GENETIC TECHNOLOGY

A New Frontier

Office of Technology Assessment

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About the Book

Genetic Technology: A New Frontier

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Genetic technologies may contribute to meeting some of the most fundamental human needs—from health care to food supplies to energy. They open up new possibilities for developing vaccines against such intractable diseases as hepatitis and malaria; they can transform inedible biomass into food for humans and animals; and they can aid in food processing. Genetically engineered micro-organisms may also be developed for use in oil recovery, pollution control, and mineral leaching.

Yet, there are problems. Technical constraints and questions about potential effects on human health and the environment are major considerations, particularly in the case of genetically engineered micro-organisms. No evidence exists that any unexpectedly harmful genetically engineered organism has been created; still, few experts believe that molecular genetic techniques are totally without risk, and there is uncertainty about the regulation of production methods using engineered micro-organisms. Perhaps a more perplexing issue is the potential impact of the new technologies on human values.

This book is one of the first comprehensive documents on emerging genetic technologies and their implications for society. The authors discuss the opportunities and problems involved, describe current techniques, and attempt to project some of the economic, environmental, and institutional impacts of those techniques. The issues they raise go beyond those of technology, utility, and economic feasibility. As we gain the ability to manipulate life, we must face basic questions of just what life means and how far we can reasonably—and safely—allow ourselves to go in the pursuit of a better future.

The **Office of Technology Assessment** was created in 1972 as an advisory arm of the U.S. Congress. OTA's basic function is to help legislative policymakers anticipate and plan for the consequences of technological changes and to examine the many ways, expected and unexpected, in which technology affects people's lives. The assessment of technology calls for exploration of the physical, biological, economic, social, and political impacts that can result from applications of scientific knowledge. OTA provides Congress with independent and timely information about the potential effects—both beneficial and harmful—of technological applications.

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Foreword

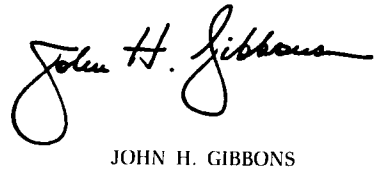
This report examines the application of classical and molecular genetic technologies to micro-organisms, plants, and animals. Congressional support for an assessment in the field of genetics dates back to 1976 when 30 Representatives requested a study of recombinant DNA technology. Letters of support for this broader study came from the then Senate Committee on Human Resources and the House Committee on Interstate and Foreign Commerce, Subcommittee on Health and the Environment.

Current developments are especially rapid in the application of genetic technologies to micro-organisms; these were studied in three industries: pharmaceutical, chemical, and food. Classical genetics continue to play the major role in plant and animal breeding but new genetic techniques are of ever-increasing importance.

This report identifies and discusses a number of issues and options for the Congress, such as:

- Federal Government support of R&D,
- methods of improving the germplasm of farm animal species,
- risks of genetic engineering,
- patenting living organisms, and
- public involvement in decisionmaking.

The Office of Technology Assessment was assisted by an advisory panel of scientists, industrialists, labor representatives, and scholars in the fields of law, economics, and those concerned with the relationships between science and society. Others contributed in two workshops held during the course of the assessment. The first was to investigate public perception of the issues in genetics; the second examined genetic applications to animals. Sixty reviewers drawn from universities, Government, industry, and the law provided helpful comments on draft reports. The Office expresses sincere appreciation to all those individuals.



JOHN H. GIBBONS
Director

Glossary

Aerobic.—Growing only in the presence of oxygen.

Anaerobic.—Growing only in the absence of oxygen.

Alkaloids.—A group of nitrogen-containing organic substances found in plants; many are pharmacologically active—e.g., nicotine, caffeine, and cocaine.

Allele.—Alternate forms of the same gene. For example, the genes responsible for eye color (blue, brown, green, etc.) are alleles.

Amino acids.—The building blocks of proteins. There are 20 common amino acids; they are joined together in a strictly ordered "string" which determines the character of each protein.

Antibody.—A protein component of the immune system in mammals found in the blood.

Antigen.—A large molecule, usually a protein or carbohydrate, which when introduced in the body stimulates the production of an antibody that will react specifically with the antigen.

Aromatic chemical.—An organic compound containing one or more six-membered rings.

Aromatic polymer.—Large molecules consisting of repeated structural units of aromatic chemicals.

Artificial insemination.—The manual placement of sperm into the uterus or oviduct.

Bacteriophage (or phage).—A virus that multiplies in bacteria. Bacteriophage lambda is commonly used as a vector in recombinant DNA experiments.

Bioassay.—Determination of the relative strength of a substance (such as a drug) by comparing its effect on a test organism with that of a standard preparation.

Biomass.—Plant and animal material.

Biome.—A community of living organisms in a major ecological region.

Biosynthesis.—The production of a chemical compound by a living organism.

Biotechnology.—The collection of industrial processes that involve the use of biological systems. For some of these industries, these processes involve the use of genetically engineered microorganisms.

Blastocyst.—An early developmental stage of the embryo; the fertilized egg undergoes several cell divisions and forms a hollow ball of cells called the blastocyst.

Callus.—The cluster of plant cells that results from tissue culturing a single plant cell.

Carbohydrates.—The family of organic molecules consisting of simple sugars such as glucose and sucrose, and sugar chains (polysaccharides) such as starch and cellulose.

Catalyst.—A substance that enables a chemical reaction to take place under milder than normal conditions (e.g., lower temperatures). Biological catalysts are enzymes; nonbiological catalysts include metallic complexes.

Cell fusion.—The fusing together of two or more cells to become a single cell.

Cell lysis.—Disruption of the cell membrane allowing the breakdown of the cell and exposure of its contents to the environment.

Cellulase.—An enzyme that degrades cellulose to glucose.

Cellulose.—A polysaccharide composed entirely of several glucose units linked end to end; it constitutes the major part of cell walls in plants.

Chimera.—An individual composed of a mixture of genetically different cells.

Chloroplast.—The structure in plant cells where photosynthesis occurs.

Chromosomes.—The thread-like components of a cell that are composed of DNA and protein. They contain most of the cell's DNA.

Clone.—A group of genetically identical cells or organisms asexually descended from a common ancestor. All cells in the clone have the same genetic material and are exact copies of the original.

Conjugation.—The one-way transfer of DNA between bacteria in cellular contact.

Crossing-over.—A genetic event that can occur during cellular replication, which involves the breakage and reunion of DNA molecules.

Cultivar.—An organism developed and persistent under cultivation.

Cytogenetics.—A branch of biology that deals with the study of heredity and variation by the methods of both cytology (the study of cells) and genetics.

Cytoplasm.—The protoplasm of a cell, external to the cell's nuclear membrane.

Diploid.—A cell with double the basic chromosome number.

DNA (deoxyribonucleic acid).—The genetic material found in all living organisms. Every inherited characteristic has its origin somewhere in the code of each individual's complement of DNA.

DNA vector.—A vehicle for transferring DNA from one cell to another.

Dominant gene.—A characteristic whose expression prevails over alternative characteristics for a given trait.

Escherichia coli.—A bacterium that commonly inhabits the human intestine. It is a favorite organism for many microbiological experiments.

Endotoxins.—Complex molecules (lipopolysaccharides) that compose an integral part of the cell wall, and are released only when the integrity of the cell is disturbed.

Embryo transfer.—Implantation of an embryo into the oviduct or uterus.

Enzyme.—A functional protein that catalyzes a chemical reaction. Enzymes control the rate of metabolic processes in an organism; they are the active agents in the fermentation process.

Estrogens.—Female sex hormones.

Estrus ("heat").—The period in which the female will allow the male to mate her.

Eukaryote.—A higher, compartmentalized cell characterized by its extensive internal structure and the presence of a nucleus containing the DNA. All multicellular organisms are eukaryotic. The simpler cells, the prokaryotes, have much less compartmentalization and internal structure; bacteria are prokaryotes.

Exotoxins.—Proteins produced by bacteria that are able to diffuse out of the cells; generally more potent and specific in their action than endotoxins.

Fermentation.—The biochemical process of converting a raw material such as glucose into a product such as ethanol.

Fibroblast.—A cell that gives rise to connective tissues.

Gamete.—A mature reproductive cell.

Gene.—The hereditary unit; a segment of DNA coding for a specific protein.

Gene expression.—The manifestation of the genetic material of an organism as specific traits.

Genetic drift.—Changes of gene frequency in small populations due to chance preservation or extinction of particular genes.

Genetic code.—The biochemical basis of heredity consisting of codons (base triplets along the DNA sequence) that determine the specific amino acid sequence in proteins and that are the same for all forms of life studied so far.

Genetic engineering.—A technology used at the laboratory level to alter the hereditary apparatus of a living cell so that the cell can produce more or different chemicals, or perform completely new functions. These altered cells are then used in industrial production.

Gene mapping.—Determining the relative locations of different genes on a given chromosome.

Genome.—The basic chromosome set of an organism—the sum total of its genes.

Genotype.—The genetic constitution of an individual or group.

Germplasm.—The total genetic variability available to an organism, represented by the pool of germ cells or seed.

Germ cell.—The sex cell of an organism (sperm or egg, pollen or ovum). It differs from other cells in that it contains only half the usual number of chromosomes. Germ cells fuse during fertilization.

Glycopeptides.—Chains of amino acids with attached carbohydrates.

Glycoprotein.—A conjugated protein in which the nonprotein group is a carbohydrate.

Haploid.—A cell with only one set (half of the usual number) of chromosomes.

Heterozygous.—When the two genes controlling a particular trait are different, the organism is heterozygous for that trait.

Homozygous.—When the two genes controlling a particular trait are identical for a pair of chromosomes, the organism is said to be homozygous for that trait.

Hormones.—The "messenger" molecules of the body that help coordinate the actions of various tissues; they produce a specific effect on the activity of cells remote from their point of origin.

Hybrid.—A new variety of plant or animal that results from cross-breeding two different existing varieties.

Hydrocarbon.—All organic compounds that are composed only of carbon and hydrogen.

Immunoproteins.—All the proteins that are part of the immune system (including antibodies, interferon, and cytokines).

In vitro.—Outside the living organism and in an artificial environment.

In vivo.—Within the living organism.

Leukocytes.—The white cells of blood.

Lipids.—Water insoluble biomolecules, such as cellular fats and oils.

Lipopolysaccharides.—Complex substances composed of lipids and polysaccharides.

Lymphoblastoid.—Referring to malignant white blood cells.

Lymphokines.—The biologically active soluble factor produced by white blood cells.

Maleic anhydride.—An important organic chemical used in the manufacture of synthetic resins, in fungicides, in the dyeing of cotton textiles, and to prevent the oxidation of fats and oils during storage and rancidity.

Messenger RNA.—Ribonucleic acid molecules that serve as a guide for protein synthesis.

Metabolism.—The sum of the physical and chemical processes involved in the maintenance of life and by which energy is made available.

Mitochondria.—Structures in higher cells that serve as the "powerhouse" for the cell, producing chemical energy.

Monoclonal antibodies.—Antibodies derived from a single source or clone of cells which recognize only one kind of antigen.

Mutants.—Organisms whose visible properties with respect to some trait differ from the norm of the population due to mutations in its DNA.

Mutation.—Any change that alters the sequence of bases along the DNA, changing the genetic material.

Myeloma.—A malignant disease in which tumor cells of the antibody producing system synthesize excessive amounts of specific proteins.

***n*-alkanes.**—Straight chain hydrocarbons—the main constituents of petroleum.

Nif genes.—The genes for nitrogen fixation present in certain bacteria.

Nucleic acid.—A polymer composed of DNA or RNA subunits.

Nucleotides.—The fundamental units of nucleic acids. They consist of one of the four bases—adenine, guanine, cytosine, and thymine (uracil in the case of RNA)—and its attached sugar-phosphate group.

Organic compounds.—Chemical compounds based on carbon chains or rings, which contain hydrogen, and also may contain oxygen, nitrogen, and various other elements.

Parthenogenesis.—Reproduction in animals without male fertilization of the egg.

Pathogen.—A specific causative agent of disease.

Peptide.—Short chain of amino acids.

pH.—A measure of the acidity or basicity of a solution; on a scale of 0 (acidic) to 14 (basic): for example, lemon juice has a pH of 2.2 (acidic), water has a pH of 7.0 (neutral), and a solution of baking soda has a pH of 8.5 (basic).

Phage.—(See *bacteriophage.*)

Phenotype.—The visible properties of an organism that are produced by the interaction of the genotype and the environment.

Plasmid.—Hereditary material that is not part of a chromosome. Plasmids are circular and self-replicating. Because they are generally small and relatively simple, they are used in recombinant DNA experiments as acceptors of foreign DNA.

Plastid.—Any specialized organ of the plant cell other than the nucleus, such as the chloroplast.

Ploidy.—Describes the number of sets of chromosomes present in the organism. For example, humans are diploid, having two homologous sets of 23 chromosomes (one set from each parent) for a total of 46 chromosomes; many plants are haploid, having only one copy of each chromosome.

Polymer.—A long-chain molecule formed from smaller repeating structural units.

Polysaccharide.—A long-chain carbohydrate containing at least three molecules of simple sugars linked together; examples would include cellulose and starch.

Progestogens.—Hormones involved with ovulation.

Prostaglandin.—Refers to a group of naturally occurring, chemically related long-chain fatty acids that have certain physiological effects (stimulate contraction of uterine and other smooth muscles, lower blood pressure, affect action of certain hormones).

Protein.—A linear polymer of amino acids; proteins are the products of gene expression and are the functional and structural components of cells.

Protoplast.—A cell without a wall.

Protoplast fusion.—A means of achieving genetic transformation by joining two protoplasts or joining a protoplast with any of the components of another cell.

Recessive gene.—Any gene whose expression is dependent on the absence of a dominant gene.

Recombinant DNA.—The hybrid DNA produced by joining pieces of DNA from different sources.

Restriction enzyme.—An enzyme within a bacterium that recognizes and degrades DNA from foreign organisms, thereby preserving the genetic integrity of the bacterium. In recombinant DNA experiments, restriction enzymes are used as tiny biological scissors to cut up foreign DNA before it is recombined with a vector.

Reverse transcriptase.—An enzyme that can synthesize a single strand of DNA from a messenger RNA, the reverse of the normal direction of processing genetic information within the cell.

RNA (ribonucleic acid).—In its three forms—messenger RNA, transfer RNA, and ribosomal RNA—it assists in translating the genetic message of DNA into the finished protein.

Somatic cell.—One of the cells composing parts of the body (e.g., tissues, organs) other than a germ cell.

Tissue culture.—An in vitro method of propagating healthy cells from tissues, such as fibroblasts from skin.

Transduction.—The process by which foreign DNA becomes incorporated into the genetic complement of the host cell.

Transformation.—The transfer of genetic information by DNA separated from the cell.

Vector.—A transmission agent; a DNA vector is a self-replicating DNA molecule that transfers a piece of DNA from one host to another.

Virus.—An infectious agent that requires a host cell in order for it to replicate. It is composed of either RNA or DNA wrapped in a protein coat.

Zygote.—A cell formed by the union of two mature reproductive cells.

Acronyms and Abbreviations

AA — amino acids
ACS — American Cancer Society
ACTH — adrenocorticotropic hormone
AI — artificial insemination
AIPL — Animal Improvement Programs Laboratory
APAP — acetaminophen
ASM — American Society for Microbiology
bbl — barrel(s)
bbl/d — barrels per day
BOD5 — 5-day biochemical oxygen demand
BRM — Biological Response Modifier Program
bu — bushel
CaMV — cauliflower mosaic virus
CCPA — The Court of Customs and Patent Appeals
CDC — Center for Disease Control
CERB — Cambridge Experimentation Review Board
DHHS — Department of Health and Human Services (formerly Health, Education, and Welfare)
DHI — Dairy Herd Improvement
DNA — deoxyribonucleic acid
DOC — Department of Commerce
DOD — Department of Defense
DOE — Department of Energy
DPAG — Dangerous Pathogens Advisory Group
EOR — enhanced oil recovery
EPA — Environmental Protection Agency
FDA — Food and Drug Administration
FMDV — foot-and-mouth disease virus
ft^2 — square foot
ft — foot
FTC — Federal Trade Commission
g — gram
gal — gallon
GH — growth hormone
ha — hectares
HEW — Department of Health, Education, and Welfare
hGH — human growth hormone
HYV — high-yielding varieties
IBCs — Institutional Biosafety Committees
ICI — Imperial Chemical Industries
IND — Investigational New Drug Application (FDA)
kg — kilogram
l — liter
lb — pound
mg — milligram
μg — microgram
μm — micrometer (formerly micron)
MUA — Memorandum of Understanding and Agreement
NCI — National Cancer Institute
NDA — new drug application (FDA)
NDAB — National Diabetics Advisory Board
NDCHIP — National Cooperative Dairy Herd Program
NIAID — National Institute of Allergy and Infectious Diseases
NIAMDD — National Institute of Arthritis, Metabolism, and Digestive Diseases
NIH — National Institutes of Health
NIOSH — National Institute of Occupational Safety and Health
NSF — National Science Foundation
OECD — The Organization for Economic Cooperation and Development
ORDA — Office of Recombinant DNA Activities
PD — predicted difference
pH — unit of measure for acidity/basicity
ppm — parts per million
R&D — research and development
RAC — Recombinant DNA Advisory Committee
rDNA — recombinant DNA
SCP — single-cell protein
T-DNA — a smaller segment of the Ti plasmid
Ti — tumor inducing
TSCA — Toxic Substances Control Act
UCSF — University of California at San Francisco
U.S.C. — United States Code
USDA — United States Department of Agriculture

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Chapter 1

Summary: Issues and Options

The genetic alteration of plants, animals, and micro-organisms has been an important part of agriculture for centuries. It has also been an integral part of the alcoholic beverage industry since the invention of beer and wine; and for the past century, a mainstay of segments of the pharmaceutical and chemical industries.

However, only in the last 20 years have powerful new genetic technologies been developed that greatly increase the ability to manipulate the inherited characteristics of plants, animals, and micro-organisms. One consequence is the increasing reliance the pharmaceutical and chemical industries are placing on biotechnology. Micro-organisms are being used to manufacture substances that have previously been extracted from natural sources. Animal and plant breeders are using the new techniques to help clarify basic questions about biological functions, and to improve the speed and efficiency of the technologies they already use. Other industries—from food processing and pollution control to mining and oil recovery—are considering the use of genetic engineering to increase productivity and cut costs.

Genetic technologies will have a broad impact on the future. They may contribute to filling some of the most fundamental needs of mankind—from health care to supplies of food and energy. At the same time, they arouse concerns about their potential effects on the environment and the risks to health involved in basic and applied scientific research and development (R&D). Because genetic technologies are already being applied, it is appropriate to begin considering their potential consequences.

Congressional concern with applied genetics dates back to 1976, when 30 Representatives requested an assessment of recombinant DNA (rDNA) technology. Support for the broader study reported here came in letters to the Office of Technology Assessment from the then Senate Committee on Human Resources and the House Committee on Interstate and Foreign Commerce, Subcommittee on Health and the Environment. In addition, specific subtopics are of interest to other committees, notably those having jurisdiction over science and technology and those concerned with patents.

This report describes the potentials and problems of applying the new genetic technologies to a range of major industries. It emphasizes the present state of the art because that is what defines the basis for the future applications. It then makes some estimates of economic, environmental, and institutional impacts—where, when, and how some technologies might be applied and what some of the results might be. The report closes with the possible roles that Government, industry, and the public might play in determining the future of applied genetics.

The term *applied genetics,* as used in this report, refers to two groups of technologies:

- *Classical genetics*—natural mating methods for the selective breeding of organisms for desired characteristics—e.g., breeding cows for increased milk production. The pool of genes available for selection is comprised of those that cause natural differences among individuals in a population and those obtained by mutation.
- *Molecular genetics* includes the technologies of genetic engineering that involve the directed manipulation of the genetic material itself. These technologies—such as rDNA and the chemical synthesis of genes—can increase the size of the gene pool for any one organism by making available genetic traits from many different populations. Molecular genetics also includes technologies in which manipulation occurs at a level higher than that of the gene—at the cellular level, e.g., cell fusion and in vitro fertilization.

Significant applications of molecular genetics to micro-organisms, such as the efforts to manufacture human insulin, are already underway in several industries. Most of these applications

depend on fermentation—a technology in which substances produced by micro-organisms can be obtained in large quantities. Applications to plants and animals, which are biologically more complex and more difficult to manipulate successfully, will take longer to develop.

Biotechnology

Biotechnology—the use of living organisms or their components in industrial processes—is possible because micro-organisms naturally produce countless substances during their lives. Some of these substances have proved commercially valuable. A number of different industries have learned to use micro-organisms as natural factories, cultivating populations of the best producers under conditions designed to enhance their abilities.

Applied genetics can play a major role in improving the speed, efficiency, and productivity of these biological systems. It permits the manipulation, or engineering, of the micro-organisms' genetic material to produce the desired characteristics. Genetic engineering is not in itself an industry, but a technique used at the laboratory level that allows the researcher to modify the hereditary apparatus of the cell. The population of altered identical cells that grows from the first changed micro-organism is, in turn, used for various industrial processes. (See figure 1.)

The first major commercial effects of the application of genetic engineering will be in the pharmaceutical, chemical, and food processing industries. Potential commercial applications of value to the mining, oil recovery, and pollution control industries—which may desire to use manipulated micro-organisms in the open environment—are still somewhat speculative.

The pharmaceutical industry

FINDINGS

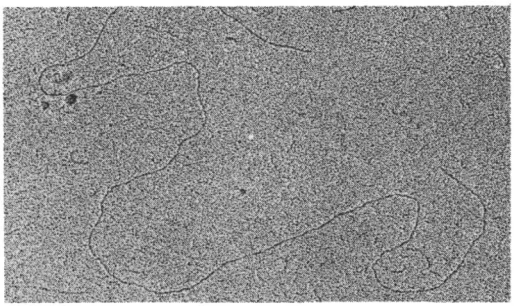
The pharmaceutical industry has been the first to take advantage of the potentials of applied molecular genetics. Ultimately, it will probably benefit more than any other, with the largest percentage of its products depending on advances in genetic technologies. Already, micro-organisms have been engineered to produce human insulin, interferon, growth hormone, urokinase (for the treatment of blood clots), thymosin-α 1 (for controlling the immune response), and somatostatin (a brain hormone). (See figure 2.)

The products most likely to be affected by genetic engineering in the next 10 to 20 years are nonprotein compounds like most antibiotics, and protein compounds such as enzymes and antibodies, and many hormones and vaccines. Improvements can be made both in the products and in the processes by which they are produced. Process costs may be lowered and even entirely new products developed.

The most advanced applications today are in the field of hormones. While certain hormones have already proved useful, the testing of others has been hindered by their scarcity and high cost. Of 48 human hormones that have been identified so far as possible candidates for production by genetically engineered micro-organisms, only 10 are used in current medical practice. The other 38 are not, partly because they have been available in such limited quantities that tests of their therapeutic value have not been possible.

Genetic technologies also open up new approaches for vaccine development for such intractable parasitic and viral diseases as amebic dysentery, trachoma, hepatitis, and malaria. At present, the vaccine most likely to be produced is for foot-and-mouth disease in animals. However, should any one of the vaccines for human diseases become available, the social, economic, and political consequences of a decrease in morbidity and mortality would be significant. Many of these diseases are particularly prevalent in less industrialized countries; the developments of vaccines for them may profoundly affect the lives of tens of millions of people.

Figure 1.—Recombinant DNA: The Technique of Recombining Genes From One Species With Those From Another



Electron micrograph of the DNA, which is the plasmid SP01 from *Bacillus subtilis*. This plasmid which has been sliced open is used for recombinant DNA research in this bacterial host

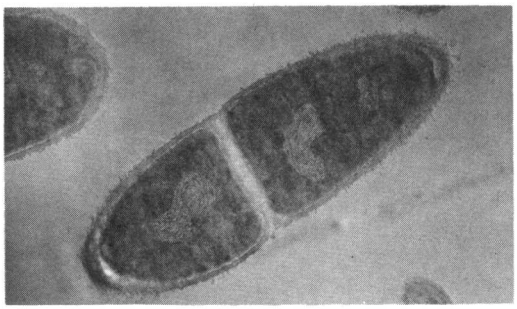
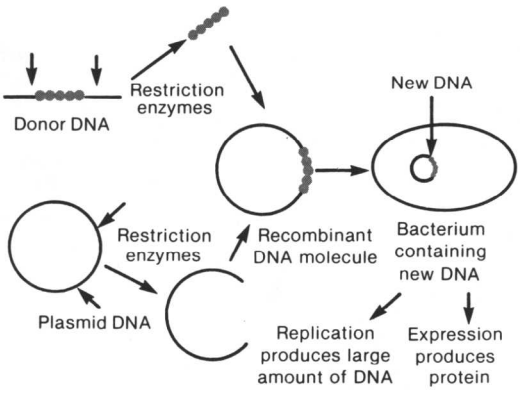


Photo credits: Professor F. A. Eiserling, UCLA Molecular Biology Institute

Electron micrograph of *Bacillus subtilis* in the process of cell division. The twisted mass in the center of each daughter cell is the genetic material, DNA



Restriction enzymes recognize certain sites along the DNA and can chemically cut the DNA at those sites. This makes it possible to remove selected genes from donor DNA molecules and insert them into plasmid DNA molecules to form the recombinant DNA. This recombinant DNA can then be cloned in its bacterial host and large amounts of a desired protein can be produced.

SOURCE: Office of Technology Assessment.

For some pharmaceutical products, biotechnology will compete with chemical synthesis and extraction from human and animal organs. Assessing the relative worth of each method must be done on a case-by-case basis. But for other products, genetic engineering offers the only method known that can ensure a plentiful supply; in some instances, it has no competition.

By making a pharmaceutical available, genetic engineering may have two types of effects:

- Drugs that already have medical promise will be available in ample amounts for clinical testing. Interferon, for example, can be tested for its efficacy in cancer and viral therapy, and human growth hormone can be evaluated for its ability to heal wounds.
- Other pharmacologically active substances for which no apparent use now exists will be available in sufficient quantities and at low enough cost to enable researchers to explore new uses. As a result, the potential for totally new therapies exists. Regulatory proteins, for example, which are an entire