Gene Technology: Possibilities and Limitations *

by Richard Braun **

1. Introduction

Genes determine the potential of all organisms from bacteria to plants to humans. Farmers have selected for millennia life stock and crop plants to improve their performance. This selection has only in the last hundred years been based on sound scientific knowledge, but clearly breeding was important much before the advent of modern science. Gene technology, developed in the last 20 years, adds new options to traditional breeding. Before the era of gene technology, a new crop variety, for instance a new line of potatoes, would be made by crossing older varieties and selecting out those progeny that showed the desired property, e.g. higher yields or improved disease resistance. In crossing, a cocktail of the genes of the two parental varieties is made and the desired progeny will need to be selected from amongst many thousand plants. The gene technologist, on the other hand, will aim to introduce the desired property by transferring a single well defined gene (or at most 2 or 3 genes) and thereby obtaining what is called a transgenic plant. The introduced gene may be a chemically modified gene from the same plant species or it may come from another species. The attraction of breeding plants (or animals) with the help of gene technology is the fact that only one very clearly defined property is altered. However, even with gene technology, the actual properties of the new variety will need to be studied carefully: the introduced gene may not be active at all or it may, amongst some of the progeny, lead to undesired properties. A crop developed by gene technology will in no way be more of a risk to human consumption or to the environment than a plant obtained by traditional breeding. I would like to stress that the process of gene technology is no more risky than the process of traditional breeding: it is the product that needs to be scrutinized, not the process by which the product is obtained.

Applied to microorganisms, gene technology can be used to induce the microbes to make "foreign" proteins. This is achieved by transferring a "foreign" gene, for instance a well characterized animal or human gene into bacteria, which will then make the protein

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coded by the introduced gene. This has been applied very successfully in the biotechnical industry over the last 10 years for making several medically important molecules. On the horizon is human gene therapy which aims to replace defective genes of the body with intact genes.

Clearly gene technology will have a huge impact on both medicine as well as food production and it is justified to call the new biotechnology a key technology of the future. However I do not in any way believe that it will pervade our daily lives as visibly and as powerfully as other modern technologies have, in particular information processing. We encounter television, computers, data processing etc. in nearly all of our daily activities and these technologies affect our life style and our behavior in a profound (some would say perverse) manner. Gene technology products will be in the medicines we take, in the vaccines we are given. Wheat, corn and later cattle will be in part bred with the help of gene technology. Gene therapy will not visibly change our world, but some of the most serious human diseases seen in industrialized societies will become more amenable to cures. In this article, I would like to concentrate primarily on medical applications of gene technology. I will also mention food production, but other totally different applications such as environmental remediation, industrial production of bulk chemicals, forensic medicine etc. will not be touched. It is also clear that basic biological research in all specialities today relies heavily on gene technological methods: recombinant DNA techniques have become a standard tool.

The actual possibilities of gene technology are restricted by the laws of nature: all the functions of every organism have to be well integrated and balanced against each other. Society will also want to impose certain regulations to minimize technology-immanent risks as well as to minimize negative indirect effects. Limitations of the first category are obvious: products of gene technology must neither be toxic to humans nor endanger the environment. In the second category ethical problems may arise, touching questions of personal responsibility and social justice.

2. Medicine

In the last 50 years the molecular basis of biology has been vastly expanded. Today every high school student knows what genes are and that proteins are the nuts and bolts of every living being. For many important diseases the underlying molecular and biochemical mechanisms have been at least partly unraveled. This has in turn led to distinct improvements both in diagnostics and to a lesser extent in therapy.

2.1. Drugs and vaccines

Human insulin was the first drug made by recombinant DNA technology on the market. Economically the most successful drug has been erythropoietin, a hormone used in patients with kidney diseases to stimulate their blood cell formation. Today some 20 products are commercially available, amongst them two vaccines against viral diseases. Worldwide another 100 products are in clinical evaluation and many of them will be on the market by the turn of the century. It is thought that by the year 2000 about half of the new drugs and vaccines will be made by recombinant DNA technology and the remainder by traditional organic chemistry.

Despite many success stories in the field, progress in some important areas has been very slow indeed. Ten years ago it was thought that an effective malaria vaccine was just around the corner. However, it was only last year that the first fields tests were started. They seem to indicate that the most promising vaccine candidates will only offer a very partial protection against this important parasite. An effective HIV vaccine seems still further away, although research on HIV is much more generously funded than research on malaria. I am mentioning these two examples as a word of caution. Although the understanding of disease mechanisms has made leaps and bounds in recent years, the development of drugs and vaccines is still a very tedious and costly business. Industries report that it costs 200 million \$ to develop a new drug or vaccine and to bring it to the market.

2.2. *Diagnosis*

Molecular tools can be used in two very different ways to diagnose diverse diseases. They can serve to identify a disease that is present or to predict from the genetic makeup of a person a disease which is likely to manifest itself in the future.

The reliable and quick identification of an illness will nearly always be of advantage to the patient. Molecular methods are currently available for identifying several viral and bacterial infections. This is particularly useful for viruses, since many of them are difficult to identify by other means. In cancer diagnosis, molecular tools are only starting to be applied. One can assume that in most cancers a mutation of a gene is the underlying cause of the disease. In some groups of cancers the exact location of a decisive mutation in an oncogene (a gene promoting cancer formation) or in a tumor suppressor gene (a gene preventing cancer formation) or some other gene may help in making a prognosis. Chromosome translocations in certain types of leukemia can be diagnosed with molecular probes. I believe that in this field molecular probes will be of increasing importance with more and more discoveries of clearly defined molecular defects being the actual and direct causes of specific types of cancers.

Predictions of a future disease are today primarily of interest in the prenatal diagnosis of monogenic hereditary diseases. Over a thousand such diseases are known, but most of them are exceedingly rare, presumably because the people affected have few offspring. Table 1 compares a few of the more common monogenic hereditary diseases: the term monogenic indicates that a single gene is defective and this causes the manifestations of the disease.

Table 1: Examples of frequent monogenic hereditary diseases

Disease	Frequency
Cystic Fibrosis	1 in 2,000
Emphysema (AAT-lack)	1 in 5,000
Thalassemia	1 in 1,000 (Mediterranean countries)
Hemophilia A and B	1 in 10,000 males
Duchenne muscular dystrophy	1 in 3,000 males
SCID (Severe Combined Immunodeficiency Disease)	1 in 10,000

One in 200 births is afflicted by a recognized, serious monogenic hereditary disease. It should be pointed out that Trisomy 21 (Down's syndrome, Mongolism) and a few other chromosomal anomalies, which are due to a spontaneous error during embryonic development and are not hereditary, are seen just as frequently, namely 1 in 200 births in industrialized countries. These proportions are important to keep in mind in debates on prenatal diagnosis: the quantitative impact of hereditary diseases is often overestimated.

For hereditary diseases there are at present no real cures. For some of them, the impact can be alleviated by various treatments such as drugs, diets or changes of life style. I would like now to concentrate on one single monogenic hereditary disease, namely Cystic Fibrosis (CF). CF is a very serious illness: patients on average have a life expectancy of 30 years. CF affects different organs, most notably the lungs, where slimy material covers the air/tissue interface, making breathing difficult and often leading to bacterial pneumonia. For some years the molecular defect underlying CF is well known: a protein controlling fluid transport across the lung membrane is either missing or is faulty. This defect is due to one of several possible errors in the gene coding for the CF membrane protein. With molecular probes the genetic defect can quite easily and accurately be diagnosed either in the developing fetus or after birth. This new diagnostic method opens up new and attractive possibilities, but also raises several ethical questions. Should every pregnancy be checked for CF? Who should be informed of the result of the check? These and similar issues are at present being discussed in many legislative bodies around the world and in most places a consensus is being reached. Testing has to be voluntary and the data obtained must be confidential. In practice this means that no screening of the general public is possible, but that physicians will advise families with a known history of CF to have the test done. It is important that the test results remain with the family and their physician. A spread of the data to insurance companies or employers would lead to an unjust discrimination of those who already suffer from their genetic makeup. Exceptions to this principle could be envisaged in cases of suspected insurance fraud, e.g. if someone takes out a high life insurance policy for a child suspected to suffer of a serious hereditary defect.

A very positive aspect of a prenatal diagnosis is that it will often assure the parents that their offspring will be healthy and this will remove very serious worries, particularly if there is a family history of a hereditary disease. On the other hand, the right of the future mother *not* to know whether her fetus is normal or not, needs to be safeguarded. This is important since there is no real cure for most hereditary diseases and abortion of the fetus will become an issue. There is, also in this context, no simple answer to the very real difficulty of accepting or rejecting abortion. Surely most people will not consider it unethical if a family wants to have an abortion of a fetus afflicted with CF, if they already have a child with this disease. On the other hand a pluralistic society has to accept that some of its members will under virtually no circumstances agree to an abortion.

Molecular tools will in future allow predictive medicine to go beyond only recognizing monogenic hereditary diseases. Predictive medicine will let people know that there is a certain probability that later in life they may expect to develop a certain type of cancer, or a certain neurodegenerative disease or diabetes. Today there are only few conditions for which predictive tests of even a modest reliability exist. They are also still very expensive. However, there is no doubt that with the unraveling of the human genome more tests, and also more accurate tests, will become available. The curiosity of people to know their pro-

bable or possible fate is surprisingly large, even if no treatment is known to delay the onset of disease, to alleviate its consequences or to cure it. With gene therapy appearing on the horizon I expect that there will be an increased interest in postnatal predictive diagnosis.

2.3. *Gene therapy*

Transplantation medicine is well established. We are accustomed to hear of kidney transplants, even heart transplants. The area is riddled with ethical problems: where do the organs come from? Who is a worthy recipient, etc? My starting point is that every major disease has a molecular basis. This in no way says that all diseases are purely genetic. Diseases often result from a genetic disposition and an additional environmental impact. The combination will lead to abnormal gene products, which in turn will be responsible for the disease symptoms.

The aim of somatic gene therapy is to correct a gene defect in affected body cells, without in any way interfering with the germ line cells. This will ensure that the genes of the next generation are not touched. Somatic gene therapy can of course only be used if the molecular defect causing the disease is known. Once this is the case, there are still formidable obstacles. How can the affected cell type in the affected tissue and organ be targeted? How can a long lasting effect be achieved?

At present monogenic hereditary diseases are in the forefront as candidates for gene therapy (Table 1). Worldwide a few dozen experimental clinical protocols have been approved. Only a small number of patients will receive treatment following each of the approved protocols. The only success noted so far is with children afflicted by SCID. They would otherwise have had to live in a plastic bubble for fear of simple infections, which for all other people are innocuous. SCID affected children are more susceptible to adventitious infections than HIV-patients or immunosuppressed patients. The gene therapy these children are now receiving is cumbersome and very expensive. Cells from their bone marrow are removed once a month, re-programmed in a laboratory with an intact gene and injected back into the children.

Much effort is put worldwide into gene therapy of CF patients. Transgenic mice have been bred which show similar symptoms as human CF patients. Such mice have been "cured" simply by letting them inhale air in which oil droplets with the correct DNA were suspended. Enough of the DNA was taken up into the cells lining the airway system to regulate their fluid throughput. Following success with the mouse model, experimental therapies on humans started a year ago. Some unfortunately had to be stopped because of undesirable side effects, but these experiments will certainly be continued in several clinics around the world. CF is the disease for which gene therapy looks the most promising.

It is still quite unclear what might be the advantages and disadvantages of diverse delivery systems for gene therapy. The simplest would be a pill, nasal drops or an eye spray. A standard injection is also easy to apply, but an *ex vivo* treatment, as explained above for the SCID children, where body cells are removed individually, treated in the laboratory and put back into the body, is cumbersome and costly. Despite these uncertainties I do not doubt that for many single gene defects gene therapies will be developed in the next 10 or 20 years.

There are good reasons to believe that other diseases involving a known molecular defect may become amenable to gene therapy. Cancers may be caused by an activated oncogene, an inactivated tumor suppressor gene, defective cell cycle components or cell

adhesion controls, missing DNA repair enzymes etc. In all these situations it seems conceptually simple to add the correct genetic information or to stop expressing the incorrect genetic information. Ideas such as these, applicable in principle also to other diseases, will take many years to test in the laboratory, in animal experiments and finally in humans. Predictions as to the time frame are of course difficult, but I would imagine that routine gene therapy for these diseases will take 20 years or so to become established. However, one needs to be clear that gene therapy will lead to new concepts and new practices in medicine.

It is obviously difficult to predict the social impact of a new medical technology before it has been clinically tested. Whilst hygiene and antibiotics dramatically reduced the impact of infectious diseases over the last 100 years and led to a surge in life expectancy by reducing childhood mortality, gene therapy of cancer and cardiovascular diseases might lead to another reduction in mortality, this time among middle aged and older adults. This of course will not come quickly. Will the advent of gene therapy lead to another surge in health care costs? I do not think so, since the costs of the new therapies will probably be offset by a reduction of long and costly traditional treatments and by a prolonged productive life span. It will be important for health insurance companies to analyze the cost structures of these new therapies so as to make those with a good benefit/cost ratio easily available to the general public.

There is at least one serious ethical limitation to gene therapy. All I have dealt with is somatic gene therapy, an intervention that only affects the person that is treated, but not his or her offspring. Sperm cells and egg cells (called germ line cells) are clearly not affected by somatic gene therapy and are not intended to be affected. Today, and probably for many years to come, we lack the technology to effectively alter the germ line cells; nobody has yet attempted to change the genetic make-up of any human progeny by gene technology. In many countries germ line interventions are forbidden by law; firstly because of the uncertainty of whether any intervention in the progeny is ethically justified and secondly for fear of introducing eugenic procedures. Personally I am glad that in Switzerland this limitation has been written into the constitution: it should reassure the general public that scientists do not aim to tamper with the anyone's children. Perhaps in 30 or 50 years this statute will appear superfluous and then it can be deleted again from the constitution. In any case gene therapy has to aim at relieving suffering, not at "improving" humanity.

3. Agriculture and food production

Breeding of crops and farm animals has been central to the long term success of agriculture. Over the last hundred years breeding has, together with other procedures, led to very much increased yields and to improved product quality. Selecting defined strains of microorganisms has contributed to more controlled productions of wine, beer, bread, cheese etc. Gene technology opens up new ways to improve strains or breeds. The impact will be far quicker with microorganisms and crop plants than with farm animals, and I will therefore concentrate on plant breeding.

In the laboratory, all of the world major crop plants can be transformed by introducing specific genes into them (Table 2). However, the only transgenic food plant on the market at present, and in the USA only, is a variety of tomato called the "FlavrSavr" tomato. It is characterized by a better flavor than ordinary supermarket tomatoes (but perhaps not better than my own backyard products). After more than 1000 field trials with transgenic

plants have been completed, it is clear that seed companies will put many transgenic varieties of maize, wheat, rape, sugar beat etc. on the market in the next few years. The new crops will benefit both the farmer and the consumer by improved agronomic properties and increased product quality. At present the public perception of food products modified by gene technology is only theoretical in Europe, since no products are actually available. In surveys the opinions voiced by many people, particularly in Northern Europe, are quite negative. I believe this will change with the availability of real products and with the increased realization that gene technology is not more than another tool in the hands of the plant breeders. This powerful tool will clearly be made use of in the years to come.

There are no specific risks of a serious nature to be expected from transgenic crop plants. The “worst case scenario” is that a herbicide resistance might perhaps (but with an extremely low probability) be transferred to a weed and make this weed resistant to this particular herbicide. This sort of accident could be costly to farmers in one season, but the farmers would certainly not use this same seed and herbicide combination a second time. There is no reasonable comparison possible between this “worst case scenario” and a nuclear catastrophe. Obviously transgenic crop plants will need to be tested for their nutritional value and checked to make sure that they do not contain any new toxic or allergenic substances. Such tests are routinely done with any new crop, not only those produced by gene technology.

Table 2: Examples of research on genetically modified crops

Product/Food	Action/Application
Bananas	Integrated pest management
Coffee	Better flavor, higher yield, lower caffeine
Corn (maize)	Insect resistance
“Euromelon”	Ripens on demand
Potato	Several disease resistances
Rapeseed	Production of hard fats, high temperature frying oil, low in unsaturated fats
Strawberries	Frost resistance
Wheat	Herbicide resistance

In the less developed countries (LDC’s) the attitudes towards transgenic crops are far more positive – for good reasons. Here there is a real fear of diminishing food supplies in coming decades. In many countries the population will double in the next 25 or 30 years. Since the area of arable land will not increase, the only option is to increase yields and thereby produce more food per hectare. This will need to be done in different ways, including a more equitable distribution of land, higher prices for agricultural produce made locally, appropriate irrigation, improved erosion controls, better food storage facilities etc. Crop varieties will also need to be improved and here biotechnology will come in. The aim may be resistance to diseases, pests, drought etc. as well as improved product composition resulting in higher nutritional values.

The large seed companies will usually not invest in risky projects for third world countries and most LDC's will not be in a position to breed new plant varieties without help and this is where our solidarity is called for. Here several international bodies have taken initiatives, in particular the Consultative Group on International Agricultural Research (CGIAR): it does excellent field research in more than a dozen centers located in diverse LDC's. Each center specializes on a single area, such as rice, maize or cattle breeding. The CGIAR institutes provide benefits to many millions of small farmers and will in the future require increased support from the industrialized countries, if massive outbreaks of famine are to be avoided. Such catastrophes would be a human disaster and would have grave political consequences for the rest of the world: more wars and more migration pressure to the North or to the already crowded cities of the South. Biotechnology is able to make a contribution to sustainable small scale agriculture in the Third World: however the social, political and economic conditions have to be appropriate.

4. Outlook

Until about 1970 technology was largely regarded as a motor of progress, leading to an improved quality of life. Today society is more ambiguous, following the realization that technologies may also have negative impacts on people and their environment. A large segment of the population has become highly critical of technology in general, or its application to particular sectors of the economy. Yet at the same time people in industrialized countries have never enjoyed such a high standard of living and the consumption of diverse goods and services is still increasing. This ambiguous attitude is very clearly seen in the poor acceptance of biotechnology and particularly gene technology.

In order for society to make use of the many potential improvements in the quality of life which biotechnology can bring, it will be important to improve its public perception. The acceptance will be improved by three sets of measures:

1. Promotion of a better understanding of the scientific basis of biotechnology by the general public.
2. Early availability of certain exemplary services and products made by biotechnology in order to familiarize people with the realities of biotechnology.
3. A regulatory framework, based on established ethical principles, aimed at increasing benefits and minimizing risks to both the population and to the environment.

In the long run biotechnology, including gene technology, will be as well accepted as most other technologies as a means of improving the quality of life of most people and their environment. Biotechnology is not a high risk technology, but thoughtful guidance in its application is still necessary to promote benefits and reduce risks and abuses.