Issues & Dilemmas of Biotechnology

Issues and Dilemmas of BIOTECHNOLOGY

A Reference Guide

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Abbreviations

AAV	adeno-associated virus
ABCC	Atomic Bomb Casualty Commission
ACS	American Cancer Society
ADA	adenosine deaminase
ADA	Americans with Disabilities Act
AGS	Advanced Genetic Sciences
AIDS	Acquired Immunodeficiency Syndrome
APHIS	Animal and Plant Health Inspection Service
ASCO	American Society of Clinical Oncology
ASPA	aspartoacylase
BAC	artificial chromosomes from bacteria
BCPT	Breast Cancer Prevention Trial
BGH	bovine growth hormone
BPPD	Biopesticides and Pollution Prevention Division
BSE	breast self-examination
BST	bovine somatotropin
B.t.	*Bacillus thuringiensis*
C	cytosine
CaMV	cauliflower mosaic virus
CBER	Center for Biologics Evaluation and Research
CCPA	Court of Customs and Patent Appeals
cDNA	complementary deoxyribonucleic acid
CF	cystic fibrosis
CFS	FDA Center for Food Safety, now Center for Food Safety and Applied Nutrition
CFTR	cystic fibrosis transmembrane conductance regulator
CLIA	Clinical Laboratory Improvement Amendments
CODIS	Combined DNA Index System

CSF	cerebral spinal fluid
DDT	dichlorodiphenyltrichloroethane
DNA	deoxyribonucleic acid
DNAP	DNA Plant Technology
DoD	Department of Defense
ECB	European corn borer
EEOC	Equal Employment Opportunities Commission
EIS	environmental impact statement
ELSI	ethical, legal and social implications
EPA	Environmental Protection Agency
ES	embryonic stem (cell)
ESTs	expressed sequence tags
EU	European Union
FDA	Food and Drug Administration
FET	Foundation on Economic Trends
G	guanosine
GC	group-specific-component
GE	General Electric
GYP	glycophorin A
HBGG	hemoglobin gamma globulin
HFA	Humane Farming Association
HGH	human growth hormone
HGS	Human Genome Sciences
HHMI	Howard Hughes Medical Institute
HHS	Health and Human Services
HIAA	Health Insurance Association of America
HIPPA	Health Insurance and Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HUGO	Human Genome Organization
HW	Hardy-Weinberg
ICPEMC	International Commission for Protection Against Environmental Mutagens and Carcinogens
IFOAM	International Federation of Organic Agriculture Movements
IGF-1	insulin-like growth factor 1
INA+	ice nucleation positive
INA−	ice nucleation negative

IND	investigational new drug
IOM	Institute of Medicine
IPM	integrated pest management
IRBs	Institutional review boards
IVF	in vitro fertilization
LDLR	low density lipoprotein receptor
LTRs	long terminal repeats
mRNA	messenger ribonucleic acid
MuLV	Molony murine leukemia virus
NAA	N-acetylaspartate
NAS	National Academy of Sciences
NBAC	National Bioethics Advisory Commission
NCGHR	National Center for Human Genome Research
NCGR	National Center for Genome Resources
NCI	National Cancer Institute
NDIS	National DNA Index System
NEPA	National Environment Policy Act
NHGRI	National Human Genome Research Institute
NRC	National Research Council
OMB	Office of Management and Budget
OTA	Office of Technology Assessments
PAGE	polyacrylamide gel electrophoresis
PCBs	polychlorinated biphenyls
PCR	polymerase chain reaction
PEG	polyethylene glycol
PETA	People for the Ethical Treatment of Animals
PhRMA	Pharmaceutical Research and Manufacturers of America
PID	preimplantation diagnosis
PM	prophylactic bilateral mastectomy
PMA	Premarket Approval Application
PMN	premarket notification
PPA	Plant Patent Act
ppb	parts per billion
PRMW	Pesticide Resistance Management Workgroup
PTO	Patent and Trademark Office
R&D	research and development
RAC	Recombinant Advisory Committee

rBGH	recombinant bovine growth hormone
rBST	recombinant bovine somatotropin
RE	restriction endonuclease
RERF	Radiation Effects Research Foundation
RFLPs	restriction fragment length polymorphisms
RNA	ribonucleic acid
rRNA	ribosomal ribonucleic acid
SCC	somatic cell count
SERM	selective estrogen receptor modulator
SIS	State Identification System
STRs	short tandem repeats
STS	sequence tag sites
TEC	Technology Evaluation Center
TIGR	The Institute for Genome Research
tRNA	transfer RNA
TSCA	Toxic Substances Control Act
UC	University of California
USDA	U.S. Department of Agriculture
UV	ultraviolet
VNTRs	variable number tandem repeats
YAC	yeast artificial chromosomes
ZP	zona pellucida

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The Origins of Biotechnology: A Primer on the Science and Beginnings of Its Regulations

Advances in biotechnology are featured on the news and inspire the formation of many commissions and government advisory committees and even more legal wrangles. Biotechnology, the use of biological processes to produce a product or process for human use and benefit, is often portrayed as a revolutionary, even dangerous, way of viewing and using nature and its elements. It is also an ancient activity. The making of beer, wine and cheese are essentially biotechnologies, though some may question the benefit of wine and beer and indeed others may even question the benefit of cheese. The domestication, breeding and selection of plants and animals for human use using conventional methods also are biotechnologies.

The biotechnology activities that raise concerns and are the stuff of headlines and news programs generally involve the application of recent discoveries in the biological sciences to alter the properties of a living organism by altering its genes, with the goal of producing a product or process for human use. Another term for the process of altering genes is genetic engineering, because the way in which useful biotechnologies are created often involves the alteration of the properties of an organism by engineering its genetic material. The difference between science and engineering is important in thinking about biotechnology. Science can be defined as "the observation, identification, description, experimental investigation and theoretical explanation of natural phenomena" (American Heritage Dictionary, 2nd College Edition). Engineering is "the application of scientific and mathematical principles to practical ends such as the design, manufacture and operation of efficient and economical structures, machines, processes and systems" (American Heritage Dictionary, 2nd College Edition). Freeman Dyson, a physicist and scientist wrote, "A good scientist is a person with original ideas. A good engineer is a person who makes a design that works with as few original

ideas as possible" (Dyson, 1979). The key distinction is between understanding and using that understanding to make something.

One event useful to mark the beginning of the modern, engineering-like and public era of biotechnology is the Asilomar conference on recombinant DNA in 1975. Exploration of the history and stakeholders in the Asilomar Conference in the next chapter will provide ways to look at contemporary debates and dilemmas. However, to understand the issues surrounding the conference as well as the current controversies, some understanding of the basic concepts, language and tools of biotechnology and molecular biology are needed. This brief primer will provide that introduction. To supplement this primer, a list of Internet sites is provided in the Appendix.

Biotechnology could only arise as a practical undertaking when two elements were in place: (1) sufficient understanding of the principles and processes that determined the properties of living organisms, and (2) the tools to modify the properties of living organisms more or less at will—the science and the engineering. The scientific discoveries that provide the understanding of biological processes, the few good ideas of biotechnology, to draw from Dyson's line, can be traced back more than 150 years to include many discoveries and tools drawn from the disciplines of physics, chemistry and genetics and their intersections in biochemistry, bacteriology, physical chemistry and X-ray crystallography. This prehistory of biotechnology particularly had an impact on two branches of biology: cell biology, the study of the structure and function of the simplest unit of life and genetics and the study of heredity, the mechanisms of transmission of traits from one generation to the next.

The discoveries in these fields critical to biotechnology are those that eventually provided understanding at the molecular level of how the characteristics of an organism are inherited and expressed. The crucial discoveries, however, began at the level of the genetics of the whole organism. Modern genetics owes its beginnings to Gregor Mendel, an Austrian Augustinian monk trained in mathematics and botany, who in the 1860s performed experiments on the inheritance of the traits of pea plants. A key to his success was that he limited his studies to categorical traits, traits with two and only two distinct forms. Mendel hypothesized that categorical traits of pea plants such as the color of seeds (yellow or green), seed shape (smooth or wrinkled), length of the stem (tall or dwarf) were determined by what he called factors. One factor was inherited from each parent, and factors were expressed in the offspring in a dominant or recessive form. Dominance requires only one copy of the factor in question to see the effect. Recessive factors required that both copies be the same to see the expression of the trait in the offspring. If an offspring inherited a dominant and a recessive factor, the plant would show the effect of the dominant factor, but could pass on the recessive

factor to the next generation. He tested his hypothesis by crossing (mating) selected pea plants and counting the offspring in each generation that expressed the factor in question, that showed the trait. He was testing his idea by crossing particular plants, predicting the number of offspring of each type and comparing the results to the prediction. Mendel's work was precise and showed that the inheritance of categorical traits was predictable and subject to quantitative, statistical analyses. He carefully documented his experiments and published the results, but his report in the *Proceedings of the Society of Natural Sciences* remained essentially unnoticed until the turn of the century, when it was independently rediscovered by three botanists who repeated his work and obtained the same results. Their recognition of his work and their publicizing of Mendel's insights provided the beginning of a rigorous science of genetics.

The ensuing decades provided insights into the biology and then the biochemistry of cells and whole organisms. The research addresses three related questions:

1. How were the properties, the factors of Mendel, or genes in current language transmitted from generation to generation in a more or less faithful way?
2. What was the chemical nature of the genetic material?
3. How did the genetic material provide instruction for the properties of the cell, the tissue, the organism and the whole body?

While much remains unknown, particularly for question 3 for complex organisms such as humans, a useful understanding has been achieved for the first two questions.

Mendel had set the stage by deducing the rules of inheritance, but moving from a set of rules to an understanding of the chemical basis for the phenomena required knowledge of the structure of the cell and the chemistry of how it functioned. This effort was driven by the belief that the clearest understanding of how living organisms worked would come from an understanding at the simplest level, moving from the whole organism to an organ, a tissue, a cell and finally to the chemicals of which the cells are made. This reductionist approach to biology was highly successful and paralleled discoveries in chemistry and physics, some of which provided not only tools, technologies and concepts but also some of the most creative scientific minds to fuel progress in biological research. Erwin Schrödinger, Max Delbruck, Linus Pauling, Max Perutz and Francis Crick were some of the physicists who applied their understanding of chemistry and physics, particularly thermodynamics, to properties of living organisms and used their insights to formulate new ways of thinking about living things. In 1944 Schrödinger presented a

series of lectures at Trinity College in Dublin, which were published as a short, but highly influential book entitled, *What Is Life?* He addressed two themes in biology, the nature of heredity and the thermodynamics of living systems. Many early researchers in what became molecular biology credit their interest in studying the molecular basis for heredity to the influence of Shrödinger's book. An important consequence of the reductionist approach to biology is that as understanding is expanded there is a presumption that the process may be amenable to the engineer's skills. What can be understood can be modified and used by humans for human benefit.

THE STRUCTURE OF THE CELL

The fundamental structural unit of all living organisms is the cell, the smallest unit capable of independent life. Viruses, which can only live by infecting cells, are an exception to this rule. Each cell is bounded by a membrane or cell wall. Cells come in many varieties. Each single-celled organism has particular properties. In multicelled organisms, from earthworms to humans, different cells play different roles and are specialized for that function. There are, however, recurring patterns of structure and function shared by all cells.

It is now recognized that there are three major forms or kingdoms of living organisms: archae, the most ancient form, able to grow under extreme conditions such as above 90°C; prokaryotes such as bacteria and certain algae; and eukaryotes, such as yeast, amoeba, plants and animals. The cells of eukaryotes have several important distinctions. Eukaryotes, but not prokaryotes or archae, have internal membrane-bound structures called organelles that carry out specific functions.

One of the organelles of eukaryotic cells is the nucleus that contains the structures carrying the genetic information, the chromosomes. In prokaryotes and archae the chromosome is not in a membrane-bound organelle but free within the cytoplasm. The mitochondrion, which functions to break down nutrients to provide raw materials and energy for cellular processes, is another organelle of eukaryotic cells. While each eukaryotic cell has a single nucleus, there are several mitochondria in each cell. It is thought that in the evolution of the eukaryotic cell, a prokaryotic cell was taken into the cytoplasm, enclosed by both its own membrane and the membrane of the engulfing cell. The prokaryote's membrane was not broken down. Mitochondria have a double membrane and carry their own genetic information, supporting this theory. Other organelles of eukaryotic cells function as sites of synthesis of new proteins (ribosomes) and modification and transport of proteins to the membrane and other sites in the cell (the endoplasmic reticulum and the Golgi apparatus).

Plant cells have organelles called chloroplasts that carry out photosynthesis, the specialized biochemistry of plants that allows them to use light energy for the synthesis of sugars from carbon dioxide and water. Certain properties of chloroplasts, the double membrane and the possession of genetic material, suggest that they, as mitochondria, developed from a formerly free-living prokaryote, in this case one capable of photosynthesis.

The cell membrane of eukaryotes is composed of predominantly lipid and proteins with some sugars. Prokaryotes have a cell wall composed of amino acids and sugars. The cytoplasm of eukaryotic cells is not simply a membrane-bound bag of organelles, but contains a complex set of structural proteins, called the cytoskeleton, which gives the cell shape and may give it specialized properties such as the ability to move, to contract or to respond to outside stimuli by changing shape.

CHROMOSOMES AND INHERITANCE

During the middle of the nineteenth century it was concluded that living beings could only arise from other living beings and that life did not arise from nonliving chemical substances. And it was also concluded that parents passed on to their offspring certain properties or traits. Mendel deduced the rules of this process with his studies of peas. In later decades, as the science of microscopy was advancing, the structures responsible for inheritance, chromosomes, were identified by careful observation of cells before and after cell division.

The chromosomes in the nucleus of cells reproduced (doubled) before a cell divided and were then distributed evenly into the daughter cells. This suggested that these structures, the paired chromosomes, carried the information that caused the daughter cells arising from cell division (mitosis) to resemble the parental cells. It was also observed that in fertilization, in sexual reproduction, the sperm contributed a single set of membrane-bound chromosomes to the egg, which contained a nucleus with a single set of chromosomes and that the two parental nuclei fused following fertilization. Thus the chromosomes carry the genetic information that determined the heritable properties of the products of asexual and sexual reproduction. In the 1940s and 1950s scientists such as Tatum, Lederberg and Zinder established that bacteria exchange genetic material by pairing and then inserting the chromosome from one to another.

A phenomenon called bacterial transformation provided evidence that inanimate chemicals carried genetic information. In the 1920s and 1930s Griffith had found that dead bacteria of S strain pneumocci (toxic to a mouse if alive, but not if the bacteria were killed) and live R strain, harmless on its own, were deadly when injected together. This suggested

that a chemical from the dead S strain had changed and transformed the R strain into an S strain. Avery, MacLeod and McCarty proved that the transforming material was DNA. But the conclusion that genetic material in general was DNA was resisted by many scientists who held on to the idea that the genetic material was protein.

Benzer and others showed that transformation occurred naturally through the means of bacteriophage, bacterial viruses that move genetic information from one bacterium to another. Hershey and Chase performed a clever and what now seems a simple experiment to find out if the protein or DNA of the bacteriphage were responsible for transformation. They grew the bacteria from which they isolated the bacteriophage in medium containing an amino acid, the building block of proteins, and a nucleotide base, the building block of DNA, into which different radioactive elements had been incorporated as precursors to protein and DNA. They labeled the bacteriophage protein and DNA with different radioactive markers that could be easily detected and distinguished. Then, using a Waring blender to interrupt transformation at different times, they showed that genetic transformation could occur when only (labeled) DNA but not protein had entered the bacteria. This conclusively showed that for the transfer of genetic information only DNA and not protein was required. DNA carried the genetic information in transformation.

While a debate raged during the 1940s and 1950s as to the nature of the genetic material in other systems, this key work on bacterial transformation by Avery, MacLeod and McCarty and by Hershey and Chase in the 1950s supported the growing belief that DNA was the genetic material responsible not only for bacterial transformation, but in general.

Scientists began to think that DNA provided the genetic information in the details of its chemical structure. Chargaff and others had determined that DNA is a chain of small molecules called bases. There are four chemically different bases: adenine (A), guanine (G), cytosine (C) and thymidine (T). Chargaff carefully analyzed the composition of DNA and found that the number of As was equal to the number of Ts and the number of Cs equaled the number of Gs. The key seemed to be in the order, the sequence, of the bases.

The question that engaged many scientists during the late 1940s and early 1950s was how DNA could provide for a copy of itself, a requirement for the DNA to transmit the genetic information from one cell to the daughter cells at cell division. In 1953 Watson and Crick published their historic paper showing through X-ray studies that DNA was double stranded and that the bases of each strand of DNA paired with the other. They commented in this revolutionary paper that "It has not escaped our notice that the specific pairing we have postulated immediately suggests a copying mechanism for the genetic material" (Watson and Crick, 1953). For the synthesis of two copies of DNA to pass on to daughter