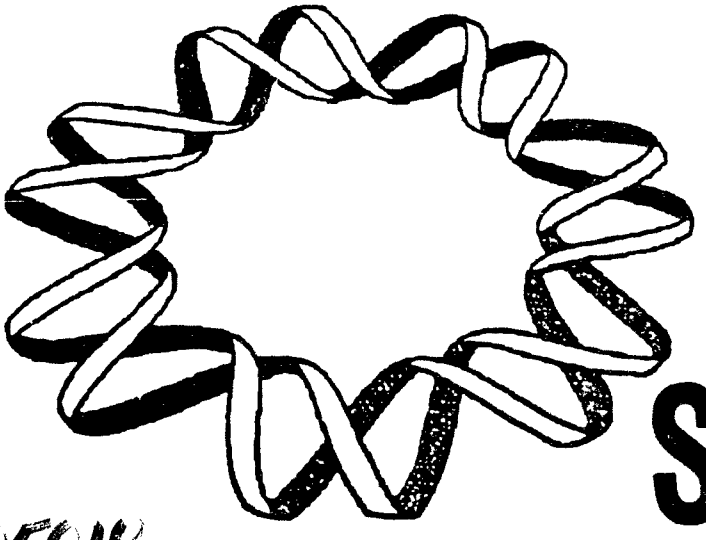
STR Technical Report 89-3

BIOTECHNOLOGY:

Opportunities

to

Enhance Army Capabilites



Army Materiel Command
Directorate for Technology Planning and Management

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Cover Design: The ring of bacterial DNA known as a plasmid, is one of the genetic elements that can be manipulated in biotechnology. The shaded segment represents a foreign gene inserted into the plasmid. Virtually any gene can be inserted, turning bacteria into minute protein factories.

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The reports describes the potential impact of biotechnology on operational enhancements in all phases of Army missions. It addresses the overall goal of Army biotechnology efforts to improve operational capabilities and solve logistical problems. By employing the protein and genetic engineering techniques of biotechnology, significant advances can be achieved in a wide spectrum of materials, processes, and systems. The document highlights the potential impact of biotechnology as a military science in order to realize the tremendous untapped potential for military use of this key emerging technology.

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December 8, 1989

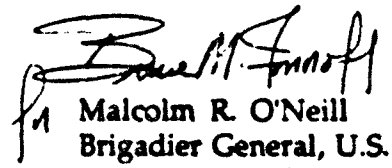
To the Army Research, Development, and Acquisition Community

Biotechnology is one of the fastest growing fields of scientific endeavor in the world. The technical capabilities derived from biotechnology techniques and biotechnology derived products are becoming well known in many fields.

Biotechnology is one of the emerging technologies that are part of the Army's Technology Base Investment Strategy (TBIS). During the 1988 TBIS Conference, the state-of-the-art in biotechnology was reviewed. Since the 1988 Conference, I directed my staff to form a biotechnology working group consisting of members of the Army and DOD R&D community to examine in greater detail some of the recent advances made in the area of biotechnology and to look further into the impact that biotechnology could have on Army systems and operations. The results of their work are contained in the enclosed report.

This report provides a broad perspective on the ways biotechnology can be applied to the many and varied needs of the Army. I encourage all to review this report and consider how biotechnology derived capabilities can be exploited to enhance all aspects of Army operations. Your comments and suggestions to the working group members are welcomed. Their names and phone numbers can be found at Appendix C of the report.

Sincerely,



Malcolm R. O'Neill
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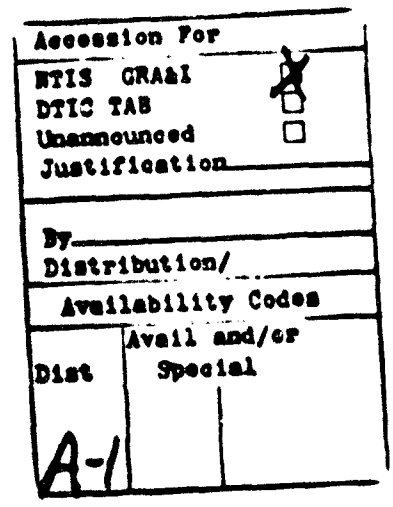
and Management

Enclosure



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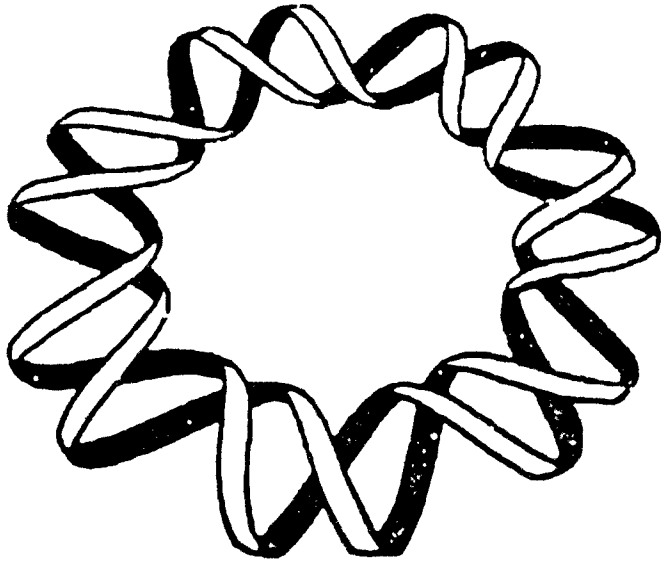

Army Materiel Command
Directorate for Technology Planning and Management

December 1989

Preface

The objective of this paper is to outline and highlight the potential impact of biotechnology on several present and future operational requirements. This paper serves to focus more attention on biotechnology as a military science in order to realize the tremendous untapped potential for the military use of this key emerging technology.

This study was prompted by questions arising at AMC's 1988 Technology Base Investment Strategy Conference and inquiries from TRADOC. To answer these questions and inquiries, an ad hoc task force was formed. The work of the task force resulted in the preparation of this study, the aim of which is to discuss not only what is being done, but also what may be possible to do in the future. Given this scope, many of the applications discussed in this report may raise more questions than they answer. However, the outlining of some ideas here may stimulate new directions in biotechnology research and cooperation and keep the U.S. Army at the forefront of this emerging technological revolution.

During the iterative process of defining the biotechnology concepts and opportunities to meet operational military needs, it was clear that input from TRADOC representatives would provide valuable insight into the operational utility of the concepts and opportunities. "If the technical barriers can be overcome and this concept brought to fruition, will it meet a real military need?" was a question which needed to be answered for each of the application opportunities and concepts. Eleven people from TRADOC, including representatives from Headquarters TRADOC, Headquarters Combined Arms Center, Ordnance School, Infantry School, Signal School, Chemical School, and Armor School met with the task force to be briefed on the concepts/opportunities in biotechnology and to provide TRADOC ideas on the military utility of the biotechnology concepts.

The feedback was overwhelmingly positive. The TRADOC representatives indicated that all of the task force's ideas would meet a military need. Although it was clear that the TRADOC representatives thought some ideas would ultimately prove to be more important than others, no attempt was made to prioritize them into a 1 to N listing because of the exploratory nature of the study.

ACKNOWLEDGEMENTS

A number of people made particularly significant contributions to the successful completion of this study. Dr. David Kaplan, Natick Research Development & Engineering Center, was the principal author of this report. As members of the task force, the following people also made major contributions to the report: Dr. Ira Skurnick, Defense Advanced Research Projects Agency; Dr.

James J. Valdes, Chemical Research Development & Engineering Center; Lt Col Wilkinson, Medical Research Development Command; and, Mr. William Rushing, Army Chief of Engineers. Ms. Pearl Gendason, Army Materiel Command Technology Planning & Management, was the overall project coordinator and working group chairperson.

Captain Warren Shultz of the Naval Research Laboratory graciously provided information on biotechnology outside of the Army and reviewed the draft report. In addition, Dr. Gerald Iafrate, Electronics Technology and Devices Laboratory, and biotechnology expert, Dr. Minoo Dastoor, of the Jet Propulsion Laboratory (JPL) in California reviewed the draft report and provided useful comments.

Serving in an advisory and review capacity were Dr. Sherry Tove, Army Research Office, Mr. John Hansen, Army Materiel Command, Technology Planning and Management, Dr. Abner Salant, Natick Research Development & Engineering Center and Dr. Daphne Kamely, also from Chemical Research Development & Engineering Center. Their insightful comments and constructive suggestions were useful and served to keep the project on track.

TRADOC's participation and input proved to be very helpful. In particular, Lt Col Steven Wade and Cpt Michael Avery readily accommodated all requests for assistance. Appreciation is also extended to Dr. Phillip Greenbaum, Foreign Science and Technology Center, and Ms. Glenda Griffin and Mr. Don Stout of LABCOM's Intelligence Office, for their assistance.

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Executive Summary

Within the past twenty-five years major advances have been made in the life sciences. New research in the life sciences, using the techniques of biology, biochemistry, and biophysics, has resulted in a new field called biotechnology. Biotechnology research endeavors have the potential of solving many of the military operational problems faced by the Army which, as a land combat force, has its personnel and equipment exposed to a wide range of natural and enemy generated environments.

Biotechnology also offers solutions to Army needs, not specifically related to battlefield environments. Among these needs are improved energy sources and new materials for military applications.

The overall goal of Army biotechnology endeavors is to improve operational capabilities and solve logistical problems. By employing protein and genetic engineering techniques of biotechnology, it is anticipated that significant advances can be achieved in a wide spectrum of materials, processes and systems. Specific applications of biotechnology in biodetection, biodegradation, bioengineered materials and specialty chemicals are expected to be available to the Army community in the future. However, biotechnologies could be applied to other Army needs as well.

Department of Defense technologies that may be enhanced through biotechnology applications are numerous. Much of the Army's biotechnology research so far has gone into the development or improvement of vaccines, diagnostic tools and possible defenses against biological or chemical warfare agents. Current nonmedical biotechnology exploratory research efforts are in the development of new materials such as adhesives and lubricants, light weight armor, composites, nonpolluting cleaners and degreasers, and ultrasensitive sensors. Decontaminants and coatings, improved rations, fuel and water production, navigation systems, and biomemories for high speed computers and robotics are further areas amenable to biotechnology applications.

Some of the ways biotechnology may be exploited for Army needs are in the production of

- *High performance fibers having both high tensile strength and energy absorption;*

- *Lighter and lower cost ceramics for use in armor, radomes, and electronics;*

- *Ultrasensitive sensors for detecting chemical and biological agents, control of manufacturing processes, and in environmental protection;*

- *Self assembling biomaterials for use in electronic components such as high current density cathodes;*

- *Reactive materials for rapid and effective degradation of chemical and biological agents;*

- *Soldier rations optimized for specific climates and missions; and*

- *Reactive materials and coatings capable of providing protection against directed energy radiation, or capable of mimicking local natural signatures to provide camouflage protection.*

The Army's approach in biotechnology research and development is multifaceted. Most of the Army's fifty million dollars per year biotechnology investment is focused on medical applications, while more modest investments are being made in areas such as synthesis of fibers, biological sensors, ordnance enhancements, and production of safe decontaminants. There are presently six Army research and development organizations involved in biotechnology endeavors. The work of these Army organizations is coupled and coordinated with work undertaken by the academic community through the University Research Initiative, as well as with programs undertaken by other DOD agencies outside the Army.

This report is a first step toward development and implementation of a long term strategy to exploit the full potential of biotechnology for Army applications. The next step is the preparation of a cohesive plan which identifies specific goals, resources, and actions to be taken.

I. INTRODUCTION

Historical Perspective

It was not until the early 1940s that scientists demonstrated that DNA was the only substance necessary to transfer characteristics from one organism to another. But the real milestone in the history of biotechnology came when the partnership of James D. Watson and Francis H. C. Crick developed a structural model of the DNA molecule by combining what was known about the chemical content of DNA and X-ray diffraction studies with what was known about the spatial and angular relationships between atoms in molecules. In 1953 Watson and Crick published their findings of the now famous double helix pattern of DNA earning them the Nobel prize. This discovery rejuvenated research in the biological sciences and has opened an era in the life sciences akin to the era in physics that was started by the theory of the atom.

This new research in the life sciences, using the techniques of biology, biochemistry and biophysics, has resulted in a new field of technology called *biotechnology*, a term coined to denote the use of biological processes to produce new and useful products.

In retrospect, biotechnology, as an endeavor of mankind, is not a new enterprise. For centuries biotechnological processes have been used for the production of alcohols, live stock breeding and foods. What is new in the current practice of biotechnology is the understanding of the factors which control the generation and operation of biological organisms, and the laboratory micro-techniques which enable experiments and processes to be manipulated at the genetic level.*

Army Needs

To date, the products of biotechnology fall into two categories - genetically engineered organisms, and the substances produced by genetically engineered organisms. Such organisms and the substances which they produce have found wide utility and acceptance in the civil sector, where genetically engineered microorganisms have been developed for the production of proteins, like insulin, and for cleaning up oil spills and waste waters. But biotechnology applications are not limited to the civil or private sectors. Biotechnology research endeavors have the potential of solving many of the military operational problems, especially those faced by the Army. The Army, as a land combat force, necessarily has its personnel and equipment most exposed to a wide range of

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* The concepts and terminology used in the field of biotechnology may not be familiar to some readers. As an aid to these readers, a short tutorial is included as Appendix A, along with a glossary of terms in Appendix B.

natural and enemy generated environments. Natural environments include diseases, limited water supplies, and temperature extremes. Enemy generated environments include chemical and biological warfare agents, and ballistic and directed energy threats.

The Army also has other needs that appear amenable to biotechnology solutions. These include energy sources for fixed and mobile facilities, decontamination of hazardous materials, and production of new materials for military applications.

Army Biotechnology Interests

The following concepts are inherent in this field, regardless of the application of interest:

1. A variety of products (i.e., enzymes, structural macromolecules, antibodies, receptor sites) are elaborated by biological systems. These products contain many unique structural and functional characterisitics which have not been reproduced or achieved through synthetic approaches. These products may be usable directly, with minor modifications, as composite structures, or as supporting matrices. In addition, not only the primary structures, but also the higher order interactions and conformations become critical in the function of these natural products.

2. A great deal can be learned from design, manufacturing, and processing principles in nature. Using relatively simple building blocks, natural systems exhibit a complexity of design meeting every environmental challenge. We stand to learn a tremendous amount about basic principles governing the design and engineering of products with enhanced functional properties which will be applicable to both biological and synthetic systems or processes.

3. With the tools now available in biotechnology, we can improve upon and exploit the products and processes that have developed in nature.

The Army's biotechnology research and development interests are multifaceted and include such topics as :

- synthesis of novel fibers, protective coatings and packaging materials;
- development of ultra sensitive sensors for biochemical substances;
- development of bioengineered foodstuffs;
- biosynthesis of explosives;
- treatment of process waste waters and contaminated soils and waters; and,

• synthesis of medicines and vaccines.

The impact of biotechnology to the area of medicines and vaccines is well known and the Army has had a significant resource investment in this area for several years.

Army Medical Applications

Common medical practices have already greatly benefitted from biotechnology discoveries and applications. Vaccines and prosthetics among many others have been significantly improved and diagnostic tools and mass production of vital substances, such as insulin, have become available for the first time. Biotechnology offers new approaches for coping with Army medical needs as well. Enhanced protection against biological warfare agents, infectious diseases, and combat casualty (i.e., septic shock) are a few areas of possible benefit. The development of vaccines with generic activity against broad classes of toxins, biological agents, and infectious disease organisms would be desirable for enhanced protection. Immunological assays, genetic probes, and receptor interactions would provide rapid and specific methods of identification of organisms to ensure rapid and appropriate diagnosis and treatment. Figure 1, "Biotechnology Diagnostic Tools ", describes three different biotechnology tools used for diagnostics. Novel vaccine carriers/delivery systems and prophylactic/therapeutic measures (e.g., drugs and vaccines) to prevent casualties are a few of the desired goals.

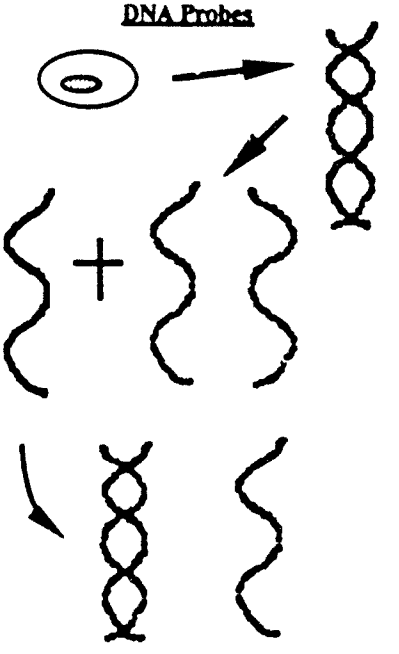
TABLE 1: DISEASES THAT MAY BE TREATED OR PREVENTED USING BIOTECHNOLOGY

CONDITION	NUMBER OF PEOPLE IN U.S. AFFECTED	DRUG OR VACCINE
Heart Attack	1.5 million per year	TPA
Cancer	1 million new cases per year	Interferon, Interleukin-2, Tumor necrosis factor, Colony stimulating factors, Growth factors, Monoclonal antibodies armed with cancer-killing drugs
AIDS	More than 1.5 million infected with the HIV	CD4, Interferon, Interleukin-2, Dideoxycytidine, Colony stimulating factor, Genetically engineered vaccines
Diabetes	600,000 to 1.1 million need insulin	Human insulin
Dwarfism	1,700 children received growth hormone	Human growth hormone
Hemophilia	20,000	Factor VIII purified with monoclonal antibodies, Genetically engineered Factor VIII
Anemia	500,000 people including 90,000 on kidney dialysis	Erythropoietin
Acute tissue rejection episode in kidneys	4,500 kidney transplant patients may experience tissue rejection per year	Orthoclone OKT3

FIGURE 1: Biotechnology Diagnostic Tools

Monoclonal Antibodies are highly specific diagnostic agents used to identify infectious diseases and other conditions. They are cloned from a single white blood cell that produces a specific type of antibody. When used in diagnostics, the monoclonal is linked to an imaging agent or drug so that when it finds its specific disease it will transmit the information to the doctor. Monoclonal antibodies have been used to diagnose various cancers, blood diseases, pregnancy and to verify the existence of HIV antibodies.

Since learning how to cut DNA into specific fragments, scientists have identified variations in the size of DNA segments, called polymorphisms, associated with certain diseases. DNA Probes are short portions of DNA that are able to attach themselves to polymorphisms associated with specific diseases. The probes are labelled with a radioactive substance and can often detect and identify a disease or infection in a matter of hours, rather than the days current tests require. The figure at right illustrates how DNA material is extracted from a cell and separated. This DNA is then exposed to a DNA probe of the suspected virus. If the probe binds with the DNA from the cell the test is positive for that virus. DNA probes are used to diagnose a variety of genetic diseases and to detect disease-causing microorganisms such as Salmonella.



As more is learned about the genetic code, scientists are able to locate and track defective genes, the role they play in diseases, and their locations relative to other genes. This process is called Gene Mapping. The complete genetic code of a human being is contained in 50,000 to 100,000 genes located in the 23 pairs of chromosomes. By breaking the chromosomes into pieces called RFLPs (restriction fragment length polymorphisms), scientists are able to mark the location of defective genes. This technology is used to diagnose cystic fibrosis, polycystic kidney disease, and familial forms of Alzheimer's disease and colon cancer among others. Currently much of the scientific community is focussed on mapping the genome, or entire genetic material of humans.

Biotechnology based tests are being used outside the medical field as well. In 1987 DNA tests were upheld as evidence in criminal cases. Law enforcement may also be helped by using monoclonal antibodies and DNA probes to test blood and anaylyze body fluids for more accurate identification of both suspects and victims.

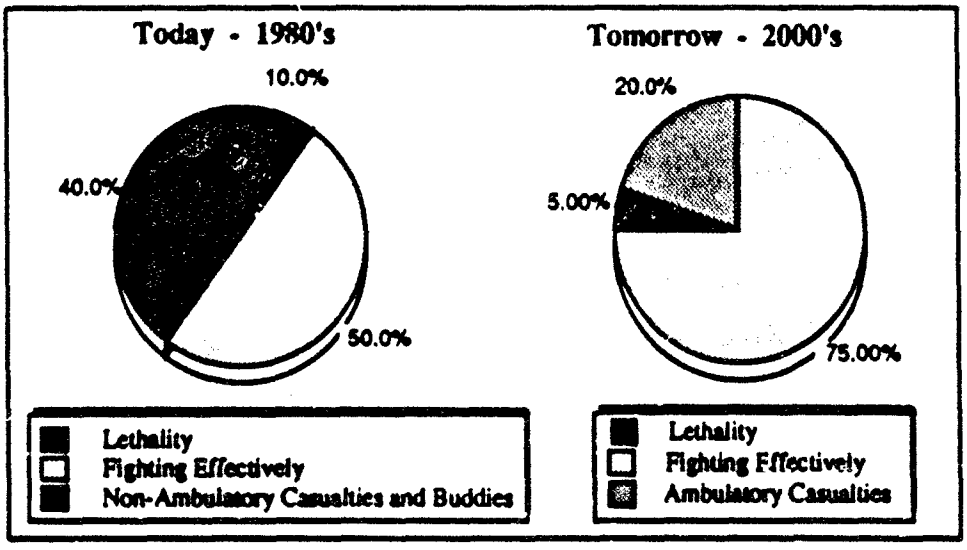
Artificial blood for combat casualty treatment and long-term storage and supply needs could be developed. Biomimetic systems could also be developed as replacements for blood, as oxygen recovery systems from water, or as organ/bone replacements or implants. Table 1, "Diseases ... ," page 5, outlines how biotechnology has already helped treat and prevent some diseases affecting millions of Americans.

Examples of the potential impact of biotechnology on medical needs for the Army include:

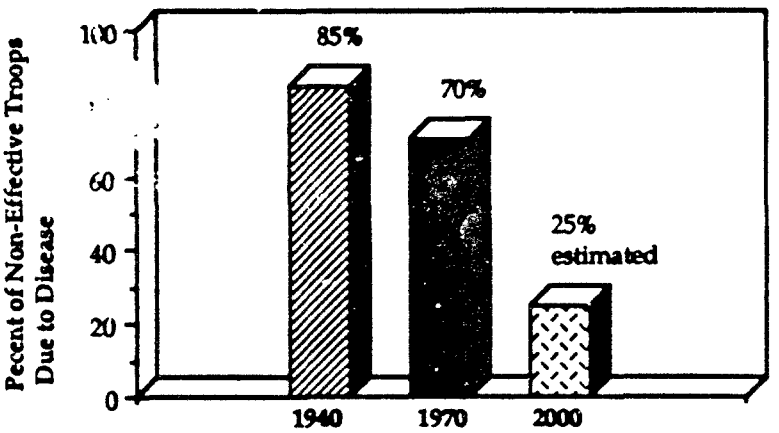
- •combat casualty care
  - wound repair, organ regeneration, nerve cell repair, and artificial blood
- •prophylaxis
  - protection from radiation and biological and chemical agents
  - immune system enhancement
- •diagnostics
  - monitoring and detection in body fluids using biosensors
  - molecular probes
- •drug and toxin therapy
  - immunoregulatory, anti-viral compounds, antitoxin drugs
- •vaccines
  - to parasites, bacterial, and viral diseases.

Graph 1, "Impact of Disease Reduction on Force Effectiveness," diagrams the toll paid in lost effectiveness due to disease and injury. Graph 2, "Percent of Force Fighting Effectively," shows the impact of biotechnology on reducing disease related lost duty time.

GRAPH 1: Impact of Disease Reductions on Force Effectiveness



GRAPH 2: Percent of Force Fighting Effectively



The application of biotechnologies will accelerate the reduction of the largest source of lost duty time – disease.

Bioengineered Vaccines - Against Toxins and Infectious Diseases

Current Problem

Available vaccines perform well against single threats. For example, there are immunizations against microorganisms or toxins. Future needs include prophylactic/therapeutic measures (such as vaccines and drugs) to prevent casualties and provide protection from wound infections which could otherwise end in septic shock and death. They provide generic protection against broad ranges of biological toxins and provide medical countermeasures to detect and defeat biological warfare threats. Immunizations could also provide single vaccination compounds giving active immunity against several organisms and provide vaccines with a low occurrence of adverse reactions. Currently available vaccines can not meet these needs.

Biotechnology Solution

Using biotechnology tools to develop vaccines will make attaining the goals stated above much more likely. Vaccines engineered for broad-based or generic activity, cell fusions, monoclonal antibodies, genetic probes for rapid identifications, synthetic and vectored vaccines, novel drug and vaccine delivery systems (i.e., liposome carriers, encapsulation), and protein engineering for improved response are potential areas of research that will permit the medical community to meet these needs.

Identification of Casualties

The military has a continuing need to identify casualties in the field (the Graves Registration function). Rapid assay methods based on DNA fingerprinting or probe analysis would provide the means for rapid confirmation of identity in the field. The use of these technologies would require only small quantities of material and would be fast, highly specific, and simple to operate. The development of field kits, artificial intelligence systems, and associated miniaturization to accompany these technical developments would also be a necessary feature.

Diagnostics

Medical diagnostics has already benefited from the development of biosensors designed specifically to recognize infectious diseases. An offshoot of the original recombinant DNA techniques that gave rise to the biotech industry is the development of monoclonal antibodies. Monoclonal antibodies are proteins produced, not through recombinant DNA techniques, but through the fusion of a tumor cell with an antibody-producing white blood cell. The result is a virtually immortal clone of cells, producing antibodies that are chemically identical. Monoclonal antibodies have a remarkable ability to attach to specific molecular configurations and are ideal therefore for a wide range of medical research applications such as exposing diseased areas to screening instruments, conferring passive immunity against disease or carrying bioactive agents to diseased tissues.

Not as well known are the applications of biotechnology to the other areas of Army interest. Thus this report, after outlining some medical applications, concentrates on biotechnology opportunities beyond the field of medicine and explores applications of biotechnology to areas as diverse as foodstuffs and radar systems. This report presents an overview of some of the possible applications of biotechnology to the present and future needs of the Army. Specifically, materials and processes are suggested which would exploit the present and emerging knowledge of biological processes, and in particular genetic engineering processes.

II. CONCEPTS AND OPPORTUNITIES

The potential impact of biotechnology on operational and logistical needs of the Army in various technical areas is outlined in the following pages. Many materials necessary for operations could be improved and/or more easily produced through the application of biotechnology, making facilities more operationally self sufficient and cost efficient. Some of the technical concepts discussed include specific results anticipated from the applications of biotechnology. These are presented by defining a current problem and outlining biotechnology solutions. Other concepts are more speculative in nature and outline current limitations that may be overcome through biotechnology applications.

A. ADVANCED MATERIALS

Bioengineered materials are polymers, compounds or mixtures of natural substances which are derived from biological systems (e.g., bacteria, fungi). They include fibers, composite ceramics, adhesives, thermoplastics, and others. The superior physical, chemical and biological properties of natural materials, and their tailorability and ability to function in environmental extremes make bioengineered materials the logical choice upon which to model useful materials or processes. Improved understanding of the principles governing the structure-function relationships of natural materials will enable scientists to engineer or manipulate organisms to produce and improve the characteristics of natural materials to meet the material needs of the Army and DoD.

Insulation, anti-ballistic protection, adhesives, lubricants, packaging materials, plastics, ceramics, and other advanced materials currently in use carry certain drawbacks in cost, weight, durability, usefulness in various situations, etc. The design and development of new biologically-based materials with enhanced performance (e.g., lighter weight, reduced production costs, decreased maintenance costs, reduced logistical burden) would yield a significant variety of operational improvements over current materials. The development of intelligent or smart materials or material systems which "learn" from the environment can also be considered.

For example, protein-based elastomers could be exploited as alternatives to butyl rubber to improve elasticity at low temperatures, to resist penetration by petroleum, oil and lubricants and to retain protective capability against chemical agent threats. Also, ceramic composite structures produced through tailored biomineralization processes, and biothermoplastics produced through fermentation-bioprocessing may be exploited. Improved composite structures and their potential for integration with other material functions (in the case of

protein-based fibers) are additional advantages to these biotechnology-derived products.

Historically, the most functional thermal insulating materials have been protein-based fibers such as wool, fur, feathers, and down. Enhanced thermal protection may come through protein-engineering. Developing bioadhesives for high strength composite materials, with potentially superior binding properties and rapid setting in wet environments, will result in extended shelf life, economic benefits, and improved capabilities for field repair. Also, bioplastics could replace traditional synthetic materials used in equipment because of greater strength, lighter weight, better economics, environmental stability, and tailorability for specific purposes. The potential for generating materials on site (such as protein-based foams) could further reduce logistical burdens.

Advanced materials are necessary for a variety of functions. The following paragraphs describe the role biotechnology plays in three types of materials and some research programs the Army currently sponsors.

1. *HIGH PERFORMANCE FIBERS*

Current Problems

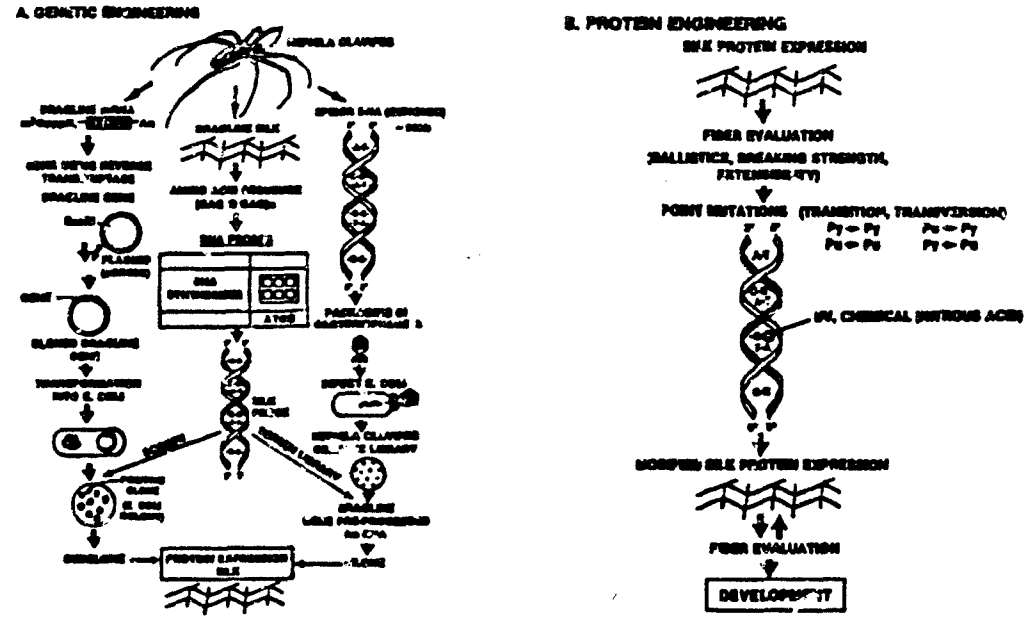
Current ballistic protection for personnel relies on Kevlar, a synthetic fiber, which, in its current form, provides fragment protection and partial protection from bullets, but does not provide protection from flechettes. Also, Kevlar costs are very high. Future Army needs include protection from all ballistic threats (fragments, bullets, flechettes) and the incorporation of high performance fibers into composite materials. New materials under development (e.g., Spectra, polybenzthiazoles) provide meaningful reductions in weight (up to 20%) but do not promote broadened performance against the three threats when compared to Kevlar. In addition, these synthetics are not easily incorporated into composites due to their non-reactive surface properties.

Biotechnology Solutions

Bioengineered protein fibers based on silk may provide a solution to these problems. Figure 2, "Protein Engineering of Spider Silk," diagrams a two stage process of bioengineering spider silk-based high performance fibers. Spider silk fibers exhibit exceptional physical properties, including high energy absorption before breaking and excellent tensile strength. The energy required to rupture silk fibers increases at higher rates of loading. This is an unusual property for fibers and is potentially important in terms of absorption of impact energy. Non-optimized silk, such as from a silk worm, has demonstrated excellent ballistic limit values, although not as good as Kevlar. Spider silk, which is superior to

silk worm silk in physical tests, has not been evaluated for ballistic performance as a woven fabric.

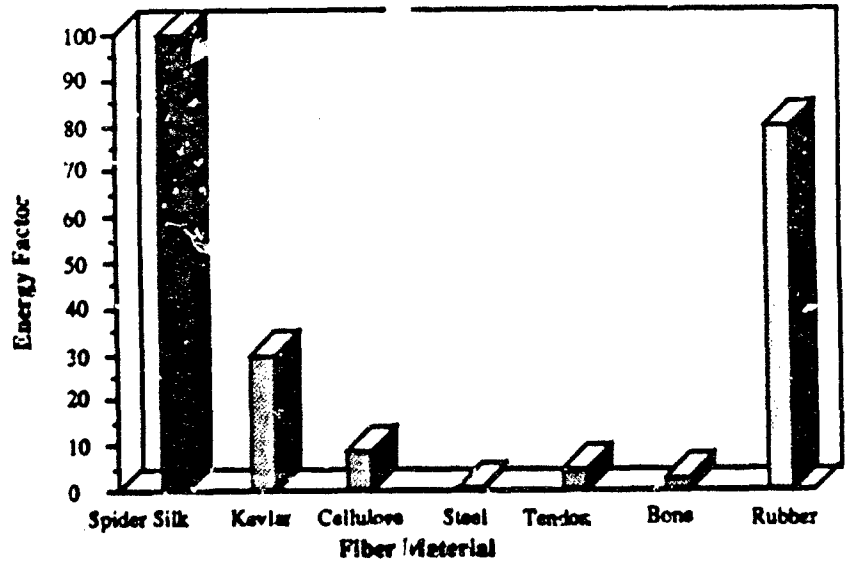
FIGURE 2: Protein Engineering of Silk for High Performance Fibers



(Adapted from TBISC'83 Conference Report, Vol.1-B. page 1127)

Graph 3, "Relative Energy Absorption to Break Fiber Materials," illustrates the relative performance of different natural and synthetic materials in fiber form.

GRAPH 3: Relative Energy Absorption To Break Fiber Materials



The production of silk can be manipulated at the genetic level to modify properties as needed, thereby representing an ideal fiber to study ballistic behavior. Silk also contains reactive functional groups which could result in strong composite interactions and the potential for integration with other material functions (i.e., chemical/biological protection). A hard surface may still be required to obtain protection from flechette threats; however, it is conceivable that because of the reactive nature of the silk protein, this surface can be better integrated with the fiber in such a heterogeneous system.

Silk proteins represent an excellent model system to guide the understanding of ballistic failure mechanisms and physical property correlations with ballistic performance. The advantages of silk fibers over synthetic can be seen in Table 2, "Bioengineered High Performance Fibers".

TABLE 2: BIOENGINEERED HIGH PERFORMANCE FIBERS

PERFORMANCE	MATERIAL			
	Nylon	Kevlar	Silkworm Silk	Spider Silk
Tensile Strength ($>10^9 Nm^{-2}$)		•		•
Ballistic Limit Value (400 m/sec)		•	•	•
Extensibility to Break (>15%)	•		•	•
Strong Integration Potential			•	•
Composite Binding Potential			•	•
Protection from Multiple Threats			*	*
High Modulus ($>10^{10} Nm^{-2}$)		•	•	•
Model System for Study			•	•
Potential for Further Improvements			•	•

*• yes, * unknown but high probability*

2. *BIOCERAMICS*

Current Problems

Equipment and hardware protection from ballistic threats is primarily accomplished using metals and ceramics, the use of which inflicts a significant weight penalty. In addition, the use of ceramic materials is limited by lack of uniformity, inclusions, impurities, and difficulties with producing small uniform sized ceramic particles (0.1 micron). The ability to produce uniformly sized particles would result in more even and reactive particle surfaces for processing and avoid the need for sintering aids. The availability of low cost, uniform ceramic particles would broaden and enhance ceramics applications. Improved ceramic composites for low observables would also enhance operational capabilities.

Biotechnology Solutions

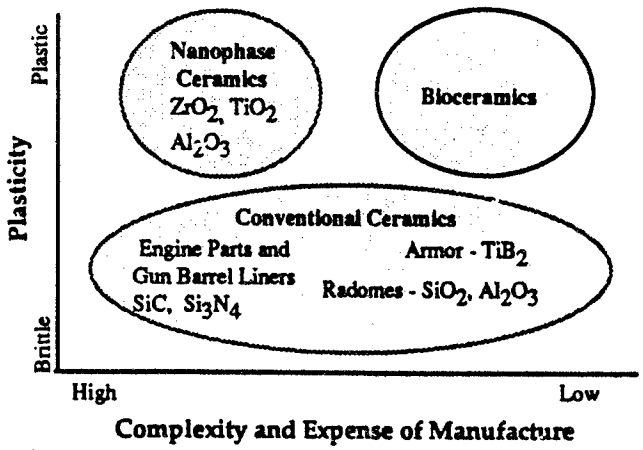
Biotechnology approaches have the potential to enhance and broaden performance and reduce costs for traditional ceramics. Table 3, "Manufacture of Ceramic Particles," and Graph 4, "Ceramic Manufacture, Complexity and Expense," illustrate how the manufacture, complexity and expense of ceramics could be significantly improved through biotechnology techniques. Bioceramic design and manufacture could improve the ballistic protection provided by the composite at a reduced weight and lower cost. These composite materials could also be designed and applied for improved vehicle, shelter and structural integrity through increased lifetimes and reduced wear, for example in communication command-post shelters.

TABLE 3: MANUFACTURE OF CERAMIC PARTICLES

CHARACTERISTIC	PROCESS		
	Nanophase	Conventional	Bioceramics
Energy Requirements (<23 calories/gram)		*	•
Cost (<$1 per pound)		*	*
Super Plasticity (forgeable at high temperature)	•		•
Uniform Small Particle Size (nanometer range)	•		•

*•yes, * unknown but high probability*

GRAPH 4:Ceramic Manufacture Complexity and Expense



The use of organic matrices to provide control over crystal morphology, orientation, and size affords new process options for achieving low cost, uniform, small size ceramic particles for shaped objects, or for composite applications. The development of these processes would provide lower cost and faster processability of ceramics and broaden ceramic applications.

The use of these products in composites would provide benefits in terms of reduced crack propagation, and overcome some of the intrinsic material limitations due to brittleness. Also, low observable properties could be enhanced by modifying the organic matrix component to provide appropriate systems control. For instance, an example of a natural material is bacterially produced magnetite, which has a highly refined crystallographic structure with well ordered, elongated, bullet-shaped, single crystallites. Such morphologies are not observed with the inorganic preparations of traditional synthetic ceramic approaches, resulting in magnetic anisotropy.

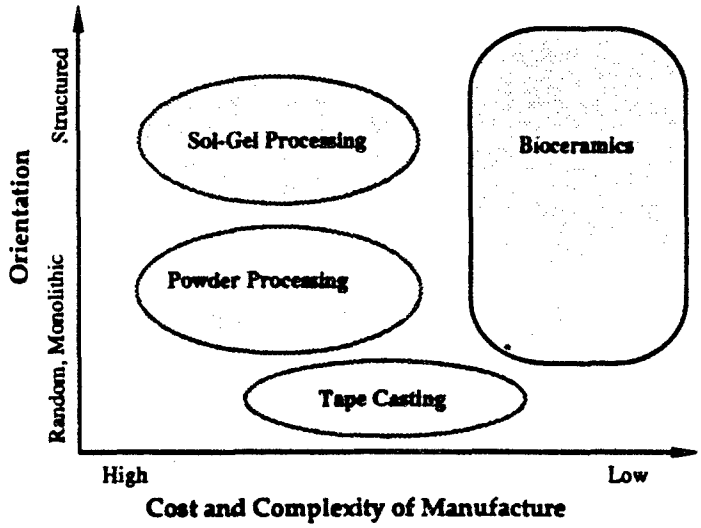
Current magnetic recording media use inorganic magnetite. Ideally it would be deposited as individual parallel needles. However, because of the magnetic forces existing between the individual particles, it is difficult to prevent agglomeration. Therefore, coatings tend to be uneven and irregular and this in turn limits computer performance. The "pre-organized" form of bacterial magnetite could allow a more perfect coating and thus result in higher information density. Table 4, "Ceramic Manufacture for Electronics Applications," diagrams the characteristics of four ceramic manufacture processes. Graph 5, "Cost and Complexity of Manufacturing Ceramics for Electronic Applications," depicts the cost versus complexity of ceramic manufacture.

TABLE 4: CERAMIC MANUFACTURE FOR ELECTRONIC APPLICATIONS

CHARACTERISTICS	PROCESS			
	Sol-Gel	Tape Cast	Powder	Bioceramic
Energy Requirements (<60 cal/gram)	•	•		•
Cost (<$100/pound)				•
Rate of Manufacture (1 lb. in < 1 hour)		•	•	•
Orientation (>60% alignment of dipoles)	•		•	•

• *yes,* • *unknown, but high probability*

GRAPH 5: Cost and Complexity of Ceramic Manufacture
for Electronic Applications



3. *BIOPOLYMER PACKAGING MATERIALS*

Current Problems

Current packaging materials are recalcitrant, e.g., not responsive to treatment, and therefore result in significant environmental contamination. Reducing signatures in the field from discarded packaging, "lightening-the-load" through the use of multi-functional materials, and enhancing storage stability for contained foods are all desired operational improvements.

Packaging materials, meeting some of these needs, are under development. However, these materials are not rapidly biodegradable and biocompatible. For example, starch-polyethylene co-polymers are being produced for packaging, but only the starch portion (usually less than 10%) is degradable, and the incorporation of the starch compromises the physical properties of the packaging film. Table 5, "Biopolymer Packaging Materials," compares characteristics of synthetic and biopolymer packaging materials.

TABLE 5: BIOPOLYMER PACKAGING MATERIALS					
CHARACTERISTICS	PACKAGING FILMS				
	SYNTHETICS			BIOPOLYMERS	
	POLY-ETHYLENE TEREPH-THALATE	POLY-PROPYLENE	POLY-ETHYLENE	CHITOSAN	POLYESTERS
Stress at break (>50MPa)	•	•		•	•
Extension to break (>20%)	•	•	•		•
Oxygen Permeability (<100cc/m^2/24 hour)	•			•	•
Biodegradable				•	•
Heat Sealable		•	•		•
Density (>1.0 to avoid floating)	•			*	•
Light Stable	•			•	•
Biocompatible Breakdown products				•	•

• *yes,* * *unknown but high probability*

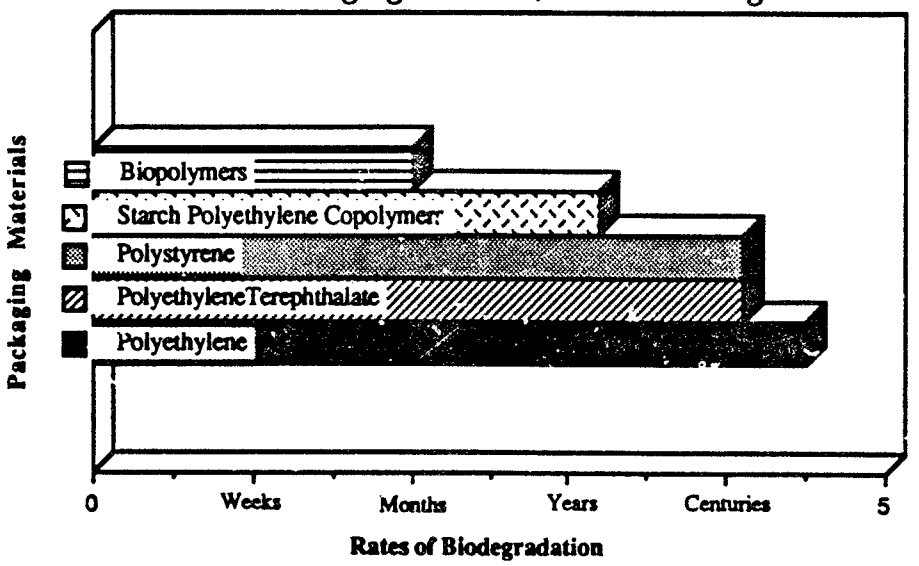
Biotechnology Solution

Biopolymers (e.g., polysaccharides and thermoplastic polyesters) can be fabricated into biodegradable packaging materials. These polymers, produced by microorganisms, can be cast (polysaccharides) or thermally processed (polyesters) into films with physical properties comparable to currently used synthetics, except that the biopolymer films exhibit lower oxygen permeabilities (for longer shelf-life for stored foods), and are biodegradable. In addition, the biopolymer films are microwavable, are stable to oils/grease, are transparent or translucent, and are biologically compatible (could be eaten).

Incorporating biopolymers to enhance degradable packaging for food and equipment will prevent field signatures and reduce logistics and disposal burdens. With appropriate pretreatments these films could also be consumed for nutritional sustenance, thereby reducing requirements for carried rations to lighten the load. The rapid disposability of these packaging films would reduce signatures in the field or in ocean environments. Graph 6, "Packaging Materials, Rates of Biodegradation," compares the rates of biodegradation of five packaging materials. An obstacle in this regard is that the mere fact of being biodegradable, in part, defeats the purpose of protective packaging by making the packaging readily subject to decay. However, genetic level controls should enable the

development of biopolymer packaging with tailored or controlled lifetimes, an area currently under study.

GRAPH 6: Packaging Materials, Rates of Biodegradation



B. BIOSENSORS

Current Problems

The chemical and biological threat is becoming more complex, and an expanded threat detection capability is required to maintain or improve our operational capabilities. Currently fielded detection systems can only detect approximately 50% of the known chemical threats. Systems under development (e.g., portable gas chromatograph/mass spectrometer and laser detectors) are expected to work against all known chemical threats, but are still limited with respect to future chemical threats. In addition, these detection systems are complex, with the associated reliability problems and high cost. The capability to detect all biological and chemical agent threats, multiple agent threats, and future bioengineered threats would provide improvements over our current capabilities. In addition, detection of industrial activities through environmental monitoring could provide early strategic information for improved readiness and arms control monitoring.

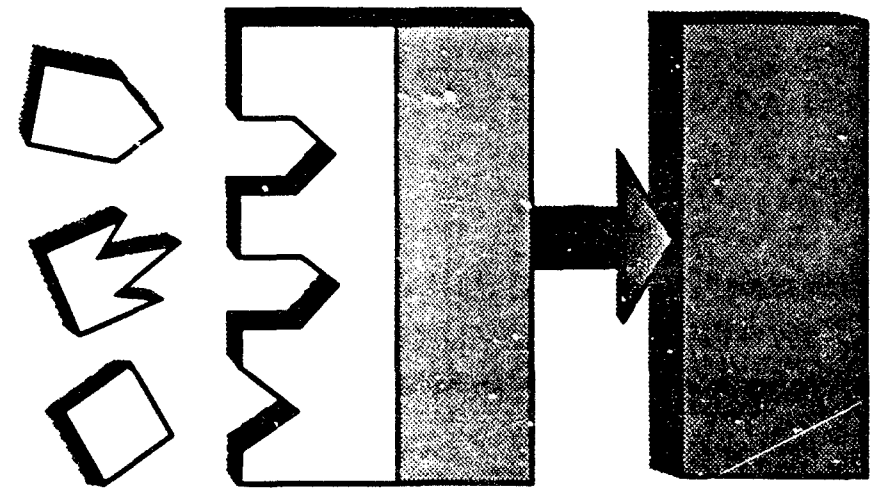
Biosensors, based on the direct combination of a matrix-bound bioactive substance (the receptor) with an electronic device for signal transduction, are able to recognize and analyze biological and chemical agents, providing the requisite speed and accurate detection capabilities for battlefield use. Biosensors combine the recognition capability of biological receptors with the transduction and amplification of microsensors, providing wide spectrum detector capabilities for toxins, chemical agents, and pathogens. As neuroreceptors, ion channels, antibodies, and other natural biological recognition sites are isolated and purified, and in a few instances cloned and produced, the possibility of engineering recognition sites for specific threat agents draws closer. Biosensor researchers are currently attempting to reconstitute or artificially mimic membrane bound reception channels for use as specific, ultra-low level analytic devices. However, the production and stabilization of receptor proteins have been major technological bottlenecks. Additional issues, such as the coupling of the biological component to a transducer, the device that converts power from one system for use in another, must also be addressed.

Natural bioluminescence reactions may provide important models for a different type of biosensor design, as described in Figure 3, "Luminescence." Figure 4, "Biosensor Design," illustrates the problems involved in a biosensor in which the response relies on the agent being studied interacting at an interface. One solution to the biosensor transducer problem may be bioengineered films and polymers which may confer enhanced stability as well as signal transduction at the microsensor interface. Apart from cloned receptor systems, whole cell methods which respond to changes in surface potential of membranes are also under development for additional biosensor applications.

FIGURE 3: Luminescence

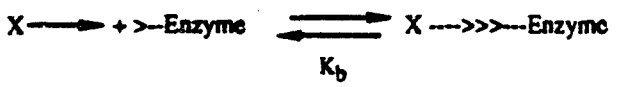
Luminescence, or light emissions by solids, is very common. Items such as cane sugar, wintergreen candy and some adhesive tapes emit light when rubbed, compresed or cracked. This form of luminscence is called triboluminescence. It results when an atom or molecule of the substance receives sufficient energy to excite an electron into an unusually high energy state. When the electron drops back to normal, the excess energy is released from the molecule as light. The spectrum of the emitted light has given scientists information on the causes of the phenomenon, but there are many mysteries remaining. Triboluminescence is already being used as a tool to understand how materials break. When we are able to manufacture luminescent materials in sufficient quantities they could be adapted to detect fractures in nuclear power plants and satellites, and other structures which endure stress.

FIGURE 4: Biosensor Design



In a biosensor on which the response relies on the analyte interacting at an interface, there are certain physiochemical requirements that must be met. For instance, where an enzyme is the sensor and is immobilized on the surface of the transducer, as shown above, there are several factors to be considered. They are listed in the table below. A problem with this kind of sensor is that as its sensitivity increases due to an increased binding ability of the receptor and the concentration of analyte molecules decreases, the overall response time of the sensor increases.

Factors to Consider in Biosensor Design



1. K binding constant (Kb)
2. Rate →
3. Mass Transport of X

As sensitivity increases due to increased Kb and concentration of X decreases, the response time increases.

(adapted from TBICC'88 Conference Report Vol.1-B, pages 1083 and 1097)

Biosensor systems using the whole cell method are referred to as bioprobes and would provide generic detection and quantitative information on biological agents. These systems would find application in certain scenarios where the identification of the specific threat is not required, such as in battlefield response. Improvements in cell culture techniques and freeze-drying methods to stabilize cells for long time frames will be required for further development of these systems. Table 6, "Biosensor Transducers," summarizes some biosensor operating modes and applications.

TABLE 6: BIOSENSOR TRANSDUCERS

Transducer System	Measurement Mode	Typical Applications
Ion-selective electrode (ISE)	Potentiometric	Ions in biological media; enzyme electrodes; enzyme immunosensors
Gas-sensing electrodes	Potentiometric	Gases; enzyme, organelle, cell or tissue electrodes for substrates and inhibitors; enzyme immunoelectrodes
Field effect transistors (FET)	Potentiometric	Ions; gases; enzyme substrates and immunological analytes
Optoelectronic, fibre optic and waveguide devices	Optical	pH; enzyme substrates; immunological analytes
Thermistors	Calorimetric	Enzyme, organelle, whole cell or tissue sensors for substrates, products and inhibitors; gases, pollutants, antibiotics, vitamins, etc.; immunological analytes
Enzyme electrodes	Amperometric	Enzyme substrates and immunological systems
Conductimeter	Conductance	Enzyme substrates
Piezoelectric crystals	Mass change	Volatile gases and vapors

(adapted from TBISC'88 Vol. 1-B. page 1095)

In addition to increasing the scope of detectable threat agents and providing generic detection of all chemical and biological agents, biosensors could provide simultaneous detection of classes of agents and be designed to work against future unknown threats. A spectrum of the actual threat agent for pattern recognition will not be required. Receptors would be designed to bind threats that are "unknown." In addition to the detection and identification of threat agents, biosensors may be able to aid in developing appropriate countermeasures and treatments, since these activities are simplified when the identity of the threat agent is known. (See discussion of C/B Defense.)

Biosensors have even broader applications than chemical/biological threat detection, however. These receptor based systems would be important in many other applications. They could be used to monitor environmental contamination in soils, ground waters, and process waters, and to assess the condition of stored products, such as mines and missiles, by detecting the degradation of the constituent materials like explosives and propellants.

C. CHEMICAL / BIOLOGICAL DEFENSE

Current Problem

Current protective systems for the Army cannot provide protection from all acknowledged chemical and biological threats. For individual protection, protective clothing systems provide absorption of chemical agent threats using charcoal. Protective overboots and gloves, as well as impermeable shells for chemical protection are fabricated from butyl rubber. This material is heavy, retains heat, and is subject to penetration by petroleum, oil and lubricants, thereby compromising its chemical/biological protective performance. The current charcoal based protection systems

- result in heat stress to the wearer, severely degrading a soldiers performance;
- present potential out-gassing problems because the agents are absorbed and not destroyed; and
- are not reusable because they can become saturated and lose effectiveness, and must be disposed of after one use.

Future biological threats may increase significantly with the advent of genetic engineering, and new chemical and toxin threats will continue to appear. Protective systems must mitigate all of these future threats whether delivered as vapor, liquid, or aerosol. Therefore, there is a need to develop generic protection systems capable of degrading chemical and biological agent threats.

Current decontamination chemicals (e.g., STB, DS2) exhibit broad-based activity against biological and chemical agents but are highly caustic. These chemicals damage materials and pose handling, storage, and contamination problems to equipment, handlers and the environment. Further, the decontamination chemicals can not be used on electronic or computer equipment, thus adding to logistics burdens, and presenting environmental concerns.

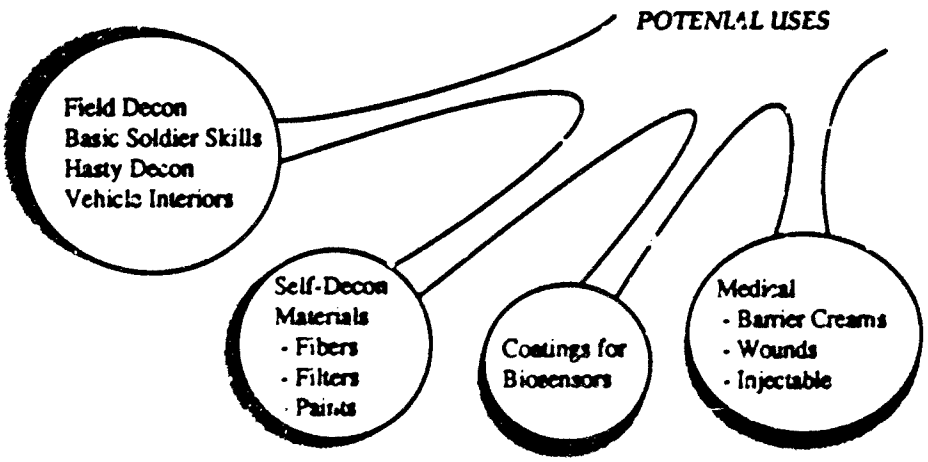
Improved active protection from all biological and chemical agent threats, without the negative impact of heat stress, would improve the performance of the individual soldier. Similarly, decontamination compounds that are mild

and can work under ambient conditions would vastly improve the decontamination of sensitive equipment such as electronics, microcomputers and internal components, as well as improve logistics and handling procedures.

Biotechnology Solutions

Reactive materials, such as biochemical catalysts, which include enzymes, peptides, enzyme active sites, catalytic antibodies and biomimetic systems offer the potential for rapid and effective degradation of chemical and biological agents under ambient conditions. Some of these reactive macromolecules can provide active protection against generic classes of chemical and biological agents, including both current and future bioengineered threats. In addition, these macromolecules could be immobilized or carried in a variety of matrices to perform their function. For example, the catalyst systems would be active against agents carried in aerosol, liquid, or vapor media and could be immobilized on fabrics or used in solutions, salves, cremes, or detergents. They may be reusable and could eliminate out-gassing concerns because the agents would be destroyed and not just immobilized or trapped. Further, they would not be susceptible to saturation because of the high catalytic turnover rates. Figure 5, "Enzymes in Contamination Control," illustrates the potential uses envisioned for enzyme-based decontamination materials.

FIGURE 5: Enzymes in Contamination Control



(Adapted from TBISC'88 Conference Report, Vol.1-B, page 1154)

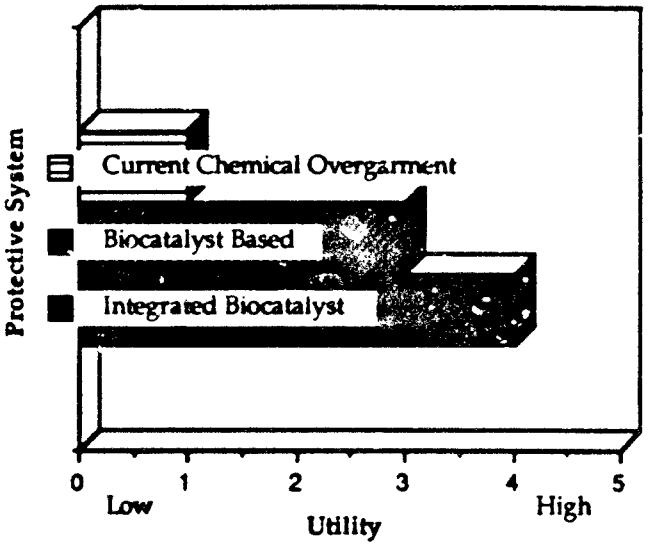
Developing multi-functional reactive coatings and finishes to provide integrated protection against both biological and chemical agents would be a major achievement. The same catalytic systems could also be used to rapidly decontaminate equipment and personnel under mild, physiologically safe,

conditions, including compatibility with electronic equipment. These reactive finishes may be incorporated into coatings, gaskets, or other materials to provide a proactive decontaminating finish, not prone to absorption and re-release or out-gassing of agents, working similarly to current waterproofing methods. The catalysts may be incorporated into foams, sprays, salves, creams, or other matrices to treat contaminated surfaces or clothing, or to decontaminate personnel and equipment. Ideally these reactive finishes would be designed to function under ambient conditions, would reduce heat stress by allowing the use of more permeable fabrics or gated pores, and could be integrated with other material functions such as ballistic protection. Lightweight protective materials derived from bioengineered rubber-like proteins could provide superior protection and performance characteristics. Table 7, "Chemical/Biological Protection," outlines the characteristics of three C/B defense systems. Graph 7, "Protective System Utility," compares the protection provided by each system.

TABLE 7: CHEMICAL / BIOLOGICAL PROTECTION - BIOCATALYSTS

Characteristic	Current System (suit, chemical protective)	System under Development (semipermeable carbon membrane)	Biocatalytic system
Generic protection from C/B agents	yes	yes	yes
Degradation of agents			yes
Avoidance of out-gassing			yes
Avoidance of saturation and loss of effectiveness			yes
Functional when wet			yes
Minimal heat stress			yes
Re-usable			yes
Protection in all carriers (aerosol, vapor, liquid)		yes	yes
Strong integration potential with other material properties (i.e. ballistics)			yes

GRAPH 7: Protective System Utility



1 = passive protection
2 = active chemical protection
3 = active biological protection
4 = active chemical and biological protection

D. BIOELECTRONICS, SELF-ASSEMBLING BIOMATERIALS

Current Problems

Electronic applications are pervasive. They are found in smart weapons, fire control systems, warning satellites, intelligence collection, among others. Radar detection systems, in particular, are limited by low angle resolution, susceptibility to jamming, and a failure to operate under all weather conditions. Also, protection, transportation and maintenance of electronic systems continue to be a problem. Future electronic systems must have more rapid computational, storage and data processing abilities, have decreased size, be resistant to jamming and have enhanced stability despite environmental extremes.

Biotechnology Solutions

Following several years of engineering advances, electronics technology is ready for another leap forward as new technologies such as nanoelectronics, optoelectronic and optoacoustic devices, monolithic microwave and monolithic devices, superlattice, and quantum electronic devices are applied. New component technologies already influence system design rendering them highly

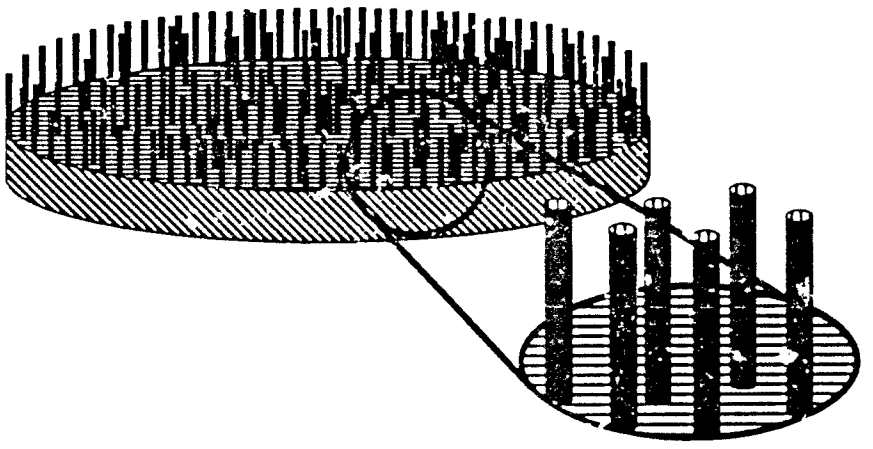
mobile and survivable and readily understandable to the operator. However, biologically designed or derived macromolecules or systems could provide improved component media for better information transmittal that would be stable to environmental variables (e.g., temperature, humidity) and lighter weight than current media. Some biomaterials exhibit large dipole moments and could be exploited for rapid storage and transmittal of electronic information. These materials include biological pigments, and conductive biopolymers suitable for fiber optics, switches, fuses, and optical memory devices. Compounds that respond in the nanosecond to picosecond range and could be used in the areas listed above are already available. Examples of electronic system analogs in the biological realm are shown in Table 8, "Electronic System the Analogs in Biological Realm."

TABLE 8: ELECTRONIC SYSTEM ANALOGS IN THE BIOLOGICAL REALM

Electronics Component	Biological System
Information Storage	Genetic codes (DNA, RNA), proteins, immune systems
Input/Output Devices	Enzymes, photo-activated biochemicals, cell receptors, redox biochemicals
Transducers	Sensory organs, active transport systems, photo-activated biochemicals, neuromuscular junctions
Switches	Bacteriorhodopsin, neuroreceptors, allosteric enzymes
Wiring	Axons, neural networks, conducting biopolymers

Radar capabilities will improve using self-assembling biomaterials. Advanced electron source materials based on biologically derived materials, such as self-assembling microstructures from lipid tubules, in composite functions with other conducting materials (e.g., epoxides and aluminum) could provide the required advanced cathode materials for the development of microwave devices driven by electron beam sources. The composite structures can be further processed to produce a "silicon lawn" with rod-like protuberances of silicon (about 1 um in diameter and 10 um tall) rising off the silicon coated base, as shown in Figure 6, "A Silicon Lawn," on next page.

FIGURE 6: Silicon Lawn



Artists conception of a "silicon lawn" advanced cathode material showing micron level tubules for advanced field emission.

These micro tubules offer a previously unavailable ability to tailor, at the micron level, the surface of a field emission cathode. When incorporated in microwave energy sources it is conceivable that higher electron current densities, more uniform or tailored electric field gradients, and more precise pulse shape and timing control could be achieved. These properties, in turn, can be used to affect the performance of radar systems in the areas of signal processing and prime power consumption. Figure 7, "Advanced Cathode Systems," outlines the advantages of a biomaterial based system over conventional radar systems.

FIGURE 7: Advanced Cathode Systems

Preliminary evaluations indicate Advanced Cathode Radar Systems based on Self-Assembling Lipid Tubules will have significant advantages over conventional high-power, single frequency radar.

A biomaterial-based system with an advanced, frequency agile microwave source will:

- *have highly capable counter-counter measures*
- *be operable in all weather*
- *present flexible deployment options*
- *have friend vs. foe detection capabilities*

Current competing technologies (e.g., embedded graphite fibers, semiconductor eutectics such as Si-TaSi) which provide similar cathode surface microstructure, have smaller aspect ratios and therefore yield a smaller field enhancement or have less uniformity control. The improved cathode performance from the micro-tubule cathode material makes many types of electron-beam driven devices practical and not just laboratory curiosities. For example, the Ubitron-type amplifier used in high-power microwave devices would benefit from this new cathode material.

Computer and electronics technologies could also benefit by applying the circuit design, density and three dimensional logic hierarchy found in the neural networks of living organisms. Understanding optical, electronic, and magnetic phenomena in living organisms would improve information processing and computer technology for electronics, robotics, intelligent machines, and artificial intelligence systems. Understanding biomagnetic memories, thin films, bioresistors, and self-organizing systems (e.g., proteins, lipids) could lead to more efficient fabrication of electronic systems, to information processing enhancement, simultaneous processing ability, more compact systems, lighter weight systems, and to faster computers resulting in more flexible and functional electronic products.

E. ENHANCED ORDNANCE

1. ENERGETIC MATERIALS

Current Problems

Existing weapons and ammunition systems are expensive, and not 100% reliable. The chemical synthesis of ordnance materials poses significant hazards to handlers, requires controlled non-ambient conditions, is energy intensive, entails high costs, and once produced, presents storage difficulties. Future needs will include a production base using synthesis methods that provide more powerful explosives and are safe for personnel and the environment. There is no synthesis methodology under development that will significantly impact on the current way of doing business in order to meet these needed operational improvements.

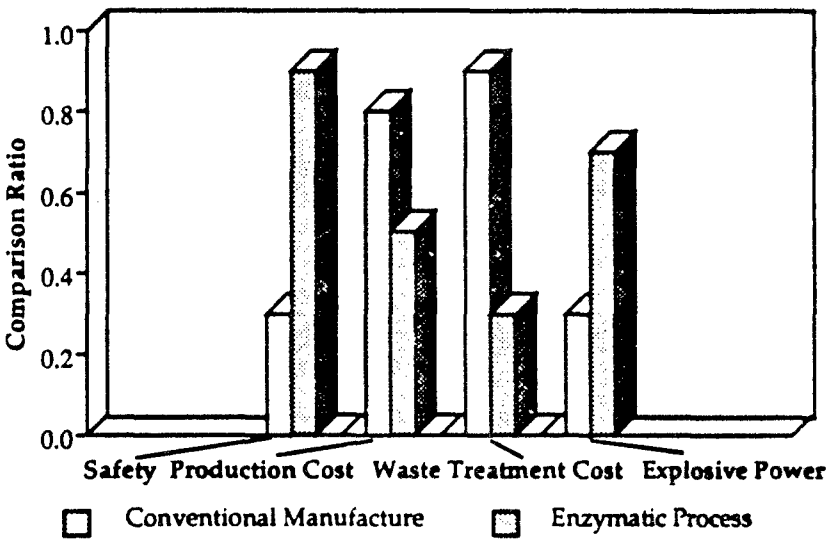
Biotechnology Solutions

Biotechnology tools may alleviate some of these problems. Adapting non-hazardous biosystems to produce, enhance, modify or degrade ordnance products would be more advantageous than current synthesis production systems. For example, enzymatically or microbially synthesized or modified ordnance

materials could be produced under ambient conditions, resulting in safe operating conditions with reduced risk to human health and the environment. Synthesis will be less costly; ordnance materials will be more stable; and the overall production base expanded. Production of high energy compounds using biosynthetic pathways will permit the formation of these products under mild, ambient, and safer conditions.

Microbial and biopolymer modified ordnance materials could provide increased effectiveness through increased fire power and a reduction in the munitions mass required. These modified munitions will also provide improved stability from premature detonation and more complete burn rates when compared with conventional systems. For example, crystalline amino acids are being used to form ultrapure detonators which are expected to result in a 30% increase in firepower. Elsewhere, creating enzyme modified energetic materials to modify the surface of propellant grains, in an effort to control gas generation rates during combustion, would improve stability and burn rates while also providing safer manufacturing processes. Biologically driven demilitarization of ordnance materials would also allow for safer handling and disposal of unused materials involving fewer hazards to the environment and handlers. Graph 8, "Enzymatic Synthesis of Energetic Materials," compares conventional manufacturing of energetic materials to an enzymatic process.

GRAPH 8: Enzymatic Synthesis Of Energetic Materials



2. *ANTI-MATERIEL*

The ability to defeat adversary equipment/systems by degradation of susceptible parts or fittings would provide significant operational benefits if they can act within a reasonable time frame. Such "soft kill" tactics render a force

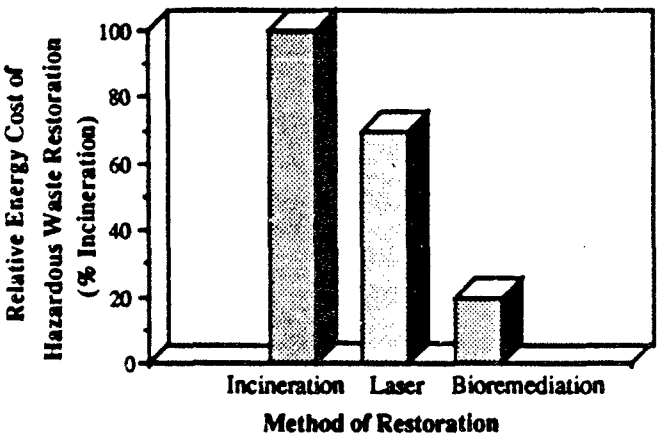
immobile or vulnerable to attack by conventional warfare means. Contamination of fuels and lubricants, and biodegradation of plastics, rubbers, and other synthetic or natural materials which are widely used in military equipment are possible target materials. For example, degradation or fouling of filters or gaskets in armored vehicles would immobilize the equipment and degradation of munitions would impair an adversary's firepower. Conductive biopolymers and metallized fibers would have numerous applications in the attenuation of microwave radiation and disruption of communications, computers, and power grids.

F. ENVIRONMENTAL BIOREMEDIATION

Current Problems

At over 100 sites around the world the Army faces major environmental contamination problems from a variety of hazardous materials including ordnance, solvents and fuels. Some of the sources of contamination are munitions manufacture, load, assembly and packaging operations; fuel operations; vehicle maintenance; and solvent disposal from paint stripping. DoD installations are faced with ordnance disposal, radionuclide recovery, explosives contamination of waste waters (i.e., "pink" water), and chemical/biological warfare agent contamination.

GRAPH 9: Environmental Bioremediation



Current technologies used to remediate these contamination sources are energy intensive (e.g., dewatering and incineration), often do not solve the problem (e.g., transport of contaminated materials to alternative disposal sites such as landfills), result in toxic by-products during treatment, are slow, or are

expensive. There is a need for new methods to resolve these environmental contamination problems (soils and waters) without damage to the environment and with minimal energy input. Newer technologies under development, such as laser and heat treatments may find application in specific scenarios, but are costly and energy intensive. Graph 9, "Environmental Bioremediation," above, gives a comparison of the relative energy costs of three methods of hazardous waste disposal. Environmentally compatible methods for protection and restoration of the environment, which conform to federal, state and local laws, would provide solutions to serious health and environmental contamination problems arising from DoD and civilian activities.

Biotechnology Solutions

Bioremediation, that is the use of genetically engineered organisms or enzymes for the degradation of contaminants *in situ* or in controlled reactors, has the potential to solve many of these difficult environmental contamination problems. Bioremediation systems would operate under ambient conditions, thereby reducing energy requirements; would be low cost; would result in the degradation of the contaminants to alleviate toxicity or hazardous properties; be environmentally compatible; and would have high catalytic activity for rapid and high turnover of contaminants to safe products.

Almost all ordnance materials studied, including TNT, RDX, HMX, nitroglycerine, etc., can be biotransformed, if not biodegraded, through the use of non-optimized microbial systems. In addition, microorganisms are very adaptable and can evolve new degradative genes, thus acquiring the ability to degrade a known persistent pollutant. Genetic engineering to exploit the key enzymes in these transformations could provide further control and modification of the degradation process to enhance degradation rates under adverse conditions.

Biotechnology derived solutions could be developed to solve a variety of serious environmental pollution problems. Examples of biotechnology-derived solutions include:

- developing microbial and catalytic methods (e.g., enzymes in aqueous or solvent systems) to degrade wastes and explosives in process waters or *in situ* (in soils or water);
- introducing biodegradable multi-spectral smokes;
- enzymatic approaches to paint stripping;
- bioengineered polymers for radionuclide recovery;
- microbial systems for recovery of strategic minerals (biomining); and,
- designing biodegradable lubricants and anti-fouling paints.

The use of ordnance-tolerant vegetation to reduce erosion, stabilize soil, and provide cover, or to biomagnify or concentrate contaminants in the soil (i.e., fast growing deep rooting plants which would be harvested and incinerated) are additional options for remediation. Environmental fate/modeling studies for transport and transformation of these contaminants in soils, waters, and plants, as well as the design and engineering of the associated treatment systems and hardware, would be required.

G. RATIONS FOR SOLDIER PERFORMANCE OPTIMIZATION

1. FOOD

Current Problems

Current military rations are designed to meet generic minimum daily requirements for micro- and macro-nutrients. Performance of mental and physical tasks shows a time-dependent decrease with either current or improved field rations when they are used as the sole food source for periods of two weeks or more. The rations are generally designed to meet the caloric and nutrient requirements for standardized human performance. They will generally provide adequate sustenance for about fourteen days before continued human performance can no longer be guaranteed. However, they are not optimized for specific combat/environmental stress scenarios, including arctic or desert battlefield stress differences, encapsulation, confinement in small spaces, or for sustainment of continuous operations. The development of novel systems for the conversion of inedible substrates or alternative food sources to nutritional materials in survival scenarios, and the improvement of nutritional quality or stability of foods are also needed.

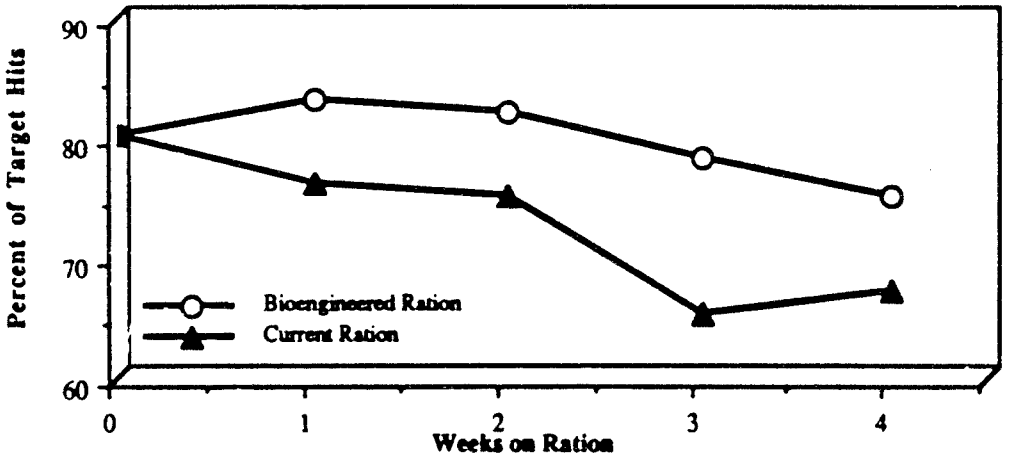
Biotechnology Solutions

Improved nutrition, storage stability, and new opportunities for nutritional supplementation/performance enhancement are possible through the application of biotechnology to food science. Generally, improvements envisioned include encapsulation for slow release of critical nutrients, carriers, or digestion aids; enzyme modified ingredients for better digestibility and energy availability; and new anti-oxidants for improved and safer long-term storage stability. Optimized rations can also be used during training to improve capability and performance. Edible packaging materials could also help in solving waste problems.

Bioengineered rations optimized for performance in specific battlefield or environmental stress scenarios can provide the necessary nutritional content to enhance performance or minimize performance degradation. For example,

enzymatically modified fats to enhance digestibility, modified amino acids to promote alertness, controlled release, and ration components that target specific organs would all provide enhanced operational performance through bioengineered rations. An improvement of 10 to 20% in performance is sought, above that supported by current rations, as is shown in Graph 10, "Bioengineered Ration System vs. Current Rations."

GRAPH 10: Bioengineered Ration System vs. Current Rations (Percentage of Target Hits on Game)



Some specific nutritional strategies that can be considered include increased fat digestion and absorption with natural surfactants such as special lecithins, which also contain choline for possible memory enhancement. Controlled and sustained release of carbohydrates by adding special polysaccharides, may serve a dual function as soluble dietary fibers and sustained energy sources. Special peptides or proteins rich in neurotransmitter precursor amino acids, such as tyrosine, serve as a reservoir for sustained delivery of anti-stress nutrients, and liposome and sustained release encapsulation systems provide controlled delivery of high impact nutrients.

Enzymatic synthesis or modification of the compounds described above, fermentation and bioprocessing for the production of these compounds, encapsulation of specific labile components, modifications in food microstructure, and targeting techniques are biotechnology examples of the tailoring of rations for performance optimization.

2. *WATER*

Water is always a mission critical resource. The lack of available water supplies in many areas, the lack of potable water, and weight penalties for carrying water all push the need to develop novel methods for soldiers to produce water in the field as needed. Improved capability to generate, recover and purify water would enhance operational performance in most environments.

Current Army bulk water purification systems rely on reverse osmosis membranes, except for the individual soldier, where charcoal-based purification is utilized. The soldier's charcoal-based water purification system can not be used for desalination. Developing a single membrane for all applications, providing enhanced flow rates for faster processing, more efficient processing of water to reduce energy requirements, stable to environmental variables, and storable in wet or dry conditions would be the ideal solution and may be reached through advanced biotechnology.

Some microorganisms survive in highly saline environments and are capable of generating osmotic gradients across membranes. The gradient systems used by these microorganisms could be exploited to develop new approaches to water purification and recovery. Some biopolymers, as opposed to current synthetic polymers, have greater stability, higher flow rates, and are non-reactive with disinfectants. They can therefore be formed into improved membranes for developing these types of gradient osmosis systems.

Novel, enzymatically-driven water producing reactions could also be exploited. Self-organizing membrane structures with selective reactivity and rapid through-put are envisioned. Genetic probes could be developed for rapid detection of pathogens potentially contaminating drinking water. In addition, anti-freeze proteins and glycoproteins could be used to prevent freezing of water in colder climates without requiring energy input. An example of this type of anti-freeze technology, found in nature, has been observed in certain fish and mammals living in the arctic and may be adapted when more fully understood (see Figure 8, "Animal Temperature Control," next page.)

FIGURE 8: Animal Temperature Control

The arctic ground squirrel, the Eskimos call the sik sik, can lower its body temperature below the freezing point of water for long periods without freezing. This ability, called supercooling, enables the squirrels to conserve vital energy during the long winter. In this way they expend only 10% of the energy they would if they were to fully warm their bodies for the entire winter. A squirrel will remain supercooled for up to three weeks, its internal temperature hovering just below freezing. Then periodically, it will raise its temperature long enough to eliminate waste then return to a supercooled state. All mammals cool down while they hibernate, a bear's temperature, for instance, will drop 5 or 6 degrees below normal. But this arctic squirrel is the only mammal known to go below zero.

H. FUEL/POWER GENERATION

The development of alternatives to fossil fuels as sources of energy would provide significant strategic benefits. Supplemental sources of energy and more efficient use of traditional fuels are needed to reduce dependency on foreign oil sources and logistic supply lines. Biological systems capable of producing usable fuels from atmospheric gases (photosynthesis systems), and enzymatically driven electrochemical systems capable of producing energy could be used to supplement traditional fuel sources.

The culture of algae for oil production, plants and plant tissue culture for fuels, and bioconversion processes for alcohols and other fuels may have a positive impact on our fuel supplies. Expanding these opportunities will permit better control of strategic fuel sources, supplement petrochemical requirements, and improve the national economic situation.

In addition to increasing the available sources of fuel, the incorporation of bioreactive materials into filters or fuels to remove or degrade fuel oxidation products or reduce bacterial contamination would prolong fuel life and increase the efficient use of fossil fuels. Biopolymer coatings to reduce corrosion and extend fuel and hardware use are possible additional benefits.

I. SPECIALTY AND FEEDSTOCK CHEMICALS

Specialty chemicals have been defined as "materials purchased by the end user not for their structure but for their end use." The Army has a need for specialty chemicals which function under environmental extremes and after long term storage. Lubricants, surfactants and other chemicals for military applications must function at extreme temperatures and other conditions not required in commercial applications. Bioengineered lubricants and surfactants could be produced with superior characteristics compared to available synthetic analogs.

Biologically derived/compatible fog oils, smokes, and obscurants which deny signal detection and can blind certain portions of the electromagnetic spectrum, such as the infrared, would provide operational benefits. Radar frequency spectral obscurants, bioprocesses that selectively block electromagnetic spectra, blinding sensors or absorbing emissions, and obscuration with multi-spectral obscurants are additional areas of potential impact for specialty chemicals. Applying the tools available now it is possible to construct enzymes and organisms with nearly any desired array of properties. Enzymes can be altered or created to function under conditions currently considered to be too severe and can be reduced in size to their catalytic cores. With these specialized enzymes, biochemical "factories" could be established in plants, animals or microbes, as the application requires, producing specialty chemicals for many desired reactions.

J. NAVIGATION - AND SIGNAL PROCESSING

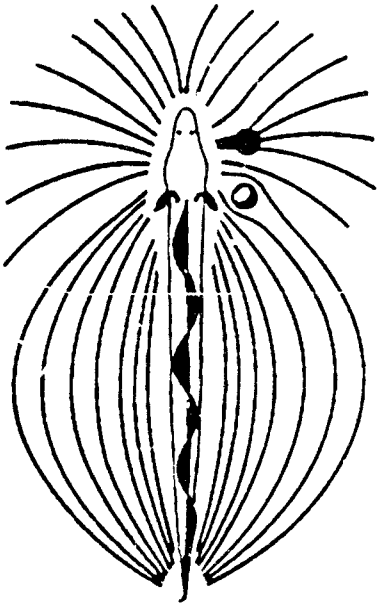
It is a well known observation of nature that many animals, fish and birds in particular, have the ability to navigate over great distances, homing in on specific nesting sites or feeding grounds. What principles of navigation are employed and what biological mechanisms are used are yet to be discovered. What is most astounding is the ability of very small birds to precisely navigate even though the reference and signal analysis biosystem is contained in a "package" sometimes weighing only a few ounces.

Mankind, of course, has a much more limited capacity. Modern Army navigation and reference systems weigh tens of pounds and must be given regular updates to counteract the effect of gyro drift and similar system deficiencies. If the navigation techniques of the animal world could be mimicked, the Army would be able to greatly simplify its equipment and enhance its capabilities.

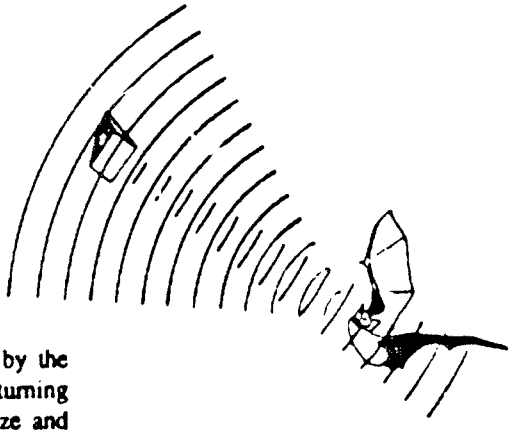
Studies of animal signal processing capabilities, including biodesign and bioengineering, may provide insights into novel approaches for signal

discrimination, enhancing capabilities in all weather and in all battlefield scenarios. Biological systems display unique capabilities in night vision, acoustic perception, homing, and signal discrimination. For example, bats function by echo sensation, and many living systems can discriminate signals in order to avoid defeat by an adversary. Some fish are capable of producing electric fields used in orientation and location of prey. These fish probe the environment detecting distortions of as little as 0.03 microvolts per centimeter in their electric field. Not only are they able to discriminate between conducting and nonconducting objects, but they are also able to learn to distinguish between very similar structures. Other fishes, such as sharks, though they do not generate their own electric field, have receptor organs sensitive to electric fields as low as 0.01 microvolt per square centimeter. (See Figure 9, "Animal Navigation.")

FIGURE 9: Animal Navigation



Electric Orientation: Gymnarchus, an electric fish, emits its own electric field. Nearby objects create distortions in the field which the fish senses and uses for orientation, to locate prey and also communicate. Good electrical conductors (black ball) concentrate the electric field lines on a particular area of the fish's body. Poor conductors (white ball) spread the field lines.



Echolocation: The ultrasonic chirps emitted by the bat are reflected by objects in its path. The returning echoes give the bat information about the size and position of the object.

Exploitation of these systems will improve sensory capabilities under adverse conditions, such as improved acoustic locators, visualization at night, and discrimination of signals against a complex and busy background. Elucidation of the processing algorithms used by animals and other organisms, for signal discrimination and avoiding confusion when two or more of these organisms are in the same location, would provide new insights into the design and fabrication of signal discriminators.

Extending human performance in terms of higher frequency communication (i.e., 12 to 20 kHz), increased olfactory sensitivity, and biomimetic/bionic sensory systems would provide additional operational benefits for our forces. Rapid target discrimination and identification of "friend or foe" could benefit from these kinds of discriminators. Radar scanning of equipment with special markings or signal discriminators may also be explored to accomplish target recognition.

K. CAMOUFLAGE

Current methods for disguising individuals, equipment and installations rely on paints, nets, clothing, and electronic jamming. The development of materials and coatings which provide enhanced blending in all environments, and with the capability to change with the environment, would provide much improved camouflage protection over current static, six color systems. Systems providing integrated detection avoidance from all elements in the electromagnetic spectrum, and all sensory signals, are envisioned through biotechnology.

No systems are currently available which provide integrated protection from all signatures. Specialized biosystems/biomaterials could be exploited to enhance our capabilities in detection avoidance. Conductive biopolymers, novel biological pigments which mimic natural signatures or change with varying environmental inputs as do some frogs and lizards, protein-based fibers for infrared and ultraviolet absorption , olfactory receptors, and acoustic absorbants could all be exploited from biological systems and developed for application to clothing and equipment to decrease detectability from a broad spectrum of signatures.

"Stealthy" personnel and equipment are envisioned through the application of these biologically-derived materials. Concealment technologies, including radar frequency spectral obscurants, are additional areas of potential impact.

L. DIRECTED ENERGY

Current protective clothing and equipment systems offer minimal protection from directed energy threats. Physical protection for personnel (optical and whole body) and equipment from directed energy threats (e.g., lasers, particle beams, radio frequency energies) would enhance survivability and performance.

Biotechnology-derived materials offer new opportunities for improved protection from directed and reflected energies. For example, current optical protection systems are typically limited in their spectral coverage. Biologically derived non-linear optical polymers for optical and sensor protection could be developed.

Bioactive pigments such as bacteriorhodopsin (a protein found in the purple membrane of extreme salt loving bacteria, which acts as a light-driven trans-membrane proton pump) are capable of transforming light energy into macromolecular changes in conformation and electrochemical gradients which may be applicable to optical protection.

Biopolymers, including self-organizing lipid tubules, capable of conducting and dispersing energy can be applied to clothing, equipment, and optics to reduce or dissipate high energy threats such as frequency agile lasers. Prosthetic treatments for the eye to provide short-term protection may also be a viable option by temporarily modifying the physiology of the eye to provide anti-directed energy safeguards. Novel ablative biomaterials can also be considered which would preferentially absorb directed energy, thereby providing protection from such high energy weapons, particularly when the energy is reflected.

M. ROBOTICS

Robotic systems are being developed as replacements for humans in situations such as loading ammunition in tanks, as mobile surveillance platforms to detect and identify troop movements, and in intelligent maintenance, diagnosis and repair systems. These systems require advanced data retrieval and processing and sensor abilities. They must also be durable in hazardous situations and reliable especially when used for assays or quality control. Robotic systems provide a "natural" application of biosensors for the sensing of chemical agents, detection of hazardous materials or explosives. If biosensors for navigation are achieved they could be applied to autonomous robots as well.

The engineering of artificial sense organs will require studies of photoactivated pigments for optical sensors, pressure transducers for

proprioception, olfactory receptors, and other novel sensory systems capable of utilizing abilities found in natural organisms. Military robots will require many of the same novel synthetic materials as commercial robots. However, bioceramics, biopolymers, and bioplastics more suited for hazardous military missions or for enhanced performance capabilities may be required.

N. QUALITY ASSURANCE AND CONTROL

Biological processes are inherently variable, and rigid quality assurance/quality control programs are needed to insure consistent procurement of biotechnology-derived products. For instance, consistent batch to batch enzyme purity is critical. Most of the required techniques have been developed in the private sector, and these techniques will have to be applied to Army-specific needs. For example, techniques such as protein composition/sequencing and fermentation conditions (for the production of various bioproducts) will be applied to Army procurements to insure they meet specific requirements.

New biotechnological methods could help analyze, control and/or produce samples with greater speed, sensitivity, and accuracy than current methods involving a great deal of trial and error. Many biotechnology products are produced by fermentation processes and are protein in nature. Batteries of specific and quantitative bioassays would be developed to test the properties of protein products such as receptors, catalytic antibodies, monoclonal antibodies, elastomeric proteins, high performance protein fibers, and enzymes to insure consistency from batch to batch.

A complete quality assurance/quality control program would also include studies of process optimization and record keeping in order to produce the quantities and qualities required for military applications.

III. THE SAFETY OF BIOTECHNOLOGY

A word should be added on the safety of biotechnology research in the United States. In 1975, shortly after the first experiments in recombinant DNA were conducted, a conference of scientists developed a set of guidelines for ensuring the safety of future genetic engineering experiments. Later the National Institutes of Health adopted similar guidelines to govern all federally sponsored research, and private biotechnology companies have complied voluntarily. Regulation of biotechnology companies is handled through the Environmental Protection Agency, the Department of Agriculture, the Food and Drug Administration, and the Occupational Safety and Health Administration. Since the start, tens of thousands biotechnology experiments have been conducted without harm to people or the environment. Because of this safety record, the original guidelines have been eased somewhat. The advisory committee, established to oversee biotechnology research regulation, has exempted some kinds of microorganisms from review as there is ample evidence that the organisms are safe. Table 9, "USDA Guidelines," outlines some of the genetic modifications under USDA oversight which have been exempted from regulation. The Army, in the conduct of its research projects, conforms to the guidelines of the biotechnology community.

TABLE 9: USDA GUIDELINES ON GENETICS

Included	Excluded
rDNA and transfer of RNA with or without gene vectors	Hand pollination
Physical methods for DNA or RNA introduction	Artificial insemination
Cross-species cell fusion and embryo rescue	Superovulation
Site directed mutagenesis of isolated DNA or RNA	Selection of somaclonal variants

(Source: U.S. Department of Agriculture)

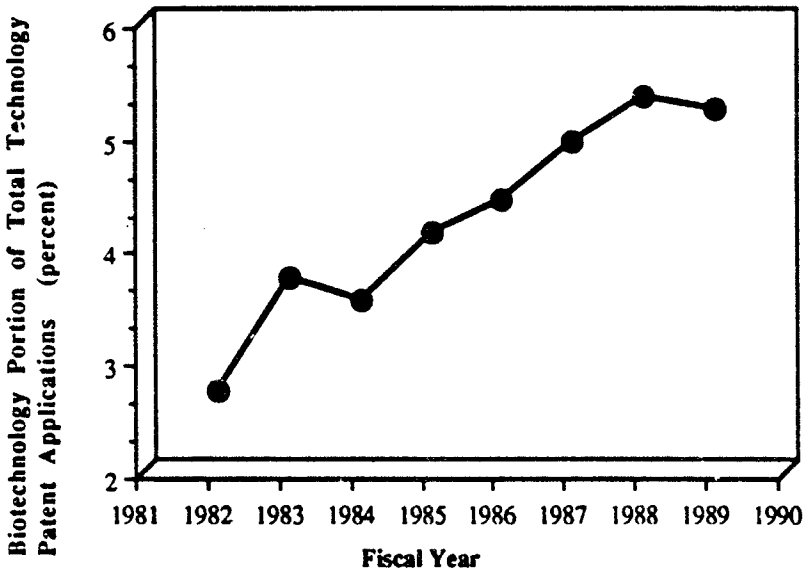
All biotechnology activities would have to be considered within the guidelines stated in the Biological Weapons Convention, April 10, 1972. All offensive biological weapons are prohibited by the Convention and the U.S. National Security Memorandum 35, November 25, 1969.

IV. BIOTECHNOLOGY INVESTMENTS

United States Investment in Biotechnology

While much of the early development of biotechnology has been through government-sponsored biomedical research, there are hundreds of companies in the U.S. alone developing, refining and utilizing biotechnology-derived information. In these companies, new drugs, vaccines, diagnostic tools, waste treatment methods, food additives and a variety of other products are being explored. As can be seen from the number of patent applications shown in Graph 11, " Biotechnology Patent Applications," new products and processes are being discovered almost daily.

GRAPH 11: Biotechnology Patent Applications

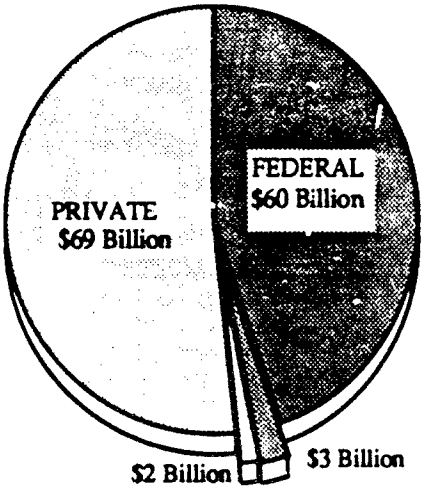


Patent applications for biotechnologies have risen dramatically since 1982. While patent applications for all technologies show an overall increase, the rate of increase of biotechnology applications is greater.
(Source: U.S. Patent and Trademark Office)

Federal and private sector investment in biotechnology research and development exceeded $4.5 billion in 1987. Of this, about $2.7 billion was the result of Federal investment. Most research and development in the private sector was performed in the medical and agricultural areas at both universities and commercial organizations. The National Institutes of Health provided 84% or $2.3 billion of the Federal spending. The Department of Defense was the second largest investor, with about $120 million. Other agencies with substantial investment in biotechnology research and development include the National

Science Foundation, the Department of Energy, the United States Department of Agriculture, the United States Environmental Protection Agency, the Food and Drug Administration, and the National Bureau of Standards. Graph 12, "U.S. Investment in R&D, 1988," illustrates U.S. investment in research and development in 1988 with biotechnology research as a component of both Federal and private sector spending.

GRAPH 12: U.S. Investment In Research and Development, 1988



U.S. investment in biotechnology for 1988 was $3 billion in the Federal sector and $2 billion in the private.

(U.S. Department of Agriculture)

In fiscal year 1990, the total Department of Defense funding for biotechnology is about $100 million, $60 million for medical research and development and about $40 million in non-medical technologies. For the Department of the Army, funding in biotechnology for FY90 is about $50 million, with about three-quarters for medical and one-quarter for non-medical biotechnology.

Army Approach to Biotechnology Research Investment

A number of general observations can be made regarding the present and future status of biotechnology.

1. The tools of biotechnology are sufficiently well developed to permit certain applications to current and future Army operational needs.

2. New and improved techniques, particularly with regard to automation, are being developed on a continual basis.

3. Three future developments will bring another leap in biotechnology. These are the ability to accurately predict how the structure of proteins and other macromolecules influence a molecule's function; human genome sequencing; and improving bioreactors for large-scale production.

4. Interdisciplinary approaches will be required to bring the research and application of biotechnology to fruition in terms of new operational capabilities. Research teams will include engineers, physicists, mathematicians, and chemists, as well as microbiologists, molecular biologists, geneticists, biochemists, immunologists, virologists, and molecular modelers.

5. Associated manufacturing capacity will be needed to translate the laboratory research and development into full scale production before operational capability is obtained. All stages will have to be addressed, including research, development, engineering, manufacturing, and processing.

Based on the above observations, the Army's approach in biotechnology research and development is multi-faceted. While the majority of present Army biotechnology investment is focused on medical applications, modest investments are being made in areas such as microbial synthesis of high-strength, low-weight fibers, elastomers and other bioengineered materials; integrating biological sensors and electronics; bioremediation; ordnance enhancement; and producing biologically safe decontaminates. As noted above, biotechnology research in such areas is expected to have great impact on Army operational capabilities.

Listed below are the Army biotechnology centers and their current biotechnology programs.

U. S. Army Natick Research, Development and Engineering Center - Bioengineered materials for enhanced performance in clothing, ballistics, shelters, packaging, camouflage, and individual chemical/biological protection; modified food ingredients for performance optimization.

U. S. Army Chemical Research, Development and Engineering Center - Chemical/biological defense, decontamination, detection, and collective protection.

U. S. Army Armaments Research, Development and Engineering Center - Improvements in ordnance performance and the production of energetic materials.

U. S. Army Corp of Engineers - Environmental restoration and water treatments.

U. S. Army Medical Research and Development Center - Development of improved vaccines and drugs for infectious disease control, combat casualty treatment, and protection from biological warfare agents.

Also, Army-wide programs in biotechnology include:

U.S. Army Research Office - Sponsors research at universities in biotechnology through a competitive granting process. Grants usually run three years with options for renewal. Areas of focus include:

(1) structure and function of proteins - including protein engineering, protein structure/function in different environments, and enzyme characterization,
(2) recombinant DNA - including cloning and gene fusion, regulation and expression of enzymes, and genetic controls over growth,
(3) biosensors - including protein modified surfaces
(4) decontamination/detoxification - related to CB defense, and
(5) receptors/neurophysiology - related to CB defense.

University Research Initiative - Cornell University was chosen as the Center of Excellence in Biotechnology for the Army in FY86 for basic research in biotechnology and biosystems. This five year program fosters interchange between Army laboratories and scientists at Cornell University. This University Research Initiative is programmed for five years and provides funds to support new research initiatives, predoctoral student fellowships, and core facility support.

The Army's approach is to proceed with research in the above mentioned areas with a goal of integrating the results into fielded systems within the next twenty years. To achieve this goal biotechnology centers in the Army will require a critical mass for technology development and will need to integrate Army activities through collaboration with university and private sector programs.

The Army will seek to utilize in-house and contractual resources to focus on those areas unique to the Army or those areas of critical need to the Army that are not receiving adequate attention in university or private sector laboratories. This will include maintaining access to state-of-the-art technology through use of contract resources and interactions with other government

activities. In this regard, it will be necessary to leverage the limited Army resources with additional funds from other DoD and non-DoD research elements. Many state run biotechnology programs have funds available which the Army may match with in-kind support. Cooperative agreements with private industry can also provide the needed support and interactions necessary for a critical mass in selected research areas. Consortium efforts focused on specific biotechnology product areas to integrate different Army centers need to be developed.

This report is the first step toward developing a long term strategy to assure that the potential of biotechnology for military applications is fully met, at least in terms of AMC's mission and areas of responsibility. The next step is to thoroughly analyze what work is currently being done, develop time lines and identify resources needed for specific opportunities with other government agencies, universities and private industry. The ultimate product will be a cohesive plan which indicates the goals, the resources needed to get there, and specific steps or actions which must be taken to reach the goals.

APPENDIX A

FUNDAMENTALS OF BIOTECHNOLOGY

OVERVIEW

Biotechnology is the manipulation of living systems or parts of these systems to produce or modify products. Using natural biological organisms and processes to produce substances is nothing new. Humans have relied on microorganisms for centuries to make bread, cheese, alcoholic beverages, etc. Antibiotics are extracted from various strains of molds and bacteria. Animals and plants have been gradually improved, through genetic husbandry (i.e. breeding animals and plants to produce offspring with the desired combinations of characteristics) and protected from diseases and insects through herbicides and insecticides. Biotechnology became a science rather than an art when the actual biochemical changes involved in these processes were understood and controlled. Discovering how microorganisms function and the unravelling of the mysteries of DNA have initiated a scientific revolution which promises to be at least as great as that ushered in by atomic physics.

Living organisms display a myriad of immensely sophisticated abilities to apply ordinary chemical laws for their own uses. The science of biotechnology encompasses the search to understand these fundamental abilities of living organisms and harness them for use in the performance of our own particular tasks.

The results of biotechnology research fall into two categories: the principles governing the biological processes and the chemical substances that can be made using genetically engineered organisms. Already pharmaceutical manufacturers have used genetically engineered microorganisms to clone great quantities of proteins, like insulin, and other biological response modifiers such as antibiotics and vaccines. Specialty chemical industries have used genetically engineered microorganisms in the production of alcohol, vitamins, high grade oils, adhesives and dyes. The synthesis of further novel chemical compounds is practically limitless and poses quite an opportunity to biotechnologists. Generally microorganisms must be carefully monitored and controlled to ensure proper results. However, some microorganisms are now being designed for use in the environment to treat waste and pollution and control pests.

FUNDAMENTAL BIOLOGY - *Involved in Biotechnology Research*

Biotechnology focuses on the cellular and molecular level activities of living things. To understand what biotechnology has already achieved and how it can be further applied, it is important to know some basic principles of living

organisms, especially the structure and function of cells, protein molecules, and the genetic material, DNA and RNA.

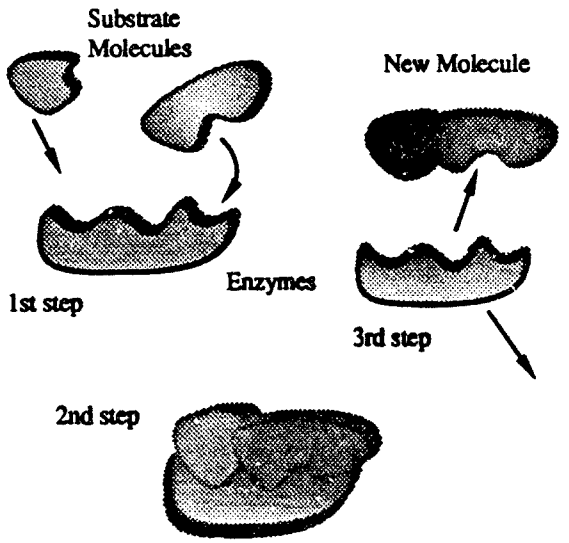
The basic unit of biological organization is the cell. Some living organisms are made of a single cell, such as microbes, others like a human body, contain over a hundred billion. Four types of microbes, with properties especially important to the biotechnologist, are fungi, algae, bacteria and viruses. Yeast and bread molds are types of fungi that man has used for centuries. Algae have the ability to obtain energy from sunlight. And bacteria have an astounding chemical versatility. Generally, cells may consist of thousands of complex chemicals constructed from relatively simple building materials found in the environment. The process within the cell which converts raw materials into useful substances is called metabolism.

Activity of Enzymes

Within the cell, the metabolic process is coordinated and initiated by enzymes which are proteins consisting of chains of individual amino acids. Amino acids are building blocks composed mostly of carbon (C), hydrogen (H), oxygen (O) and nitrogen (N) atoms. The number, type and order of the amino acids gives the protein molecule its individuality. There are 20 primary naturally occuring amino acids. Given that they may combine in chains of any order and number, and form three dimensional shapes, alone or in combination with other chains, the variety of possible protein molecules is immense. The human body, for example, has over 30,000 distinct types of proteins each with a different function; some carry oxygen, some protect from infections, others give tendons their strength and resilience. A great deal of biotechnology research is concentrated on proteins that act as enzymes.

Enzymes are biological catalysts that speed up chemical reactions. They are named after the reaction they assist. For instance, the enzyme *Alcohol dehydrogenase* catalyzes the removal of hydrogen from a molecule of alcohol. The key to an enzyme's power lies in its three dimensional shape. Every chemical compound has a characteristic shape and an enzyme will interact only with a shape it matches or recognizes, much in the same way as a key fits a lock. Once an enzyme joins with its particular compound and completes its task, it is released, unharmed and undiminished, ready to act again, as often as a million times per minute. (See Figure A1, Enzyme Activity.) These properties of enzymes - high selectivity and high catalytic turnover - offer the biotechnologist incredible speed and precision in controlling which molecules are selected to react and in the continuity of the final product. Without the guidance of enzymes, chemical reactions within the cell would be chaotic. Using enzymes, a cell can metabolize raw materials effectively and quickly without unwanted or harmful by-products.

FIGURE A1: Enzyme Activity



The enzyme molecule combines substrate molecules, forming new substances, without change to itself.

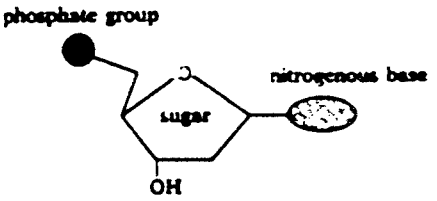
Genes and Genetic Codes

The nature and function of living things is greatly dependent on the activities within individual cells. Within each cell, raw materials are metabolized, with the aid of enzymes, into substances useful to the organism. The blueprint, or specifications, designating exactly which substances the organism requires is encoded by the genes. Each cell of an organism, be it a single-celled microbe or an organism as complex as the human body, contains the entire blueprint or genetic code of the organism.

The genetic code is a compilation of genes. Genes are made of deoxyribonucleic acid, or DNA. A gene directs the production of proteins in accordance to the pattern of its DNA. DNA contains four basic building blocks called nucleotides. The nucleotides form long chains of varying patterns and lengths. It is these differences which lead to the production of different proteins. As illustrated in Figures A2 and A3, the DNA molecule is composed of two nucleotide chains bonded together and twisted into a double helix. While the length and pattern of DNA chains vary, the bonding, or linking up of nucleotides between the chains and holding them together is very specific and unalterable. The pairing is illustrated in Figure A4. This unvarying partnership

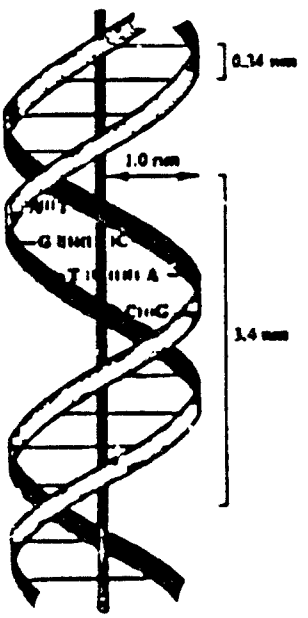
of nucleotide bases enable the cell to make exact copies of its DNA and to assemble proteins in a consistent, reproducible way. Figure A5 illustrates the replication and protein production processes which occur within the cell.

FIGURE A2: DNA Nucleotide



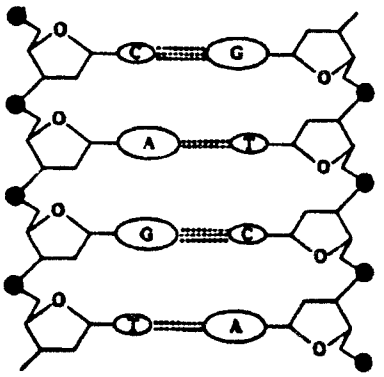
A phosphate and nitrogenous base are attached to deoxyribose, a five carbon sugar.

FIGURE A3: DNA Double Helix



The Watson-Crick model of DNA

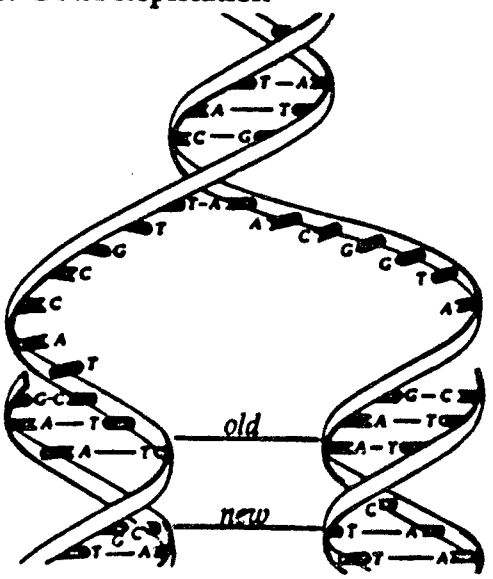
FIGURE A4: DNA Chain



Uncoiled, ladderlike chain of DNA shows the pairing of nitrogenous bases.

Purines		Pyrimidines	
A-adenine	~	*T-thymine*	= *2 hydrogen bonds*
G-guanine	~	*C-cytosine*	= *3 hydrogen bonds*

Figure A5: DNA Replication



In order for a DNA molecule to replicate, the two strands of the DNA double helix separate, breaking the bonds between the bases on each strand. The 'free' bases of each strand then pair with nucleotides from a pool of such molecules provided by the cell. Enzymes join the newly selected bases into a chains. In this way two identical DNA molecules are created from the original. The specific airing of the bases guarantees faithful reproduction.

Genetic engineering, the science of altering the genetic material within a cell to induce them to perform new functions, is possible because of the universality of the genetic code. Every living organism uses virtually the same system to translate genetic information into proteins. This uniformity allows scientists to take, for example, human genetic material directing the production of insulin and insert it into bacteria where it will reproduce insulin, transforming the bacteria into a miniature insulin factory.

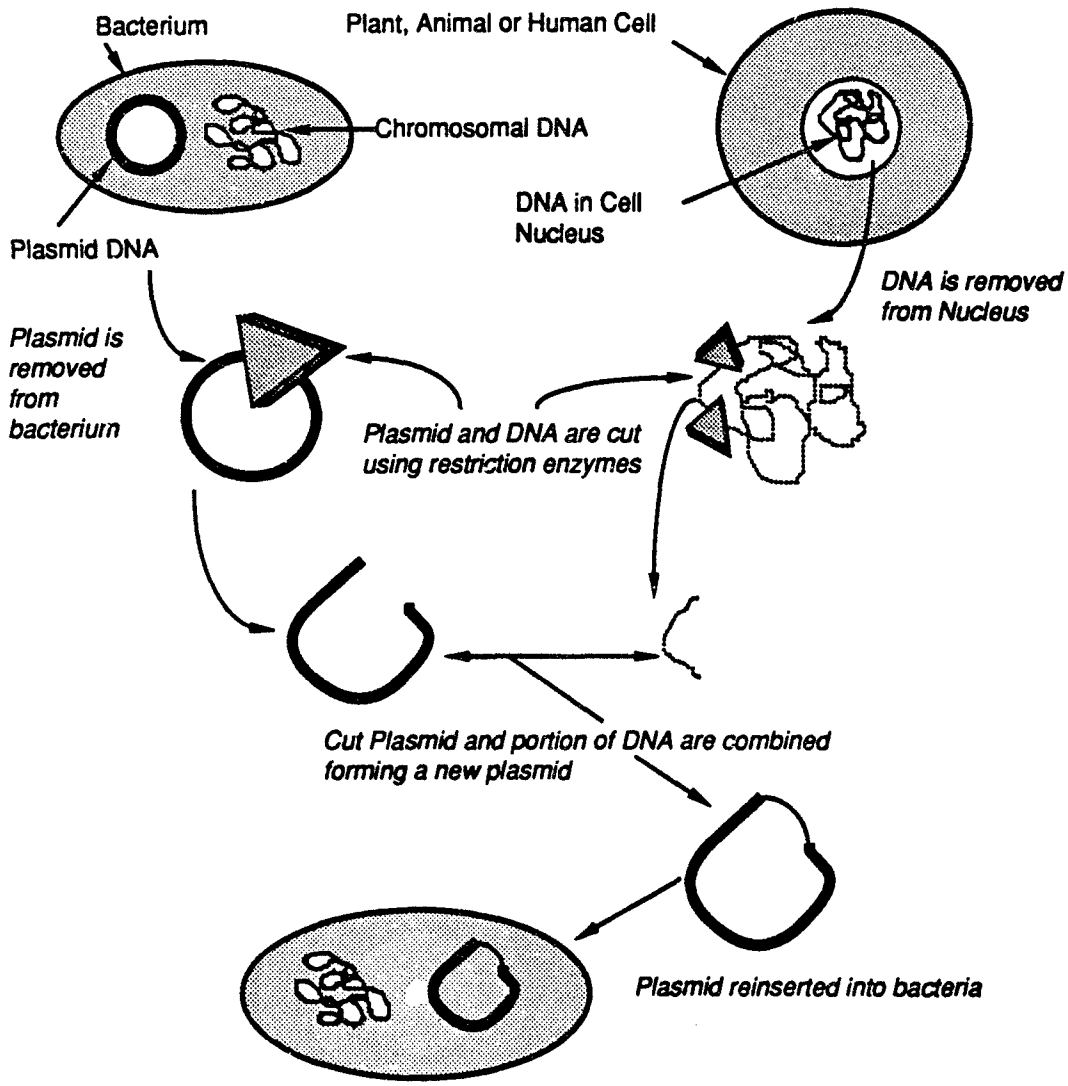
Key Biotechnology Tools

Key technology tools developed by biotechnologists include those techniques used for the direct manipulation of living systems (eg., microorganisms, plants, animals) or their genetic components, as well as supporting techniques such as molecular modeling. Four key tools are described here.

Genetic Engineering - Genetic engineering is the manipulation and control of gene expression or the transfer of genetic information between organisms in order to improve/increase production (expression) and/or improve product recovery. Genetic engineering , in its broad sense, may involve any of the following:

- recombinant DNA/cloning;
- the use of restriction enzymes (to cut DNA at specific locations);
- transformation/transfection of cells (to insert foreign genes into new organisms);
- gene probes (to detect the presence of specific DNA or RNA sequences);
- monoclonal or polyclonal antibodies (to detect protein products);
- polymerase chain reactions (to amplify DNA);
- abzymes (catalytic antibodies) to cut proteins at specific locations;
- the use of specific cloning vectors;
- DNA/RNA/protein isolation and purification;
- cell fusion, including hybridomas, for the amplification of antibody products; and/or,
- the formation of transgenic animals and plants through the introduction of cloned DNA into fertilized eggs or callus tissue.

FIGURE A6: Genetic Engineering



Recombinant DNA technology, or genetic engineering became possible when scientists learned to use certain enzymes to precisely rearrange genes. Using these enzymes, researchers are able to isolate genes that produce useful proteins and insert these genes into plasmids, which are rings of genes that are able to move into and out of bacteria. Once a gene becomes part of a plasmid inside the bacterium, the gene produces its specific protein. The bacterium, in effect, becomes a minute protein factory. When grown in fermentation vessels, these bacteria allow manufacturers to produce large quantities of the desired protein.

Fermentation/Bioprocessing - Fermentation or bioprocessing is the growth of organisms for the production of desired products. These products are either natural products or derived from recombinant DNA procedures.

Fermentation/bioprocessing includes:

- using bioreactors for microbial and cell culture;
- immobilized cells, enzymes, or antibodies;
- control of cell growth in large volumes;
- cell harvesting and recovery; and,
- purification of products.

Protein Engineering - Protein engineering is the manipulation of protein structures. This may include

- changes in the genetic code,
- chemical modification of natural protein structure, or
- the addition of unnatural amino acids, in order to modify the structure/function of a protein.

Site-directed mutagenesis and cassette mutagenesis are protein engineering techniques used to modify the genetic code, followed by expression of the protein product. Proteins are built of amino acids which govern the folding of the protein product. This folding pattern, into a specific three-dimensional conformation, then determines the final functional properties of the protein. These properties can be modified further through the influence of the surrounding environment (eg., pH, ionic strength, temperature, moisture). As yet, the three dimensional structure of only very few proteins is actually known.

Molecular Modeling - Molecular modeling is the computer simulation of macromolecular structures in order to predict conformational characteristics and energy states.

Utilizing computers to design and modify new macromolecules offers a tremendous advantage by shortening the time required to bioengineer the "best" or optimized solution to a particular problem. Computer calculations of bond energies, energy constants, folding, and stabilities assist in:

- identifying the most stable conformations of protein structures and active sites;
- guiding appropriate structural modifications or analog constructions; and,
- *de novo* design of desired structures for specific functions.

While computer technology significantly shortens the laboratory work required to obtain a specific product, a major puzzle still facing biotechnologists is the inability to predict the shape a protein chain will have when it folds, even if the entire primary sequence is identified.

APPENDIX B

GLOSSARY OF SOME BIOTECHNOLOGY TERMS

Ablate- to remove by cutting, erosion, melting, evaporation, or vaporization

Abzymes- catalytic antibodies

Aerobic- needing oxygen for growth

Affinity chromatography- a technique used in bioprocess engineering for separation and purification of almost any biomolecule on the basis of its biological function or chemical structure. The molecule to be purified is specifically and reversibly adsorbed by a complementary binding substance (ligand) and immobilized on a matrix. The substance of interest is first bound to the immobilized ligand and then dissociated to recover by changing experimental conditions.

Allosteric enzyme- an enzyme that can exist in two distinct spatial conformations, often more active in one form than another

Amino acids- an organic compound carrying an amino group (-NH_2) and a carboxyl group (-COOH), the building blocks of proteins. There are twenty common amino acids: alanine, arginine, aspargine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine.

Anaerobic- capable of growing in the absence of oxygen

Anisotropy- not isotropic, having properties that differ according to the direction of measurement

Antibiotic- chemical substance formed as a metabolic byproduct in bacteria or fungi and used to treat bacterial infections. Antibiotics can be produced naturally, using microorganisms, or synthetically.

Antibody- any globular protein produced in response to a specific antigen that counteracts the antigens effect esp. by neutralizing toxins, agglutinating bacteria or cells , or precipitating soluble antigens

Antigen- usually a protein (e.g., a toxin or enzyme) or carbohydrate substance capable of stimulating an immune response

Assay- technique for measuring a biological response

Attenuation- weakening or reduction of concentration of a substance; reduction of the amplitude of a signal

Autotroph- an organism capable of manufacturing its own food by synthesis of inorganic material

Bacteriophage- a virus that seeks and kills bacteria. Also called phage.

Bacteriorhodopsin- a protein found in the purple membrane of extreme salt loving bacteria which acts as a light-driven, trans-membrane proton pump

Bacterium- any of a large group of microscopic organisms with a very simple cell structure. Some manufacture their own food, some live as parasites on other organisms, and some live on decaying matter.

Base- on the DNA molecule, one of the four chemical units that, according to their order and pairing, code for the different amino acids. The four bases are: adenine (A), cytosine (C), guanine (G), and thymine (T). In RNA, uracil (U) substitutes for thymine.

Bioactive- biologically active

Bioadhesive- macromolecules produced by biological organisms which bind substances together

Bioassay- determination of the effectiveness of a compound by measuring its effect on animals, tissues, organisms or cells in comparison with a standard preparation

Biocatalyst- a biological substance that initiates a chemical reaction enabling the reaction to proceed under different conditions than otherwise possible (as at a lower temperature)

Bioceramic- mineralized complexes produced by biological organisms under ambient conditions

Biochemistry- the chemistry or chemical processes of living things
Biodegradable- organic compounds that can be broken down (esp. into innocuous substances) or mineralized by living things such as microorganisms
Bioelectric- electric currents produced by living things, capable of receiving or responding to electric current
Bioengineering- the use of living organisms or their capabilities to produce and/or modify products in a controlled fashion
Bioleaching- using the metabolic activity of microorganisms to oxidize metals and extract useful products such as iron, copper and uranium
Biologic response modulator- a substance that alters the growth or functioning of a cell. Includes hormones and compounds that affect the nervous and immune systems.
Bioluminescence- the production of light by living things or that light itself (e.g., a fire-fly)
Biomaterials- any substance or material used for or suitable for use in prostheses that comes in direct contact with living tissues
Biomimetic- imitation of a biological system or material
Bionic- having normal biological capability or performance enhanced by electronic or electrochemical devices
Bioplast- a minute quantity of living protoplasm capable of reproducing itself
Biopolymer- a polymeric substance (as a protein or polysaccharide) formed in a biological system
Bioremediation- the use of natural or genetically engineered organisms or enzymes for the degradation of contaminants *in situ* or in controlled reactors
Biosynthesis- the formation of organic compounds by living organisms
Biotechnology- development or modification of products by a biological process. Production may be carried out by using intact organisms, such as yeasts and bacteria, or by using natural substances (e.g., enzymes) from organisms.

Callus- a cluster of undifferentiated plant cells that can, in some species be induced to form the whole plant
Catalyst- an agent (such as an enzyme or a metallic complex) that facilitates a reaction but is not itself changed during the reaction
Cathode- an electrode at which reduction occurs, for example if at a silver electrode [Ag+ (aqueous) - e- --> Ag(solid)] then the silver metal is a cathode
Cell- the smallest structural unit of living organisms that is able to grow and reproduce independently
Ceramic- of or relating to the manufacture of any product made essentially from a nonmetallic mineral (as clay) by firing at a high temperatures (e.g., porcelain, brick)
Chromosomes- threadlike components in the cell that contain DNA and proteins. Genes are carried on the chromosomes.
Clone- a group of genes, cells, or organisms derived from a common ancestor. Because there is no combining of genetic material (as in sexual reproduction), the members of the clone are genetically identical to the parent.
Cloning- process of deriving cells/organisms asexually from a single parent and hence genetically identical
Crystallites- any of numerous minute rudimentary, crystalline bodies found in glassy igneous rocks
Crystallography- the science of crystal structure and phenomena

Demilitarization- elimination of ordnance materials
Diagnostic- a product used for the diagnosis of disease or medical condition. Both monoclonal antibodies and DNA probes are useful diagnostic products.
Dielectric- a nonconductor of electricity, especially a substance with electrical conductivity less than a millionth (10^{-6}) of a mho

DNA probe- a molecule (usually a nucleic acid) that has been labeled with a radioactive isotope, dye, or enzyme and is used to locate a particular nucleotide sequence or gene on a DNA molecule

DNA- deoxyribonucleic acid, the self replicating molecule which forms the genetic material (chromosomes) found in the cells of all living organisms

Double helix- a term often used to describe the configuration of the DNA molecule. The helix consists of two spiraling strands of nucleotides (a sugar, phosphate, and base), joined crosswise by specific pairing of the bases.

Elastomers, any of various polymers having the properties of natural rubber

Enzyme, a protein catalyst that facilitates specific chemical or metabolic reactions necessary for cell growth and reproduction

Eutectic- of, pertaining to, or formed at the lowest possible temperature of solidification for any mixture of specified components (e.g., Si - TaSi); especially said of alloys; or a solid made this way

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Feedstock- the raw material used for chemical or mechanical processes

Fermentation- a process of growing microorganisms for the production of various chemical or pharmaceutical compounds. Microbes are normally incubated under specific conditions in the presence of nutrients in large tanks called fermentors.

Flechettes- a steel missile or dart fired from guns

Fusion- joining of the membrane of two cells, thus creating a daughter cell that contains the nuclear material from parent cells; used in making hybridomas.

Gene- a segment of chromosome. Some genes direct the syntheses of proteins, while others have regulatory functions.

Genetic code- the mechanism by which genetic information is stored in living organisms. The code uses sets of three nucleotide bases (codons) to make the amino acids that, in turn, constitute proteins

Genetic engineering- a technology used to alter the genetic material of living cells in order to make them capable of producing new substances or performing new processes

Genetic screening- the use of a biological test to screen for specific genes related to characteristics, inherited diseases or medical conditions.

Globulin- a simple protein which is water insoluble but soluble in a dilute salt solution

Glycoproteins- a compound of a protein with a carbohydrate (as in egg whites or blood serum)

Growth hormone- (also called somatotropin), a protein produced by the pituitary gland that is involved in cell growth

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Heterotroph- an organism obtaining nourishment from organic substances, as do all animals and some plants

Hormone-a chemical that acts as a messenger or stimulatory signal, relaying instructions to stop or start certain physiological activities. Hormones are synthesized in one type of cell and then released to direct the function of other cell types.

Hybridoma- the cell produced by fusing two cells of different origi... In monoclonal antibody technology, hybridomas are formed by fusing an immortal cell (one that divides continuously) and an antibody-producing cell.

Immune system- the aggregation of cells, biological substances (such as antibodies), and cellular activities that work together to provide resistance to disease

Immunity- nonsusceptibility to a disease or to the toxic effects of antigenic material

Immunoassay- technique for identifying substances based on the use of antibodies

Immunodiagnostics- the use of specific antibodies to measure a substance. This tool is useful in diagnosing infectious diseases and the presence of foreign substances in a variety of human and animal fluids (blood, urine, etc.).

Immunotoxins- specific monoclonal antibodies that have a protein toxin molecule attached; the monoclonal antibody is targeted against a tumor cell and the toxin is designed to kill that cell when the antibody binds to it

Interferon- a class of lymphokine proteins important in the immune response. There are three major types of interferon: alpha (leukocyte), beta (fibroblast), and gamma (immune). Interferons inhibit viral infections and may have anticancer properties

Interleukin- a type of lymphokine whose role in the immune system is being extensively studied. Two types of interleukin have been identified. Interleukin 1 (IL-1), derived from macrophages, is produced during inflammation and amplifies the production of other lymphokines, notably interleukin 2 (IL-2); IL-2 regulates the maturation and replication of T lymphocytes.

Isomer- a chemical compound that contains the same elements and numbers of atoms as another compound, ion, etc. yet arranged in a different structure and exhibiting different properties

Isomerase- an enzyme which converts one isomer to another

Isotropic- identical in all directions

Kevlar- trade name of a high modulus synthetic aramid polymer based on the condensation product of p-phenylene diamine and tere-phthalic acid

Labile compound/complex- unstable under certain conditions

Leukocyte- a colorless cell in the blood, lymph, and tissues that is an important component of the body's immune system; also called white blood cell.

Lipid- any of a variety of compounds insoluble in water but soluble in ethers and alcohols, includes fats, oils, waxes and steroids

Lysozyme- an enzyme present in, for example, tears, saliva, egg whites and some plant tissues that destroys the cells of certain bacteria

Macromolecule- a very large molecule such as a protein or nucleic acid

Metabolism- all biochemical activities carried out by an organism to maintain life

Microbial herbicides/pesticides- microorganisms that are toxic to specific plants/insects. Because of their narrow host range and limited toxicity, these microorganisms may be preferable to their chemical counterparts for certain pest control applications.

Microorganism- any organism that can be seen only with the aid of a microscope. Also called microbe.

Molecule- the smallest particle of a substance that retains all the properties of the substance and is composed of one or more atoms

Monoclonal antibody- highly specific, purified antibody that is derived from only one clone of cells and recognizes only one antigen

Morphology- the structure and form of an organism, excluding its functions

Natural active immunity- immunity that is established after the occurrence of a disease

Natural passive immunity- immunity conferred by the mother on the fetus or newborn

Nitrogen fixation- a biological process (usually associated with plants) whereby certain bacteria convert nitrogen in the air to ammonia, thus forming a nutrient essential for growth

Nucleic acids- large molecules, generally found in the cell's nucleus and/or cytoplasm, that are made up of nucleotide bases. The two kinds of nucleic acid are DNA and RNA.

Nucleus- the structure within eukaryotic cells that contains chromosomal DNA

Ordnance- military weapons collectively; specifically ammunition or items containing high explosives

Passive immunity- immunity acquired from receiving preformed antibodies
Pathogen- any disease producing microorganism
Peptide- a chain of amino acids linked by peptide bonds, a bond resulting form a condensation reaction between the amino group of one amino acid and the acidic group of another
pH- a measure of the acidity or alkalinity of a solution, numerically equal to 7 for neutral solutions, increasing with increasing alkalinity and decreasing with increasing acidity
Photosynthesis- conversion by plants of light energy into chemical energy, which is then used to support the plants' biological processes
Piezoelectric- (piezo indicates pressure) the generation of electricity or electric polarity in dielectric crystals subjected to mechanical stress, and conversely, the generation of stress in such crystals subjected to an applied voltage
Plasmid- a small circular form of DNA that carries certain genes and is capable of replicating independently in a host cell
Plasmin- a proteolytic enzyme that dissolves the fibrin of blood clots
Plasminogen- the precursor of plasmin that is found in blood plasma and serum
Polyclonal- derived from different types of cells
Polymer- a large molecule consisting of a chain of the same small molecules bonded together by condensation or similar reactions
Polymerase- general term for enzymes that carry out the synthesis of nucleic acids
Polypeptide- long chain of amino acids joined by peptide bonds
Polysaccharides- any carbohydrate that is a polymer of simple sugars
Prophylaxis- the prevention of or protective treatment for disease
Protein- a compound class containing carbon, hydrogen, oxygen, and nitrogen; a long polypeptide chain (i.e., chain of amino acids linked by peptid bonds)
Pyroelectric- exhibiting or pertaining to the generation of electric charge on a crystal by change of temperature

Receptor- part of a cell which functions similar to an antibody in combining with outside molecules; specialized tissue or cells sensitive to specific stimulus, often in a sense organ
Recombinant- the rearrangement of the genes in an organism
Reduction- a half reaction in which a molecule receives electrons
Restriction enzyme- an enzyme that breaks DNA in highly specific locations, creating gaps into which new genes can be inserted
RNA- ribonucleic acid; a universal polymeric constituent of all living cells, consisting of a single-stranded chain of alternating phosphate and ribose units with the bases adenine, guanine, cytosine, and uracil bonded to the ribose, the structure and base sequence of which are determinants of protein synthesis

Sensor- a device that responds to a physical stimulus and transmits a resulting impulse, e.g., nose, eyes
Silicon microchip- a tiny silicon chip with thousands of electronic components and circuit patterns etched onto its surface
Sintering- heating of an aggregate of fine metal particles at a temperature below their melting point so as to cause them to weld together and agglomerate
Splicing- the removal of introns and joining of exons from DNA to form a continuous coding sequence in RNA
Substrate- material acted on by an enzyme

Surfactant- an organic surface-active compound consisting of two parts: 1) a hydrophobic portion, usually including a long hydrocarbon chain; and 2) a hydrophilic portion which renders the compound sufficiently soluble so as to be dispersible in water or other polar solvent

Tissue plasminogen activator (tPA)- a protein produced in small amounts in the body that aids in dissolving blood clots

Toxin- a poisonous substance produced by certain microorganisms

Transducer- a device that is actuated by power from one system and supplies power, usually in another form, to a second system; something that brings about the transfer of (as a gene) from one microorganism to another by means of a viral agent

Transduction- the transfer of genetic material from one host cell to another by a virus or phage vector

Transfection- infection of a cell with nucleic acid from a virus, resulting in replication of the complete virus

Vaccine- a preparation that contains an antigen consisting of whole disease-causing organisms (killed or weakened), or parts of such organisms, and is used to confer immunity against the disease that the organisms cause. Vaccine preparations can be natural, synthetic, or derived by recombinant DNA technology.

Vector- the agent (e.g., plasmid or virus) used to carry new DNA into a cell

Virus- a submicroscopic organism that contains genetic information but cannot reproduce itself. To replicate, it must invade another cell and use parts of that cell's reproductive machinery.

Viscosity- measure of thickness of a solution or resistance to flow

APPENDIX C

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