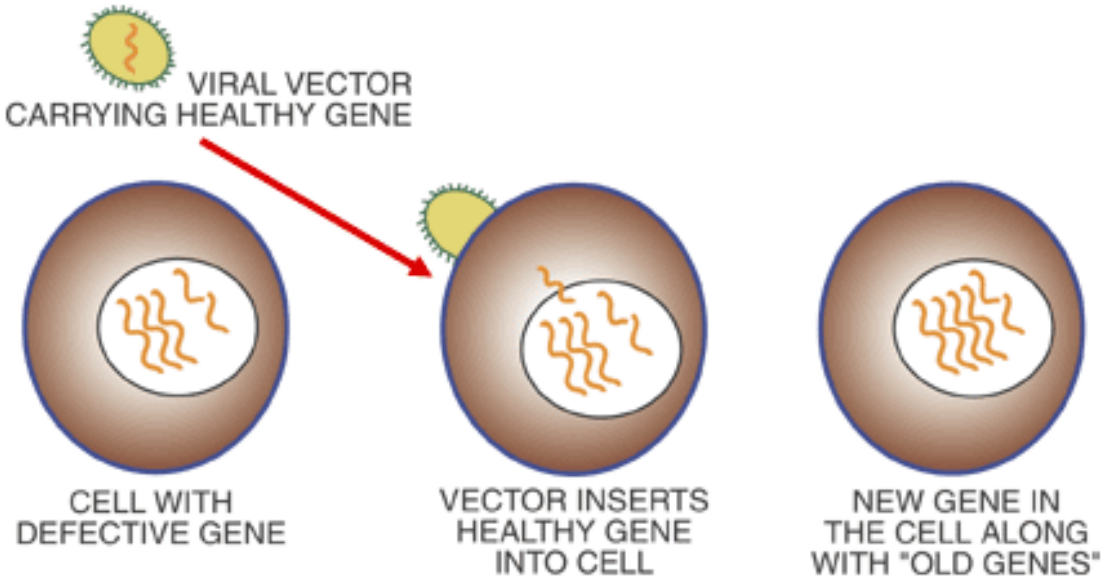

Figure 2. In genetic engineering of human tissue, the missing or defective genes are "replaced" using a viral carrier to insert the new gene amongst the existing genes. This process is not without risks, as sometimes an overwhelming, even lethal, immunological reaction results. In addition, the random mixing of the new DNA into existing chromosomes can disrupt existing genes or their regulation, with undesirable results.

Image Source:

http://www.arhp.org/files/diagram5.gif

As another example, some investigators are considering the development of human-chimpanzee chimeras. Given that chimpanzees are already very closely related to us, sharing about 98% of the human genome [8], adding the right additional genetic material by such means as fusing a human and a chimpanzee embryo might be expected to produce a perfect test vehicle for research into human disease, as well as provide an excellent source of organs and tissue for transplantation purposes (xenotransplantation).

It appears, however, that successful xeno-transplantation programs may still be a great many years away. Although over the last few decades chimpanzee kidneys, baboon livers, porcine skin and even porcine islet cells of Langerhans (which make insulin) have all been transplanted experimentally, all these organs have been promptly rejected.

In addition to concerns about inducing and maintaining immune tolerance, fears about the transmission of viruses from xenografts into humans also exist. This is because there are a number of viruses that are benign to some animal species but potentially harmful to humans, especially when undergoing immune suppression therapy.

Unfortunately, enthusiasm for such potential future benefits must be tempered in the light of some unfortunate clinical events which have occurred in recent years.

On September 17, 1999 Jesse Gelsinger, an 18-year-old boy, died when an experimental gene therapy treatment at the University of Pennsylvania went tragically wrong. Jesse suffered from ornithine transcarbamylase deficiency, the result of an unfortunate sporadic genetic mutation that made him unable to breakdown much of the ammonia produced as a natural consequence of his body's breakdown (catabolism) of dietary protein.

Jesse's doctors were hoping to treat his condition by implanting the missing healthy gene into his liver cells using a gene carrier, or vector, in this case a common virus (adenovirus) directly administered into his hepatic artery. Since some seventeen patients had been successfully treated for other genetic disorders using similar techniques, they were confident of success, or at least, of not harming Jesse. They were wrong. Jesse died unexpectedly of multi-system organ failure 4 days after starting the treatment, likely from a severe immunological response to the adenovirus. An enquiry followed that identified a

number of problems with the clinical trial process. Jesse's father sued and subsequently settled out of court for an undisclosed amount [9].

In another heartrending story, in 2002 the famous Necker Hospital located in Paris, France announced that two young boys enrolled into a gene therapy research protocol for the treatment of X-linked Severe Combined Immune Deficiency Disease (X-SCID, also known as "bubble baby syndrome") had developed a form of leukemia characterized by an uncontrollable proliferation of a particular type of T-cell [10]. Since the announcement, one of the boys has died. The presumed mechanism involves "retrovirus vector integration in proximity to the LMO2 proto-oncogene promoter, leading to aberrant transcription and expression of LMO2" [10], LMO2 being a human gene involved in hematopoesis.

These two episodes highlight two potential dangers associated with gene therapy: untoward, sometimes lethal, immunological reactions, and the development of mutations that may lead to the development of cancer.

In addition to pure safety concerns, some of the notions discussed above have ethical implications that merit careful discussion. As noted earlier, some scientists are now putting human genes into an assortment of animals. Such considerations raise issues as to what it means to be a human. If we put human genes into animals, does that make the animals more human and, if so, do they have more rights than ordinary animals?

In the case of human/chimpanzee chimeras, the development of such a "humanzee" would raise particularly difficult ethical questions [11]. Should such an organism enjoy some rudimentary form of human rights? Might it be forced into doing menial labor or even used to perform dangerous jobs, like cleaning up nuclear spills?

In the situation where human genes are added to animal embryonic brain tissue, one theoretical concern would be that of creating an organism with human consciousness trapped in an animal body, perhaps directly or even indirectly as a result of mating two such especially endowed animals. While admittedly quite far-fetched, the possibility of this happening requires contemplation. As a result, some scientists and scientific organizations such

as the National Academy of Sciences have developed stem cell research guidelines that prohibit the breeding animals that carry human stem cells. As a further measure, some ethicists and scientific organizations would forbid the transplantation of human stem cells into higher primates like chimpanzees to reduce even further any chance of producing a humanized animal with human intelligence. However, because animals that have been "humanized" by stem-cell transplant techniques may offer excellent opportunities for testing new drugs and therapies, such research initiatives will likely continue to be developed. There may thus be a temptation to continue to add human material until the end result is more human than animal.

In conclusion, while genetic engineering has demonstrated many spectacular achievements, the successful implementation of clinical gene therapy programs has turned out to be more difficult than originally anticipated, facing obstacles such as the development of multi-system organ failure and cancer in some human test subjects. In addition to risk and safety considerations, a number of complex ethical issues enter into the discussion when human genes are placed into nonhuman organisms such as chimpanzees.

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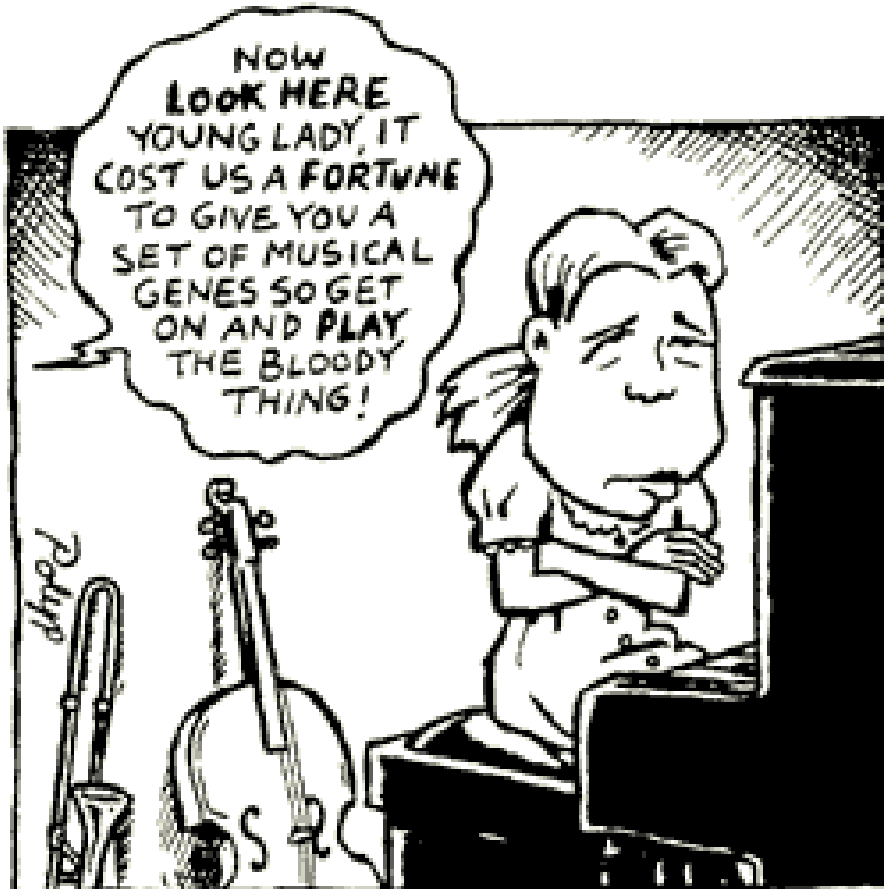

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