

CHAPTER FIVE

GENETIC MODIFICATION OF HUMANS AND LABORATORY ANIMALS

1. DIALOGUE AND GENE THERAPY

The Human Genome Project produces knowledge of relevance to human gene therapy research. This means that gene therapy can be viewed to some extent as an application of results from this project even if the research on gene therapy started before any results were published.

Gene therapy research raises many 'ordinary' issues in research ethics, for instance, choice of disease and dialogue with patients. Ultimately, however, it is the potential in the long term of gene therapy that has to be considered. Responsible geneticists have to take part in a dialogue with the general public and politicians on a number of important issues: Which applications of gene technology to humans are morally defensible? To what extent is it morally acceptable to modify the human genome? Are there limits that should never be transcended? At present, somatic cell gene therapy is the only kind of gene therapy that is actually tested. But what about germline gene therapy? Should scientists be permitted to carry out germline gene therapy research? This is perhaps the most controversial ethical issue in human genetics. Germline gene therapy is contrary to, for example, the Convention of Human Rights and Biomedicine issued by the Council of Europe (Council of Europe, 1996). Moreover, in a report issued by the American Association for the Advancement of Science (AAAS, publisher of *Science*) a total moratorium is called for.¹ On the other hand, a few important geneticists have recently suggested that germline gene therapy research should be started.²

With this in mind, more space will be devoted to germline gene therapy than to any other specific issue discussed in this book. This might give the book a slightly unbalanced character. It reflects, however, the extra-ordinary controversiality and importance of the issue. Another controversial issue is genetic enhancement, whether somatic or germline. Ethical problems raised by this issue will be discussed as well.

¹ See URL: www.aaas.org/spp/dspp/sfrl/germline/main.htm

² See URL: www.ess.ucla.edu:80/huge/report.html.

However, genetic modification of animals has been carried out long before any genetic modification of humans. In addition, transgenic animals are used in human genetics research, for instance, as disease models. This makes it necessary to discuss ethical problems raised by the genetic modification of animals as well, despite the fact that this book is about human genetics. The final section of the chapter will be devoted to such a discussion.

Different Kinds of Genetic Modification

Gene therapy can be defined as a set of approaches to the treatment of human disease based on transfer of genetic material (DNA) into an individual. Transfer may be achieved *in vivo* or *in vitro*. In the former case, gene delivery is made directly to blood or tissue, in the latter case indirectly through the introduction of cells modified in the laboratory to harbor foreign DNA. One important method for the transfer is to use viral vectors, but there are also other methods (Smith, 1999; Brenner, 1999).

In 1980, the first unauthorized experiment of somatic gene therapy was performed (Cline). Ten years later the first officially authorized experiment was carried out (Rosenberg et al.) (cf. Walters, Palmer, 1997, pp. 17-36). At present, several thousand patients have participated in trials around the world (Walters, 1999). Many scientists maintain that gene therapy has a great potential in the long term for the treatment of human diseases. But presently, clinically effective gene therapy is the exception.

When we discuss the ethical aspects of gene therapy, it is sometimes important to make a distinction between ethical issues raised by:

- gene therapy research, and
- gene therapy.

In the former case, special problems of research ethics arise. In the latter, social aspects of the use of gene therapy are of central importance.

In an ethical discussion, it is also important to distinguish different kinds of gene therapy. In the 1980s LeRoy Walters suggested a classification that has become very commonly used (Walters, 1986). He made a distinction between the following kinds of genetic modification:

- (1) somatic cell gene therapy,
- (2) germline gene therapy,
- (3) somatic cell genetic enhancement, and
- (4) germline genetic enhancement.

Research on somatic cell gene therapy is presently the only kind that is carried out by scientists, and it is not particularly disputed. The other kinds of genetic modification, however, are all, as indicated above, very controversial.

The classification is now being challenged. The distinction between somatic cell gene therapy and germline gene therapy is not completely strict. Somatic cell gene therapy might sometimes have unintended effects on the germline. Moreover, the

line between therapy and enhancement is even more fuzzy. Should disease-related enhancement, e.g. improvement of the immune system above normal, be classified as enhancement or as therapy?

Recently, a supplement to the classification has also been suggested. It has often been presupposed that genetic interventions are limited to the nuclear genome. Given recent advances in genetics, however, the mitochondrial genome and diseases must be considered as well. This adds a new dimension to both somatic gene therapy and germline gene therapy (Richter, Bacchetta, 1998, pp. 304-306).

It might be disputed whether all these distinctions are ethically relevant. But it is quite clear that they are useful to keep in mind in any debate on gene therapy and its ethical implications, at least in order to understand the debate as such.

Somatic Cell Gene Therapy Research: Ethically Problematic?

How one judges somatic gene therapy depends to some extent on which prototypical cases one starts from. If somatic therapy is used as a prototypical case, somatic gene therapy appears to provide just certain new methods, not something radically different. Somatic gene therapy is viewed like any other somatic therapy, although the treatment is targeting diseases at a more fundamental level than ordinary treatment.

If, on the other hand, the natural order in terms of an unmodified genome is used as a prototypical case, then somatic gene therapy raises qualitatively new ethical problems. Proponents of this view may argue that the genome is such a fundamental part of the human person that any genetic intervention will affect the essence of what it is to be human. Other treatments only affect the phenotypic expression of the genome. Somatic gene therapy affects the genotype itself.

I am critical of this latter view but its prevalence among the general public makes it necessary to discuss the ethical acceptability of somatic gene therapy in itself. Another reason is certain events during the last couple of years that have made somatic gene therapy research controversial in a way that it never was during the previous decade. I am thinking of the deaths of people participating in somatic gene therapy trials.

Dead Patients and Failures to Report Adverse Events

In September 1999, Jesse Gelsinger, an 18-year-old patient participating in an adenoviral vector gene transfer clinical protocol at the Pennsylvania University, died. His death was not a result of his underlying condition, but seemingly due to an immunological reaction as a direct result of administration of a gene transfer product. Since this kind of research started in 1990, this is presumed to be the first

death directly related to the gene transfer itself.³ Since the Gelsinger case, however, there has also occurred another death of a patient participating in a somatic gene therapy trial, this time at Tufts University. Several other failures to report adverse events have also been disclosed.⁴

All this has made somatic gene therapy controversial to an extent it never was before. Even people who have previously been very positive to somatic gene therapy have been forced to at least rethink the issue. It is vital that responsible geneticists take this new situation seriously.

Moral Imagination: Arguments in Favor of and Against Somatic Cell Gene Therapy

So, is somatic gene therapy ethically acceptable? Can responsible geneticists carry out somatic gene therapy research? At the very least, before they do such research, they should use their moral imagination and take into account different viewpoints and arguments. I shall present the most important arguments in favor of as well as against, although rather briefly. Some recur in a slightly different form in the discussion about germline gene therapy and I shall analyze and discuss them more extensively in that context.⁵ In my analysis I shall not distinguish between research on and use of somatic gene therapy. I shall simply assume that the arguments would be the same. As a contribution to dialogue, I shall also briefly comment on each argument. In order to facilitate ethical reflection, the presentation will be rather systematic.

There are basically two kinds of ethical arguments in favor of somatic gene therapy. They are based on the principles of beneficence and autonomy, respectively. The argument based on the principle of beneficence stresses the medical benefits of somatic gene therapy. A central goal of health care is to fight disease. Somatic gene therapy is a new way of doing this. Moreover, it could be one important way of bridging the 'therapeutic gap'. In my opinion, this argument is completely acceptable.

Other arguments are based on the principle of respect for autonomy. One argument stresses the autonomy of the scientists. Scientists should be free to do whatever research they want including research on somatic gene therapy. Scientific freedom is an important value and restrictions of this freedom will have negative effects. Another argument focuses on patient autonomy. If patients or the parents of ill children, request somatic gene therapy it should be provided given that there are sufficient resources. Another argument stresses the respect for reproductive autonomy. If prospective parents request somatic gene therapy on their fetus, this should also be provided on the same condition.

³ *Teen Dies Undergoing Experimental Gene Therapy*, Washington Post, September 29, 1999, p. A01. See also URL: www.nih.gov/about/director/07122000.htm.

⁴ *Gene Researchers Admit Mistakes, Deny Liability*, Washington Post, February 15, 2000, p. A03.

⁵ A recent overview of the arguments can be found in Holtug, 1997.

The argument from scientific autonomy is not acceptable in itself. I have already discussed the question of scientific freedom in general. There should be some ethical restrictions on the choice of subject in scientific research. This does not mean, however, that somatic gene therapy research should not be conducted. It only means that this has to be justified by other arguments than one referring to scientific freedom. The other arguments from autonomy, however, are quite acceptable.

If we turn to the arguments against somatic gene therapy, they can be classified into three categories. The first includes arguments from respect for integrity. Some argue that the genome is such a fundamental part of the human person that any genetic intervention will affect the essence of what it is to be human. Other therapies affect only the phenotypic expression of the genome. Somatic gene therapy affects the genotype itself. This means that somatic gene therapy violates the integrity of the genome and thereby the integrity of the person. Sometimes this kind of argument is articulated in terms of 'playing God'. Humans are doing what only God should be doing. Another version talks about violating 'natural order'. The natural state of the human genome should not be tampered with.

These arguments from integrity are all open to serious objections. One general problem is that they seem to presuppose certain life views that are not generally shared. If you do not share these life views, they hold little weight. This in turn makes them less appropriate as a basis for the professional policy of the geneticists. However, I will not deal with these arguments right now. I will discuss them extensively in the section about germline gene therapy. In my opinion, they are not tenable as arguments against somatic gene therapy research.

The second category of arguments against somatic gene therapy includes arguments from the principle of nonmaleficence. They stress the unknown risks of somatic gene therapy. The specific risks of somatic gene therapy are of at least two types. Some arguments focus on scientific uncertainty and clinical risks, other arguments on social risks. Somatic gene therapy research will by necessity be surrounded by great scientific uncertainty due to its experimental nature. Moreover, there might be certain clinical risks. The transferred gene might be abnormally expressed leading to toxicity. Viral vectors might lead to infections. Cancers might emerge. These arguments should be taken very seriously as illustrated by the death of Jesse Gelsinger. It is clear that no scientist should carry out somatic gene therapy research without sufficient safety precautions. However, if the clinical risks can be expected to be minor, somatic gene therapy should be allowed. This is something that the principle of beneficence demands.

Other objections focus on social risks and slippery slopes. Somatic gene therapy in analogy with genetic testing and screening might lead to discrimination and stigmatization of persons who continue to live with diseases or disabilities that are subject to intervention with somatic gene therapy. Their human value might be reduced by such intervention, or at least they might feel so, which is bad enough. In this way somatic gene therapy might reinforce existent social discrimination of

Responsible Genetics

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