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Report on Human Gene Therapy

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I. INTRODUCTION

1. This Report on genetic therapy was prepared on behalf of a Subcommittee established by the International Bioethics Committee (IBC) for the full Committee's use at its September 1994 meeting. The Subcommittee's members are listed in annex B. The Subcommittee's two Rapporteurs, Professor H. Edgar and Professor Th. Tursz freely used (without formal attributions) written contributions and suggestions made by members. The Rapporteurs also deliberated with their colleagues on the Bureau of the IBC to focus the Report on the issues most relevant to UNESCO and its mission.

The Report in draft was extensively discussed in September 1994 by both the Gene Therapy Subcommittee and by the full membership of the IBC. This Final Report incorporates the changes suggested.

2. UNESCO's central mission includes the promotion of science and science education throughout the world. Informing people about genetic discoveries is an important challenge and responsibility. These discoveries will shape how future humans think about themselves in relation to the world around them. In addition, the information will have intensely practical consequences. It will lead, through the interrelationship of science with technology, and technology with practice, to major changes in medical diagnosis and treatment.

UNESCO is also an institution concerned with securing to all the peoples of the world fair participation in the benefits that flow from scientific and technical advances. How will that be accomplished with technologies such as gene therapy? The claim to share the benefits from genetic information is a particularly strong one. The "Genome Project" will be maximally successful to the extent that it can study effectively the variability of human genetic makeup around the world. Many of the important advances will result from comparisons - asking what genetic factors differentiate this group from that one - when two groups are observed to differ strikingly in susceptibility to particular diseases. The wider the participation, the greater the prospect of discovery. When all may contribute, all should share. These are claims that UNESCO has a special voice in pressing.

Many in the developing world, however, look on the Genome Project with conflicted views, particularly that aspect that contemplates genetic therapies. Is it right to devote so many resources to therapies that are likely to be so expensive? Is doing so consistent with national obligations to protect the basic rights declared at Alma-Ata? Is it plausible that genetic therapies will be affordable by any but the wealthiest societies? Will they help many people? Are there relationships between these technologies and other technologies so that public health may be more broadly secured? The Subcommittee believes the answer to all these questions is yes.

Finally, UNESCO is an institution with a special role in promoting human rights. There is a widespread realization that genetic information and its manipulation pose special dangers to human rights. That understanding is the crystallization of too much unhappy human experience with ideologies that used genetic or purported genetic criteria to celebrate some persons, and deny to others their full human dignity. In the late 20th century, claims that one person's genes are better than another's are sure to ignite conflict.

3. These considerations require attention to the value issues raised by the Human Genome Project as a general matter, and gene therapy in particular. This branch of genetic engineering is developing rapidly, in both government-sponsored and commercial research settings around the world. The justification for its development is compelling, namely the relief of human suffering through remediation of disease. And yet the technology itself, and the theoretical limits of what can be done, are a function of scientific and engineering principles, and not of social constructs such as what makes a condition a disease, and what constitutes permissible therapy for it. Indeed, the very term "human gene therapy" selects out for analysis presumptively beneficial procedures. Its use threatens to obscure the shared premise - with which all members of the Subcommittee agree - that the benefits for those who suffer, and the principles of free scientific inquiry, make appropriate the development of the technology, even as we recognize the risk that national and international social and legal institutions may prove inadequate to control fully its future misuse if, as, and when scientists overcome the many technical barriers that limit it.

4. The technology of genetic interventions may ultimately permit humans to direct evolution by choosing the traits and heightening the capacities they wish to engineer into the young. For this Subcommittee, any such pervasive engineering would violate fundamental rights of individuals so constructed.

From the standpoint of the bench scientist, struggling to secure transduction of human cells and stable long-term expression of proteins by the cells so treated, claims to such future omnipotence must seem far-fetched indeed. There are some who argue that serious discussion of such notational cases is a mistake, arousing popular fears and misjudgements of present issues for no good end. There may prove absolute barriers to engineering propensity for complex behaviors, all of which are environmentally mediated. The propensity to genetic reductionism is a great risk of the Genome Project, and we may unwillingly support it by premature discussion of a remote and improbable future.

In thinking about the pace of development of gene technology, however, we do well to recall that Watson and Crick's elucidation of the DNA model is barely 40 years old. The scientific advances since then have come at a breathtaking rate. The pace of advance will accelerate, not slacken.

II. DEFINITIONS

1. This Report assumes the reader's knowledge of the rudiments of reproductive biology, genetics, cell biology and protein synthesis. DNA is, of course, central to it.

We define human gene therapy as the deliberate alteration of the genetic material of living cells to prevent or treat disease.

We define somatic cell gene therapies as procedures that alter the DNA of the body's differentiated cells, that is cells that lack capacity to transmit genetic material to children.

We define germline gene interventions as those that change the DNA of reproductive cells.

We define and use the term genetic technology to denote the full set of scientific and industrial procedures for understanding and manipulating any organism's genetic characteristics and the expression of those characteristics.

Although our definitions are entirely conventional ones, there are a number of important points to make about them.

2. The term human gene therapy came into use because it identified as presumptively beneficent, through the use of the word therapy, technologies that might have provoked more opposition if called human genetic engineering. Particularly in the 1970s, when any development of any means for altering the genetic capacity of human cells was hotly debated and bitterly opposed by some, the question, if asked, “What are the good uses of human genetic engineering?” might have produced a response, “None”. Human gene therapy sounds benign by contrast.

Relying on the term therapy to distinguish desirable ends from undesired ones is problematic for familiar reasons, and particularly so in an international and cross-cultural context. Therapy is a complex socially-constructed idea which has no necessary linkage to any universally-agreed upon concept of disease. The point may be illustrated by differences between societies, and the same society at different times, at whether and to what extent infertility is and was regarded as a medical problem as against a personal condition.

Thus, this Report, like every previous report and statement we know about, and there have been at least 25, approves of somatic cell gene therapy to treat diseases, and disapproves germline interventions where the goal is to enhance human traits. Nonetheless, our language may hide the fact that the interested community has no shared understanding of how to distinguish therapy and enhancement. The implications of that uncertainty, as it applies to somatic cell therapy and germline interventions may be postponed for later discussion, save only to note that similar issues cloud use of other gene technologies. For example, under what circumstances, if any, is it therapy to administer human growth hormone to a short child whose parents wish him taller? The problem is with the words "therapy", and "disease", and not with whether genes make the chemical at issue outside or inside the body.

3. The sole novelty in this Report, compared to the many other excellent reports and analyses that have been prepared about gene therapy, is its focus on the fact that somatic cell gene therapy - if it works well enough to be much used at all, for there are many barriers still to be overcome - will be much more frequently used to treat conditions such as cancer and HIV-infection, rather than the inherited single gene disorders around which so much of the early discussion of gene therapy has focused. The Rapporteurs believe the technical barriers will ultimately be overcome, and that gene therapy will be practised widely.

Gene therapy is a broadly enabling technology. Research physicians have barely begun to scratch the surface of its plausible uses. Ironically, the better gene therapy works, the faster memory will fade that it started as therapy for genetic defects. Ultimately, we may need measures and pressures to ensure that victims of rare disease are not left therapeutic orphans once again, while the technology-revolution their suffering launched serves as a platform for treating more common health problems.

4. Our Report could, of course, maintain the focus on genetic disease as traditionally understood by simply defining human gene therapy as therapy directed at such problems. Yet the principal bioethics sources do not define gene therapy that way [see, e.g. the Clothier Commission (1992), the Declaration of Inuyama (1991), the Declaration of Bilbao (1993)]. Like us, those reports define genetic therapy in terms of intentional manipulation of human DNA. Indeed they make glancing mention of other possible uses of gene therapy. The bioethics literature, nonetheless, focuses almost exclusively on the ethics of treatment of individuals with inherited single gene disorders.

This preoccupation is understandable in historical context. The scientists who developed gene therapy procedures sought therapies for these genetic diseases (although they mentioned wide uses from the start) (Anderson & Fletcher, 1980). The ethics discussion responded to them and their work. Moreover, gene therapy seemed like the only possible therapy for many genetic diseases. Perhaps for that reason, a protocol aimed at a then untreatable single gene disorder in children, ADA deficiency, helped overcome whatever hostility might have existed to intervention on human genes. Cancer and AIDS, by contrast, however difficult they may be to cure, have no shortage of enthusiasts for therapeutic approaches that do not involve gene therapy. Moreover, these are not as interesting paradigm cases for bioethicists. For bioethicists, the focus on genetic disease brought to center stage the important problem of labeling genetic conditions as good or bad, and the issues of germline enhancement that captivate and trouble the world.

5. Does it matter whether gene therapy's future includes so much besides genetic disease? Yes and no. Certainly, the central bioethics issues do not change. There is universal consensus that somatic cell gene therapy should be regulated like other experimental therapies. If our prediction proves true, and genetically transformed cells increasingly are used like other drugs, such developments will simply serve to emphasize the appropriateness of treating these therapies like other experiments.

But, we think, many issues will be seen in a different light, particularly with the advent of techniques for eliminating genetically transformed cells by activating so-called "suicide genes" inserted along with the therapeutic gene.

First, ethics committees have set up rules for analyzing gene therapy protocols' cost and benefits that build on a model of life-time treatment of children. Is that still the right model?

Second, enabling technologies lead to spin-off developments in many related fields of practice. The question whether social investments in gene therapy may be squared with justice in distribution of resources may appear in a different light when one realizes the breadth of applications, and the usefulness of standardized means for controlling gene expression in agricultural and even industrial settings.

Third, the fact that genetic technology is involved should not categorically resolve the issue whether such technologies may be used on somatic cells for purposes other than treating serious disease. Such interventions may at some future time be performed for the same reasons that now justify drug therapy.

One final point has particular relevance for UNESCO. If gene therapy is an enabling technology, then research institutes all around the world will want to use it sooner rather than later, each competing for applications others may have overlooked, or for uses particularly important in their own medical environment. How can the complex rules for safely working with the viruses and vectors that underlie the technology be effectively integrated into international practice? The issue is not only one of getting formal adherence to treaty provisions requiring national rules on the safe handling of genetically altered organisms; it also requires education and sponsored cooperation across scientific cultures.

6. The Report does not treat the ethics of *in vitro* fertilization followed by genetic testing and selective embryo implantation, or simply screening and selective abortion, because these procedures are not human gene therapy as we define it. For reasons discussed later, however, the availability of such procedures, however controversial they may be, sharply circumscribes the need and role for germline gene interventions.

III. TECHNOLOGIES AND APPLICATIONS

Gene Insertion

1. Successful gene therapy requires altering DNA in human cells. In theory, this alteration may be accomplished by "repairing" DNA already present within the cell, or by taking out a DNA sequence that does not code properly and replacing it with one that does. At present, no such precise interventions are possible.

All current gene therapy approaches add new genetic material to that already present within the cell. Such approaches require first getting novel DNA sequences into cells, and second getting the cells thus altered actually to make (or "express") the desired protein in a manner appropriate for the therapeutic need. The machinery must then work for a long enough period of time to make it useful.

The technologies for gene insertion can be divided into those that rely upon viral mechanisms, and those that rely on chemical means or on direct physical insertion of DNA.

To date, the great majority of researchers have sought to insert genes into human cells by relying upon genetically altered viruses. The approach takes advantage of the "evolutionary selection of the host-virus relation" (Kotin, 1994). In other words, the shell of the virus has been shaped by evolution so that it both gets past the barrier of the cell's outer membrane, and enlists the cell in making viral protein without immediately killing the cell. (If it cannot do that, it would not be a successful virus.) Therefore, by replacing part of the viral genes inside the shell with human ones, or otherwise engineering the virus to carry them, the therapeutic package can pass into the cell, and potentially take advantage of nature's engineering.

Among the different viral vector systems that have been or are under investigation are those that start with retroviruses, adenoviruses, adeno-associated virus, parvovirus, herpes simplex virus, hepatitis virus and vaccinia virus.

We briefly discuss two of the most popular viral vectors, retroviruses and adenoviruses. To date, retroviral vectors have been the technology most frequently employed. The starting virus is a mouse retrovirus. The advantage of retroviruses is that they integrate into the cell's DNA through reverse transcription. Thus the transformed viral vector sequences become part of the genome of the cell which they infect. These sequences are then replicated when the cell divides, and are present, in theory, to continue producing the novel protein in the next generation of cells.

The disadvantage is that these retroviruses can only infect dividing cells, such as blood cell progenitors and cancer cells. If the cells of interest do not divide, and cannot be made to divide, or do so very rarely, then retroviral vectors will not work for therapeutic purposes.

a. Retroviral vectors raise at least three types of safety issues, each of which has been extensively researched. Many viruses, retroviruses included, may potentially be hazardous in their "wild" state. In the United States and Europe, rules and recommendations about laboratory procedures have been worked out and are widely followed. Their goal is to

assure that transformation is accomplished without inappropriate risk to laboratory workers or through inadvertent release to the environment. Yet, no rules are obeyed all the time; people will make mistakes. For that reason assessments have been done about the harm likely in the event of an accident, and they suggest dangers not substantially greater than, if exceeding at all, other risks that are traditionally taken in working with viruses and other dangerous substances in the laboratory.

Second, in producing vectors for human use, care must be taken that there is no contamination of production with "replication competent retrovirus". The transformed virus cannot make new virus within the cell because it lacks the genes to do so. But production mishaps can occur, and they must be guarded against.

Third, there is no present ability when using retroviral vectors to control where in the cellular genome the virus integrates. In theory, the new sequences could integrate in a way that disrupts other cellular functions. In all likelihood, the cell thus limited would stop working or work poorly. In procedures where cells are infected (transduced) with the altered virus outside the body (*ex vivo*), the cells where the new gene works are often the only ones that are taken, and grown, and given back to the patient. If some small percentage of treated cells die, there is no problem. There are trillions of cells, and in most organ systems, new ones are constantly made. One may hypothesize, however, remote chances of the integration occurring at a site that triggers cellular oncogenes or turns off tumor suppressing genes in a way that might lead the cell to begin rapid and uncontrolled division. The chance that cancer could be caused by such chance events is reportedly vanishingly small, and there is no evidence to support the prospect even after thousands of experiments in murine systems (Anderson, 1994).

b. Adenoviruses, the most popular alternative, are a set of common viruses. They include, for example, viruses that cause the common cold. Their advantages for gene transfer are that they can be used to infect virtually any human cell. Therefore, cells that do not divide may be transduced. Use of adenovirus has been popular in protocols directed to epithelial cells in patients whose lungs are afflicted by cystic fibrosis. However, the adenoviruses remain in the cell as episomes, meaning that the sequences do not integrate into the genome. Thus, the virus with its novel DNA sequence is eliminated when the cell ultimately divides. Use of adenovirus also presents complex safety issues, particularly the prospect that novel viral sequences contained in engineered cells may recombine, leaving the virus that brought them to the cell, and integrate into ordinary wild-type adenoviruses already present in the cell. If that occurs, the therapeutic genes may be shed into the environment, packaged in a virus that can infect others. The issue was discussed by one of the Rapporteurs, Professor Th. Tursz, in his gene therapy paper presented to the IBC in September 1993.

c. Chemical and physical means for inserting novel DNA structures have been much less thoroughly studied. Genes can be introduced into liposomes, but the transduction efficiency is limited. Direct physical injection of DNA as a plasmid may be accomplished, but so far the approach works only in muscle cells.

d. A sense of the extraordinary complexity and heavy demands for validated safety procedures that those who prepare gene transfer systems for human use must meet may be gained by consulting the document of the United States *Food and Drug Administration* (FDA) "*Points to Consider in Human Somatic Cell Therapy and Gene Therapy*" (1991).

Gene Expression

2. Getting novel DNA sequences into cells is only the first part of the problem. Effective therapy requires that protein be expressed at appropriate levels. In some applications, the cell needs some of it, some of the time. In others, the protein must be passed from the cell into the surrounding bloodstream. Therefore, effective systems to direct gene expression (systems which, of course, are themselves gene sequences) must be included along with a "therapeutic" gene. One possibility is to leave the inserted human gene under the control of the virus's regulatory mechanism. In effect, the virus is enlisted to make the desired human protein, rather than the viral proteins it would have made in its unaltered state. But increasingly the view is that viral promoters do not work well in people, as against in cell cultures. Therefore, finding better ways to obtain operational expression, and on-going control of expression is crucial.

All this complex biological machinery must function not for a few minutes or a day. For therapy to work, it must continue to function over time, and with dividing cells like blood cell progenitors, it must continue to work as cells divide. And if cells that are transduced have a short life until they are replaced by the body's new ones, gene therapy requires repeated re-administration of the therapeutic gene product, at least if treatment of a genetic disease is the goal.

The bioethics literature gives surprising little attention to the need to repeat treatments again and again. Writers discuss somatic cell gene therapy from the perspective of a germline approach; as if administration of the therapy changes this patient forever (but unlike germline interventions, poses risks to no one else). On risk-benefit analysis, such gene therapy is wonderful if the somatic therapy works, but dreadful if there are side-effects, for there is the patient, doomed by changed genes, forever enduring the harm. Yet in most organ systems old cells die and new ones are made, the relevant question being how fast the cells are replaced. Most current experimental somatic cell gene therapy protocols propose treatments that will not keep gene altered cells in the body forever, unless virus somehow migrates from one cell to another, a result that is both unintended and improbable. For example, the ADA-deficient children treated in Anderson's first protocol needed re-administration of altered T-cells at eight week intervals.

Somatic cell gene therapy systems work only so long as the transduced cells either live or give rise to new cells in which the inserted gene is also present. In an experimental model, one can avoid a "lifetime cure" by choosing for transduction cells that die sooner rather than later. Yet, many organ systems have so-called stem cells, master cells that both reproduce themselves, and have the capacity, when triggered by various cell proteins called cytokines (cellular hormones), to differentiate into the full set of cell types that either constitute or do the work of the organ system in question. For example, it is known that blood stem cells are in the bone marrow, and that from these stem cells come red blood cells, platelets, and all the white cells of the immune system. Gene therapy aimed at such stem cells is already underway, for if enough of them can be treated, and if the inserted genes continue to work cell division after cell division, then a true lifetime treatment is possible (much like a bone marrow transplant from a brother to a sister might be considered as a lifetime gene therapy protocol). Yet the task of identifying comparable stem cells for other organ systems, if they exist, for example the liver, or the intestine, and finding ways effectively to transfect enough of them to get lifetime therapy is a monumental one, and barely underway.

These are some of the present research hurdles. To be sure, many plausible and exciting improvements have been announced. For example, it may be possible to package genes for insertion in standard cassettes. These cassettes may include systems for switching genes on and off, and destroying transduced cells by activating implanted "suicide genes" if the patient suffers side-effects or if the cell has completed its mission. Yet, the distance between concept and practical application, experience shows, is a very long one.

Even so, solving these problems is not the kind of is-it-even-plausible-problem that many would argue engineering complex traits in the germline would prove to be.

Gene Therapy Applications

3. Gene therapy protocols are underway in the United States, China, France, United Kingdom, Italy, the Netherlands, and perhaps elsewhere. But the United States has done the greatest number of them. The future of gene therapeutics may be appraised by considering protocols in the planning stage or approved by the United States *Recombinant DNA Advisory Committee* (RAC). The publication edited by one of the principal founders of gene therapy, Dr. W. French Anderson, "*Gene Therapy"* (Mary Ann Liebert, NY), provides particularly useful articles and a window on current practice.

a. The easiest gene therapies to conceptualize are those directed to genetic disease caused by absence or failure of a single gene. The metaphor is cellular repair. Thus, if a hemophiliac's liver cells does not produce the necessary clotting factor, Factor VIII, because they lack the gene that codes for its production, his cells may be engineered so that gene is inserted and expressed, and then those cells transfused back to him. Such single gene

dominant or recessive diseases have been the paradigm for virtually all ethics discussions of somatic cell gene therapy. And, Anderson's protocol for treating children with ADA deficiency with transduced T-cells was the first true gene therapy protocol.

There are more than 4.000 monogenic diseases, but many are very rare. As Baird (1994) notes, such single gene conditions are a small percentage of the total of heritable genetic diseases.

b. The cellular repair metaphor may also be used where cells are producing proteins that are implicated in, or have a causal role in a disease process, such as, for example, occurs in cancer cells. These cells instruct themselves to divide again and again.

There is no present way to remove a particular gene which is producing an unwanted protein, although forms of "genetic surgery" are frequently hypothesized in the literature, and are in research. But already (at the experimental stage, of course) one gene can be controlled by inserting another gene that blocks or neutralizes its unwanted production. A protocol recently approved permits physicians to insert a normal P53 gene (a tumor suppressor gene) into non-small cell lung carcinomas that are P53 defective. The cells are repaired by giving them back the operable P53 gene they had or should have had. The hope is that this new source of P53 will suppress the message that leads to uncontrolled division.

There are, however, near-term prospects for use of "antisense" genes. These RNA sequences are designed so that they make small molecules that will bind to, and thus interrupt, the cell's manufacture of the undesired product of a gene, particularly oncogenes, that is a gene that "turns on" cell division (Anderson, 1994). Here the repair metaphor breaks down. The cell is engineered to make a chemical that no human cell has ever made naturally.

c. There are many illustrations of gene therapy approaches where human cells are given novel properties. For example, cells can be engineered to produce substances that will protect them from viruses. For example, in theory cells so equipped can block integration of the AIDS virus. An alternative approach is to engineer the cell to produce a protein that blocks the AIDS virus' ability to replicate its protein within the cell. As Anderson (1994) notes, viral diseases may be called "acquired" genetic disease.

d. Cells can be engineered to protect against the side-effects of other, entirely conventional, medical therapies. For example, cancer chemotherapy is toxic to bone marrow cells. It cannot be administered at doses as high as might be desirable to kill cancer cells, because the bone marrow cells responsible for producing new blood cells will die. By putting the so-called *multiple drug resistance* (MDR) gene into those bone marrow cells, the cells may gain the capacity they lack in nature to pump out, rather than be destroyed by, chemiotherapeutic toxins. If so, the patient can be given more chemotherapy. A protocol for putting MDR genes into hematopoietic stem cells has been approved.

e. There are many gene therapy proposals for tricking or enhancing immune functions. For example, it may prove desirable to insert foreign or novel histo-compatibility genes into the patient's immune system, in order to induce tolerance to an organ transplant from a person or animal from which the inserted genes come. Similarly (although it would not be human gene therapy as we define the term), there is considerable work underway to engineer animals with human immune genes, so that organs taken from them will not seem foreign to the patient's immune system.

f. Whether protocols intended to stimulate immune responses, so-called cancer vaccine protocols, are properly called gene therapy may be debated. (Indeed, one could call the practice of vaccination with attenuated live virus a form of gene therapy, since the object is to add DNA to the cell.) Genetically transformed cells are used to enhance immune response. One protocol puts a novel gene into cancer cells, so those cells produce an antigen on the cellular surface. The patient's immune cells attack it, and become more sensitized to the other antigens found on that type of cancer cells.

Similarly, it may be possible to stimulate immune system responses by putting genes that make cytokines into the patient's cancer cells. There are many approved protocols following this approach. The hope is that when the cancer cells make immunostimulants, it will trigger heightened immune cell response against the tumor.

g. Cells may be engineered for drug delivery purposes. Such cells will make some therapeutic protein inside the body. (It may be a sensible alternative to manufacturing the drug in a factory, shipping it around the world, and injecting it into the patient.) The cells may be injected at the site where biological activity is desired. The recent arthritis protocol, described presently, is an illustration.

Alternatively, inasmuch as cells "home", through complex trafficking mechanisms, it may prove possible to engineer cells so that they go to the proper site in the body and once there, provide continuous endogenous delivery of a protein drug that could not otherwise be gotten there without unacceptable side-effects.

h. Finally, gene therapy approaches may successfully treat disease simply by inserting "suicide genes" into target cells of interest. While it is not a particularly good metaphor for the genes, others use it, so this Report does too. Introduction into gene therapy systems of such genes is important practically and conceptually. For example, cells transduced with the herpes simplex thymidine kinase gene die when treated with *gancyclovir*, a drug already available on the market. One possible therapeutic use is to treat brain tumors. Brain cells do not ordinarily divide, and any cells that are dividing in the brain are presumptively tumor cells. If the viral gene insertion system infects only dividing brain cells, the tumor cells may be targeted and destroyed.

The therapeutic possibilities of "suicide gene" are extensive inasmuch as there is apparently a substantial "bystander" effect when cells die. In other words, if cell A dies, there is a heightened probability that cell B next to it will die too. If you can get A to the desired place next to tumor cell B, with a suicide gene in place, A's death may cause B's death, and B's death C's and so on.

Finally, and most importantly for regulatory, cost-benefit purposes, "suicide genes" may be considered a simple "off" switch. Put the cells in, and when they are no longer needed, eliminate them by administration of a molecule that triggers the gene. The gene therapy metaphor is no longer necessarily (or even ideally) one of a do-we-dare-risk-it, once-in-a-lifetime-treatment, of a person who will never be the same again. It is a drug whose half-life can be rather well controlled.

Successful applications of all these approaches are, of course, for future proof. There is not one of them that is certain to work, let alone ready to use. Enough has been said, however, to make it plain that on a technical level there is vast potential for somatic gene therapy in contexts remote from genetic disease. The techniques may be plausibly tried, at minimum, in blood diseases, cancer, cardiovascular diseases, pulmonary diseases, liver diseases, dermatological diseases, and infectious diseases. And the era of active gene therapy is less than five years old.

What is Gene Therapy Used For?

4. The conclusion that gene therapy will be most frequently used for treatments other than conventional monogenic disease leaps out from the present evidence and trends. The scientific barriers that remain confirm that view, as do the market-size issues that will shape commercial work.

a. Present Uses. As of mid-1994, there were 74 approved gene therapy protocols world-wide. Of these, only 16 concern conventional monogenic diseases (Anderson, 1994). The majority of the 58 are cancer and cancer-related protocols. The nomenclature is tricky here, because cancer is a genetic disease, and HIV is an acquired genetic disease, and the whole premise of the Human Genome Project is that many diseases not thought of as genetic may be better understood and managed by understanding what happens at the genetic level. However, from the standpoint of the bioethics discussion of gene therapy, there is no question that the focus has been almost exclusively on monogenic inherited diseases. The bioethics debate has focused on the tip while ignoring the iceberg.

The focus of contemporary United States work may be gained by review of the protocols approved at the June 1994 meeting of the *National Institutes of Health* (NIH)-RAC, as reported in the industry newsletter *Biotechnology Newswatch* of June 20 1994:

i) transfer of the gene for the interleukin-1 reception antagonist, *ex vivo*, into tissue from the synovium joints of patients suffering from rheumatoid arthritis, with re-implantation to the knuckle joints prior to their scheduled surgical replacement. The modified cells will also be transduced with a "suicide gene", so that they may be eliminated by administration of a drug if there are any observed toxicities.

ii) Direct injection of plasmid DNA incorporating the gene for carcino-embryonic antigen into the muscle tissue of 15 patients with metastic colorectal cancer.

iii) A marking protocol designed to test whether tumor infiltrating lymphocytes concentrate at metastic tumor sites (with Neo).

iv) A marking protocol to test whether bone marrow stem cells reconstitute the hematopoietic system at the same rate, more quickly, or slower, if they have been treated with so-called growth factors, that is cytokines that prompt blood cells to differentiate into particular lines like the various types of white cells (with Neo).

v) A "cancer vaccine" protocol to transduce glioblastoma cells with genes that express cytokines to stimulate an immune response against the tumor (with IL-2).

vi) A cancer vaccine protocol introducing IL-12 sub-unit genes (P35 and P40) *ex vivo* into the patient's fibroblast cells, which will then be injected into the tumor in the hope of both a direct anti-tumor effect, and an immune stimulatory response.

vii) A protocol putting multiple drug resistance genes into peripheral blood mononuclear cells of patients with breast cancer.

viii) A protocol to administer wild-type P53 tumor suppressor genes via an adenovirus vector injected into the tumor, with subsequent use of chemiotherapeutic agents to finish the cells off.

ix) A protocol for inserting a normal gene into blood stem cells that is missing in patients with Fanconi anemia, a rare inherited disorder.

[Cancer: 7; auto-immune disease: 1; monogenic disease: 1.]

b. Scientific Issues. The relative prevalence of one kind of protocol as against another says nothing about the probabilities that gene therapy will soon be widely exploited to treat the many single gene diseases. But the slower pace of development has a grounding in the engineering complexities. To treat many of the single gene disorders, there has to be sufficient control of gene expression to assure that cells produce the proper amount of protein when it is needed over a sustained period of time. Treatment for the individual's entire life is contemplated, and for many of the diseases, treatment must be initiated in childhood, or else the disease will have already caused irreparable damage. By contrast, if cells are engineered that can simply be injected into a particular site, deliver drugs there, and then be ignored or eliminated by giving a drug, one need not solve the whole problem in one step. And there are many therapeutic opportunities that can be modeled this way. Perhaps the most widely reported recent United States development was that gene therapy, in an animal study, worked to control the proliferation of smooth muscle cells following arterial injury of the kind commonly caused by balloon angioplasty. Transduced cells (equipped with a suicide gene), produced a drug that blocked the proteins that cause the rapid healing of the artery, a healing so rapid that blocks of excess cells formed that closed the artery down. A new treatment for restenonis, a "*huge clinical and economic problem*" given the frequency of clogged arteries, and angioplasty to treat it, may be on the way (*Gene Therapy for Clogged Arteries Passes the Test in Pigs*, Science 265: 738, August 1994).

c. Market Functions. The conclusion is further strengthened by considering the economic issues. Gene therapy started in the public sector, but has increasingly become the focus of intense effort by biotechnology firms, large and small. They are competing to employ the available public sector and academic talent. Firms characteristically seek larger rather than smaller markets, and they do so even when pursuing genetic disease. Interestingly, 8 of the 16 approved protocols directed to heritable genetic diseases concerned cystic fibrosis, the most common serious genetic disorder among Caucasians. Gene therapy will be used for genetic disease, but it is a mistake to make it the paradigm case.

IV. ETHICAL ANALYSIS

1. The IBC has many potential tasks, from providing information to suggesting principles for international legal recognition. In its ethics evaluative role, it must suggest ethical principles that are grounded in universal ideas even as it takes account of the happy diversity of cultural and religious traditions that co-exist in the world.

The principles and materials of international human rights law may yield a rich supply of doctrines for evaluating what should be done in discrete bioethics cases. An interesting recent Report, "*The Promotion of Human Rights in the Life and Health Sciences, Recommendations to the United Nations*", organized by Audrey Chapman, contains suggestive discussions of this point. Human rights law contains provisions that are analogous to the principles that flow from analysis of moral obligations implicit in doctor-patient relationships, which is the starting point, for example, of much of the Anglo-American bioethics literature, as well as the bioethics traditions in other communities. Moreover, and happily these various traditions converge in their treatment of experimental medicine, our principal field where there is substantial consensus on the questions to ask, and the procedures to follow.

In appraising gene therapy, these principles, at minimum, must be taken account of, and built upon. Each is drawn from international instruments:

1. the respect for human dignity and worth;
2. the right to equality before the law;
3. the protection of rights of vulnerable individuals;
4. the right not to be subjected without free consent to medical or scientific experimentation;
5. the right to the highest attainable standard of physical and mental health and associated rights to health care;
6. the right to protection against arbitrary interference with privacy or with the family;
7. the right to enjoy the benefits of scientific progress and its application; and,
8. the right to freedom for scientific research.

Inasmuch as all present gene therapy constitutes medical and scientific experimentation, (and a rather extreme form of it), the right "*not to be subjected without free consent*" to it is guaranteed. "Free" consent implies informed consent, with no coercion. The duties imposed on researchers and procedures for implementing them have been spelled out in other internationally significant documents. The Nuremberg Code was the foundation. That Code was formulated in the unusual context of the international war crimes trial, for purposes of stating the internationally-recognized principles that might permit researchers to engage in conduct that would otherwise be a violation of subjects' rights (and indeed, where injury was risked or caused, a serious crime). The Declaration of Helsinki, prepared by the World Medical Association, derived from and builds on the Nuremberg Code. In turn, the World Health Organization (WHO) and the Council for International Organizations of Medical Science (CIOMS) based their influential "*International Guidelines for Biomedical Research Involving Human Subjects*" on the Helsinki Declaration. The guidelines' purpose is to indicate how fundamental ethical principles should guide the conduct of biomedical research involving human subjects. In its most recent version (CIOMS/WHO, 1993), one finds as "general ethical principles", the proposition that:

> "*all research involving human subjects should be conducted in accordance with three basic ethical principles, namely respect for persons, beneficence and justice*".

This is precisely the language of the Anglo-American tradition with respect to human experiments, stressing principles of autonomy, cost-benefit analysis, and justice in distribution of benefit and risk.

Application to Somatic Cell Therapy

2. So far as we know, there has been no committee anywhere that has recommended outright prohibitions of all somatic cell gene therapy. The excellent 1982 Report "*Splicing Life*" (*United States Presidential Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research*) laid the groundwork for world-wide recognition that the ethical problems presented by such therapies are not fundamentally different from those presented by other research techniques. All members of the Subcommittee concur.

Contrary arguments, we believe, would have to be based on claims that:

a) there is an impermissible high chance of accidents causing large destruction to persons, property or the environment that will ultimately occur through accidental release of viral or other materials;

b) accidents in somatic cell therapy sooner or later will result in the alteration of germline cells; or,

c) the creation of somatic therapies puts us on the slippery slope to wrongful germline interventions, slope which we cannot hold.

The first argument has echoes in debates about the construction of nuclear power plants. We believe the premise wrong, even on the assumption accidents may happen. Furthermore, to accept the argument would imply the impermissibility of the full range of genetic technologies, technologies that will have major impact in world economic life. The prohibitions that would flow from accepting this risk argument are not limited (if it be thought a limit) to treatments of ill people.

As to the second argument, researchers cannot rule out or depreciate the prospect that some mishap may alter someone's germline cells, particularly as techniques to administer gene insertion *in vivo* are developed. Is the possible accidental alteration of a germline cell a basis for total prohibition of all somatic cell gene therapy? We think not.

Risks may and must be minimized by maintaining a constant focus on safety. But more important, the human genome is by no means stable. It constantly changes through mutation, including many mutations that result from human activities. Most mutations, of course, are selected against. They fail to survive. The same would be true with these kinds of accidents.

The slippery slope argument, by contrast, is itself an argument without stopping point. It would lead to bans on airplanes because they might be used to drop bombs (Sass, 1988). If people believe maintaining sharp boundaries against germline intervention is important, we think social, legal and professional standards will hold the line adequately, particularly given the technical challenges such interventions would have to overcome.

These possible arguments against somatic cell therapy do not respect adequately rights to freedom in scientific research, the duty to protect the vulnerable, and the rights to enjoy the benefits of scientific progress.

Ethical Oversight of Somatic Cell Therapy

3. The principal problems in somatic cell therapy involve adequate supervision both of the safety of research practices in the laboratory, and of the decision to initiate humans trials and the methods for securing full information from them.

We will not rehearse discussions elsewhere (e.g. Clothier Commission 1992) about the kinds of detailed knowledge and preparation that should be required before approving vectors and genes for clinical trials. From any ethical standpoint we know about, the central responsibility is to maximize the gains and minimize the risks, and ultimately decide whether or not the benefits realistically to be gained make legitimate asking others to run the risks involved (Ivanov, 1993).

Three points about this process are worth mentioning, because they flow from our belief that gene therapy will prove to be a broadly enabling technology. First, if we are right, new possibilities for its use will be hypothesized constantly. The desire to use the technology may not coexist with the knowledge of how to do it safely. The international community has a strong interest in facilitating transfer of appropriate assistance to maintain safety standards.

Second, periods of sudden enthusiasm for new medical technologies put pressure on the preservation of human rights in medical research. Physicians should not hastily adopt techniques without adequate preparation. Research protocols need interdisciplinary review with particular diligence, and a careful impartial weighing of risks and benefits. Experimental subjects need both full and fair explanation of the procedures, and honest information about the relative balance between research interest and therapeutic prospects. In particular, consent submissions that inform a patient "*this may benefit you*" - without disclosing realistically the many uncertainties, and the improbabilities of having solved all the technical barriers on the first try - should be avoided.

Third, discussions of consent to somatic cell therapy experiments in the literature seem driven, and driven to excess given the technology's present use, by models of experimenting on children with genetic disease. In such settings, of course, the requirements of prior proof of principle and realistic likelihood of success are maximal. A lifetime of treatment is contemplated in a person who cannot yet speak adequately for his or her own interests. But one should not fasten on adults who suffer genetic disease impossibly high standards for protocol initiation. As the influential Clothier Commission noted, we may foresee cases of terminally ill adults consenting to gene therapy research, recognizing its probable lack of direct therapeutic benefit. That model has long characterized cancer research (and perhaps too much so), but its prevalence may explain the relative ease of securing cancer protocol approvals.

The basic approach should be: the more that genetic therapy becomes like any other therapy, the more research review should be assimilated to conventional procedures when the techniques of gene insertion are standard ones. This process is underway in the United States, with the absorption of the *Human Gene Therapy Review Committee* into the parent *Recombinant DNA Advisory Committee*; the readiness by the RAC to permit "compassionate use" of gene therapy protocols, and the recent proposal and tentative agreement for FDA to take over from RAC, review of gene therapy proposals presenting no novel issues. The first gene therapy protocol, Anderson's 1989 ADA experiment, was reviewed 15 times by 7 different regulatory bodies. A mere five years later many protocols can be approved on a standard FDA review.

Fair Distribution of Resources

4. If we are correct that gene therapy has a chance to be an enabling technology, with widespread uses, the oft-expressed concern that the economically developed world is spending its medical resources wastefully in developing them is misguided.

It is true, of course, that the first uses of any complex technology are extraordinarily expensive to provide. It costs hundreds of millions of ECU's, yen, or dollars to engineer a new automobile or generation of computer chip. Gene therapy is every bit as complex. With all technologies, however, costs drop the more widespread the use. Moreover, improvements in strategy and design may sharply reduce cost through improvement in product. Computers more powerful than any that existed in the world in 1960 now sell in the Developed World as commodity goods, available by mail order delivery only. It is not likely that gene therapies will be subject to comparable reductions in costs based upon scale of production, but there is no reason to suppose they will necessarily increase the total social costs spent on grappling with the diseases they are used to treat. Moreover, if one thinks of improvement in vaccines, both engineering new ones and making old ones work better, as a form of gene therapy, then the opposite is true.

More importantly, the study of gene processes, and the switching and controls that are necessary for therapeutic approaches will have wide application to control of biological processes in other settings, from agriculture to industry. "*Nature is lazy*" is a phrase that suggests how often researchers find that biological processes in one system are but adaptations of the way many systems work. The reason, of course, is that they all descend from DNA's experience in making more DNA. There is essential unity in all of life.

These observations say nothing, however, about whether and to what extent gene therapy applications most relevant in the developing world can be practised there at reasonable expense, within a reasonable time.

Somatic Cell Therapies and the Problem of Enhancement Engineering

5. Recent gene therapy discussions insist that somatic cell procedures should be reserved for "serious disease". The Subcommittee concurs in that view because of the highly experimental nature of procedures, and the lack of sufficient experience for determination of the incidence and seriousness of side-effects that accompany various types of cellular alterations.

A cell performs complex chemical processes, through many pathways. It is far too soon for confidence that imposing on it a new "manufacturing" responsibility with energy requirements that must come from somewhere, will not somehow affect the way it (and through action on it, action on other cells) performs other tasks. Second, how stable is transfection? Do inserted genes always stay put or can they recombine and move to other cells, and if so how frequently does this happen and with what effects? It takes thousands of cases and years of experience for confident elimination of all the unhappy possibilities. No responsible ethics committee could at present approve a protocol directed at a disease it did not regard as serious.

What is a serious disease? Despite the diversity of cultures and world views, we believe the international community would reach virtual unanimity on a long list of serious diseases, and that list would include current targets of gene therapy protocols such as cystic fibrosis, ADA deficiency, Fanconi's anemia, cancer and AIDS. Moreover, some kinds of protocols that enhance human performance, for example by putting in genes that protect an individual against serious disease, must be conceptualized as protocols aimed at that serious disease, and not objected to as efforts to improve mere behavioral traits.

The differences of opinion about whether to classify disease as serious will be at the margin, and at the borderline where disease prevention and lifestyle intersect. For example, is a protocol designed to reduce ordinary cholesterol levels aimed at a serious disease, if the serious disease could be avoided by eating less fat? Interestingly, the *Report of the Norwegian Ministry of Health and Social Affairs to the Starting on Biotechnology Related to Human Beings* (1992-93 at 69) accepts the limitation to serious diseases. The Report further notes that by implanting protective genes one may avoid disease, and suggests future "*flexible limits*", such as, for example, "*implanting pigment cells in the skin to avoid sunburn*".

Whether or not there is unanimity about what constitutes a serious disease does not seem to us an important issue in the international context. What matters is whether, within the particular society, the disease is defined as serious, so as to warrant the risks of experimental treatment.

The harder problem is that the "serious disease" limit is obviously used by commentators to avoid the necessity for present discussion of the ethics of using somatic cell gene therapy, at some future time, for purposes of enhancement. Does the serious disease limit rest on moral views about respect for human dignity, or is the prohibition simply that small gains do not warrant big risks? At some point, and measured in years rather than decades, the risk issues will be largely answered with respect to many of the technical aspects of gene therapy, particularly for uses that do not involve long-time maintenance with engineered cells. At that point, should somatic cell gene therapy procedures that are designed to enhance performance in some way or another be regarded categorically as violations of international human rights principles, or other moral values, and, if so, which ones and why?

One must start by noting that the medical model is a very expansive one. Many "conditions" become "diseases", or almost so, if, as and when, physicians develop the capacity to change them. Tooth decay is the "natural" fate of humankind, but we call it a disease and intervene to stop it. If a protein were found that overcame the "natural" loss of memory with age, (perhaps by strengthening CNS links that naturally fray with time, for illustration purposes only) then we would define the memory loss as a disease, and use the protein, and not conceptualize our activity as performance enhancement.

Second, if some kinds of enhancement are wrong, the "wrongness" should not depend on the fact that "gene therapy" is the technology used to accomplish the result.

Somatic gene therapy must be analyzed by the general principles governing the uses and limits of medicine. The time will come when cells can be engineered for endogenous drug delivery, and then eliminated from the body by administering small molecule drugs, engineered to bind to the relevant cellular receptor-site that activates the inserted gene that causes cell death. Somatic cell "enhancement" therapies modeled on the use of such cells must be treated equivalently with whatever rules exist for drug use generally.

The "enhancement" case most frequently discussed in the bioethics literature is whether it is ethical to insert a gene to produce human growth hormone in a short but seemingly otherwise physically normal child. (We say seemingly because the bioethics literature constantly simplifies real world complexities to pose moral arguments more clearly. It is very hard to have assay systems that answer precisely what cells are doing. As just one example, the "normal" growth gene may be working, but some other gene, we know nothing about, may be limiting the protein's effect.)

The correct answer must be that if it is permissible to use the protein when the gene makes it in bacteria, it is permissible to use the gene when it is added to a cell, particularly because cellular administration of the gene may be safer. All gene therapy adds to enhancement as an ethical topic is the possibility that it may expand the range of enhancements possible, if, for example, some proteins require controls of dose, administration in sequence and specificity as to site of action, that could not be obtained by any other manner of administration.

Enhancements are problematic but ubiquitous in human society, from tattoos, to women and men piercing their ears to permit better display of their earrings. Guitarists may intentionally tear ligaments to permit the thumb to cover more frets. "Cosmetic" surgery has its uses and abuses. Social controls are imposed when "enhancements" may pose serious risks to health, and when they are thought unfair to others who are competing in a "game" which is defined so as to make their use an unfair advantage. The use of steroid drugs by athletes to build muscle mass is the common example. And, of course, for many or most societies, the use of public resources for such ends would be thought questionable in light of principles of just distribution.

There is a considerable literature on these topics that often gets pushed to the side as if somatic cell enhancement were a problem of a different sort. We think not. Particular uses of biochemical modulators must be examined against those models, if and when they are proposed.

In short, the Rapporteurs see no need for the International Community to speak out now against possible future misuses of enhancements, without first having a description of their characteristics. The fact that they may use proteins that the body makes itself is not itself sufficient reason to prohibit them.

It may, however, be appropriate to speak out against any possible use of such procedures to diminish human capacities.

Application to Germline Gene Intervention

6. Germline gene intervention (the term we use in preference to germline gene therapy, as "therapy" suggests the germline is somehow ill, which is not the case) has grabbed the world's attention. Imagining a world in which some people - the state, physicians, parents - have authority to select the genetic characteristics of the next generation, choosing chemical constituents to produce desired traits as if they were baking a cake, provides the conjurer with the occasion to reflect on the true nature of individual rights and human dignity.

On the whole, thinking about ultimate values is a good thing. Yet such futures are often described in a way that ignores the moral values that inhere in the complexity and contingency of individual development. Mozart's genes do not guarantee Mozart's talent.

All major statements about germline intervention condemn its present use. That position is clearly correct. That genes can be put into animal germlines, and made to express, does not begin to answer safety issues for human use. Moreover, are there animal models that can predict the impact on the human brain? Enormous technical problems would have to be solved to make the technology realistic in light of the risks, particularly the control of gene

expression throughout the organism's process of cellular differentiation. Moreover, one must have basis for predicting confidently the consequences of novel or altered genetic material in the workings of each and every cell type. So far as we know, there have been no efforts anywhere in the world to attempt germline intervention on human beings.

The prohibition on germline therapy is a matter of formal legislation in some nations (e.g. Sweden) and is accomplished through regulatory controls in many others, for example United Kingdom and the United States. Present prohibition does not deny the possibility of future use. Yet, there are important European documents that condemn germline therapy unequivocally. For example, Recommendation 1100 of the Council of Europe states: "*Any form of therapy on the human germinal line shall be forbidden*". Two important recent reports, the Clothier Commission (1992) and the Declaration of Inuyama (1990), however, do not categorically rule out germline interventions. In the United States, a number of prominent commentators believe that discussion should begin about developing interventions for the germline (Anderson and Fletcher; Wivel and Walters, 1993). Their call for present discussion reflects no disagreement about its present ethical impermissibility. It recognizes that the future policy process for approval will take a long time, and that more discussion now will make it more likely that appropriate policy will be in place in the future when technical capabilities are at hand.

It may be right to debate the ultimate value questions. But those who suggest the desirability of germline therapy have not, the Rapporteurs believe, made a plausible case for any near term substantial use for it, and certainly no case that the gains would be worth the extraordinary efforts required.

Genetic intervention in the germline sounds most attractive as a technology for permitting a couple or individual to spare their descendants the burden of genetic disease. So, for example, a person at risk for a disease caused by a dominant gene might seek the procedure to guarantee that his future children would be free of it. If it is moral, as it surely would be, to remedy his condition by somatic cell gene therapy, why not cure it once and for all by germline techniques? Before considering the moral dilemmas inherent in that question, ask whether it is ethical to risk harm if there is a safer alternative. If one had the knowledge sufficient to attempt a germline intervention in these settings, it seems certain one would know how to accomplish the same end without employing germline techniques.

Treating the adult's cells *in vivo* to remove the gene is a technology not even envisaged. By contrast, sorting sperm (or eggs) using DNA probes to separate those that carry the gene from those that do not falls into the category of not presently feasible. If it could be done, however, one could solve the problem by using "good" sperm and discarding rather than repairing sperm that carried the gene. (Similarly, research - published after this paper was prepared and discussed by the IBC - suggests the possibility of identifying sperm stem cells, and perhaps altering them *ex vivo*, and restoring those grown from cells that were successfully repaired.)

The probable starting point for germline intervention, however, is the human zygote at the four cell stage, fertilized through *in vitro* fertilization. Certainly, that is the only present way to do it. Animal models suggest that gene insertion that will differentiate into every cell is feasible. But if a particular zygote can be identified as carrying (or lacking) the gene, and therefore be appropriate for treatment, why would one try the extraordinary procedure of repair rather than selecting for implantation a zygote that did not have the gene? Such screening procedures are in use, on an experimental basis, in a few hospitals around the world. For example, at a hospital in Israel, procedures for selective screening of zygotes, using so-called PCR technique to test the DNA in one cell of the four-cells was used to screen for cystic fibrosis.

There are many who strongly oppose any selection or discarding of zygotes, and for these persons that opposition is itself a sufficient basis to protest the development of germline interventions. Opposition to selecting zygotes goes hand-in-hand with opposition to non-therapeutic experiments on zygotes that will never be implanted. For example, German law prohibits non-therapeutic experiments on the human zygote. While all acknowledge the special respect owed to the fertilized egg throughout its development, what actions are

required or prohibited by that respect is an issue on which the world community is deeply divided. This Report does not attempt argument on the issue. Obviously, it is crucial for germline interventions.

No human germline interventions can be safely developed, we think, without the opportunity to test whether genes inserted somewhere (sperm, egg, zygote) in fact are replicated appropriately in the first stages of cellular differentiation.

The largest plausible need for germline intervention is to treat affected zygotes, once and for all, on behalf of persons who disapprove of abortion or selective implantation. If safe interventions were developed over their protest, these persons might wish to have the procedure done in preference to selective abortion or implantation, which they believe is immoral. We would think, however, that developing a technology to serve principally those who disapprove its development on the deepest moral grounds, is a public policy option with limited appeal.

There may be other needs. There may be couples where each partner is homozygous for a particular recessive gene, say the cystic fibrosis gene. For this couple, no "normal" children are possible because no copy of the gene is present in the DNA of either. There may be such couples, but the prospect of launching a technological enterprise so vast to serve them seems too implausible to justify relaxation of the prohibition on developing germline intervention.

There may perhaps be other conditions where the alternative is not feasible, but again, so far as we are aware, they are very rare. If we correctly understand the limited plausible uses, the need to initiate policy revision now for later seems lacking.

That said, the uncertainties both of scientific knowledge and the pace of technical improvement cautions against saying "never" unless there is some important moral value to be served. For example, if it were discovered that some new virus entered brain cells early, and produced dementia after a latency period, is it inconceivable that germline intervention might be the best (and only) way of protecting humans from it? New viruses are obviously possible. Who knew that retroviruses even existed forty years ago?

Therefore, although we are not convinced that the policy process needs to move forward now, it seems appropriate to consider whether there are sound reasons for categorically barring germline interventions. Do concepts of human dignity and respect for human life require categorical condemnation of germline intervention?

Protection of human dignity and worth puts important limits on tampering with the reservoir of potentialities inherent in the gene pool. But are categorical prohibitions desirable? They might be based on:

- the need to experiment on zygotes. We will not comment further on this issue;
- impermissible risks to the future child.

There is much merit in this view. Any experiments will necessarily require inferences from animal models, but what kind of animal model can adequately indicate the effects of altering every single cell in the body, and what effect those alterations may have on uniquely human qualities such as cognition? One might say, categorically, that the risks will always be too great to justify intervention, and certainly so against conditions that have long been thought part of the human condition, such as memory loss with age. After all, there is no present patient who is sick and in need of treatment, whose benefit is to be weighed against risk.

The philosophical question of whether or not future persons have a "right" not to be experimented with before they are persons with interests of their own is a deeply interesting philosophical one. So too whether their hypothesized interest in disease free existence can be weighed in the balance against the risks. Whether or not the language of "rights" is appropriate, however, common language regards people as "wronged" when they are injured by activities that occurred before their conception, regardless of whether or not they have the right to maintain a lawsuit. We think, for example, of preconception exposure to toxic substances. If one can think of the interests of future persons this way, then the presumptive legitimacy of parental consent to speak on their behalf is consistent with the rest of our institutional arrangements.

The issue then is whether there are not disabilities so severe that one may impute to parents the right to speak for their descendants, and legitimate risk-taking on their behalf. We think there are. Moreover, we think that to invoke a child's right to an unaltered genetic makeup so as to visit on him conditions incompatible with prolonged life is too paradoxical to be accepted.

The third objection to germline interventions is that mistakes cannot be recalled. If, for example, in tampering with the organism's genes, scientists somehow launch a new genetic problem on the world, the gene they create may spread its way throughout the population. In effect, adding a new gene to this zygote is research to which I, a third party, have not consented on behalf of my future children, who may be affected by an accident. Such theoretical logic as this position may have, however, ignores the flux of the human gene pool, treating it as a work of art rather than an on-going process. We do not think the person who is exposed to radiation is running risks for which he needs our consent, on the theory that he might be burdening our common descendants. What makes germline intervention problematic is the intentional character of the enterprise.

A final argument against germline intervention is that it is somehow beyond human right to interfere with the fundamental process of life, and that this prohibition cannot be overcome by the highly ambiguous notion of "diseased" genes. To be creditable, this argument must say why intentional interference with the germline poses moral issues sharply different from the unplanned, but nonetheless significant impact of human activities on it. It must also insist on such a distinction in the face of the child's suffering ills that by hypothesis might have been safely prevented.

The Rapporteurs would not categorically oppose any and all imaginable intervention on the germline.

Germline Enhancement

7. The prospect of using germline interventions to improve the basic traits of humanity, is everywhere condemned. We believe it impermissible also, for standard reasons.

First, we cannot hypothesize how issues of risk versus benefit could possibly be weighed to favor proceeding. The plausible uses of germline intervention, even coupled with extensive experience with somatic cell therapy, would not ground experience that this kind of intervention can be safely done. There can be no "suicide genes" here. Therefore, although we can imagine some somatic cell enhancements that might not be wrong, it would be just as wrong to force them on our children's children as it would be to forcibly medicate an adult with a drug.

Secondly, human individuality and community is linked to the claim that you are who you are, the product like all of us of chance. It is wrong to burden individuals with a programmed destiny, and make them victims of genetic expectation.

Finally, for one set of humans to claim to foresee what traits the world will need in the distant future is wrong.

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In the end, our recommendations fits a familiar pattern, although it will prove controversial for some.

1. Somatic cell gene therapy is permissible, regulated as an experimental therapy.
2. Its use for enhancement purposes may be widely prohibited, but it should not be categorically disapproved as unethical in all imaginable circumstances.
3. Germline interventions are indefensible at present, but they should not be categorically disallowed.
4. The use of germline interventions for enhancement purposes should be categorically prohibited.

ANNEX A

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ANNEX B

UNESCO

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