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**DEPARTMENT OF DEFENSE**

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**DEVELOPING CRITICAL  
TECHNOLOGIES/SCIENCE &  
TECHNOLOGY (DCT/S&T)**

*SECTION 4: BIOMEDICAL TECHNOLOGY*



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## **PREFACE**

Developing Critical Technologies/Science & Technology (DCT/S&T) is a product of the Defense Critical Technologies Program (DCTP) process. This process provides a systematic, ongoing assessment and analysis of a wide spectrum of technologies of potential interest to the Department of Defense. DCT/S&T focuses on worldwide government and commercial scientific and technological capabilities that have the potential to significantly enhance or degrade U.S. military capabilities in the future. It includes new and enabling technologies as well as those that can be retrofitted and integrated because of technological advances. It assigns values and parameters to the technologies and covers the worldwide technology spectrum.

DCT/S&T is oriented towards advanced research and development including science and technology. It is developed to be a reference for international cooperative technology programs. A key component is an assessment of worldwide technology capabilities. S&T includes basic research, applied research and advanced technology development.

## SECTION 4—BIOMEDICAL TECHNOLOGY

### *Scope*

4.1	Etiological Factors.....	4-3
4.2	Defeat or Management of Biological and Chemical Attack .....	4-9
4.3	Management of Trauma, Stress, and Treatment.....	4-19
4.4	Tactical Medical Command and Control .....	4-31

### *Highlights*

- Endemic organisms, the major cause of infectious disease in deployed forces, can be dealt with using new technologies.
- Human genome sequencing will reveal disease and stress susceptibility factors.
- Pathogen genomics permits rapid detection/identification of agents.
- Immune system enhancers and novel antibacterial and antiviral compounds promise protection from or defeat of biological hazards.
- Interfacing biomedical technology with communication and information systems is enabling for global surveillance of endemic disease.
- Telemedicine provides opportunity to stabilize and enhance survivability of traumatically injured persons.
- Growth factors enhance wound repair and neural tissue regeneration.

### **OVERVIEW**

This biomedical science section addresses those technologies in the biomedical arena that will affect the operational readiness and sustained force projection capability of the U.S. Army, Navy, and Air Force. Subsection 4.1 considers the etiological factors of infectious disease and susceptibility of persons to disease and stress. Biodiversity plays roles in the evolution of disease and in developing seed stocks that prevent total destruction of a food material. Biodiversity also provides protection to the human population from potentially catastrophic events. Nonlethal weapon effects are considered in this section. The effects of new technologies on treating, managing, and protecting individuals and groups from infectious disease are considered in subsection 4.2. Innovative approaches to training first responders to biological or chemical attack are also included. The protection of the forces from conventional weaponry, and the treatment of traumatic injuries, including damage to the nervous system, are presented in subsection 4.3. Telemedicine approaches, treatment of wounded forces at sites distant from medical facilities, and affordability issues are also discussed. Technologies enabling for medical command strategies are presented in subsection 4.4. The time line between development of the technology and the capability of inserting that technology into a system (i.e., application readiness) and the issues of “affordability” are considered in each subsection. All the technology items identified here are driven by broad requirements and applications and all have substantial non-military commercial applications and support infrastructures. The industrial sectors supporting the biomedical science thrusts include health/medicine, pharmaceuticals, food processing, cosmetics, computers, communications, and electronics.

## ***Identification of Developing Biomedical Technologies Related to Military Applications***

The “Developing Biomedical Technologies” have been categorized into three functional sets: infectious diseases and protection, trauma, and stress.

### ***Developing Biomedical Technologies as related to infectious disease, trauma, and stress:***

#### *Infectious disease related*

- Rapid genomic analyses of biological agents and of human susceptibility to disease, toxicants, and stress;
- Rapid diagnosis of infectious disease by genomic/antigenic analyses and sensors;
- Database for infectious diseases worldwide;
- Microchip encoding of medical history;
- Containment and transport of infected persons;
- Remote diagnosis and surgery; and
- Novel antivirals, antibiotics, vaccines, and drug development.

#### *Trauma related*

- Blood coagulation factors;
- Artificial organs, including blood, and growth factors for neural repair; and
- Novel prosthetic materials.

#### *Stress related*

- Performance enhancing or sustaining chemicals (vigilance/attentiveness);
- Analytical measures and metrics for human performance;
- Iconographic and audio-visual displays and ergonomic tools;
- Nonlethal weapons including physiological/psychological assault; and
- Ingested/injected materials to identify location of persons.

## SECTION 4.1—ETIOLOGICAL FACTORS

### *Highlights*

- Genomics of pathogens are being determined.
- Susceptibility factors of human genome are being characterized.
- Worldwide database of endemic diseases is being compiled.
- The interface between human susceptibility, virulence factors, and worldwide endemic disease will now make possible prediction of risk, required treatments, and a human factors element of readiness of deployed forces.

### **OVERVIEW**

The biomedical components of etiological factors in disease include genomics of biological agents, human genomics, global surveillance of infectious disease, and nonlethal weapons. The management of physical injury is considered in subsection 4.3.

The development of clinical infectious disease in the human subject is the result of the interaction between the human host and the pathogen. The genome of the pathogenic organism and the susceptibility of the subject to the organism are factors in disease manifestation. The pathogenicity of viruses and of bacteria is a function of the genomic composition of the microorganism. There are common genomic sequences shared by biological agents which increase the pathogenicity of these organisms. These sequences, identified as pathogenicity islands (PAIs), have been characterized for several agents on the Australia Group list. Knowledge of the sequences can be used both to construct deoxyribonucleic-acid (DNA)- or ribonucleic-acid (RNA)-based sensors or to develop antiviral or antibiotic pharmaceuticals that will delay or reduce the pathogenic effects of the organisms. Individual susceptibility to a pathogen is a function of the nutrition, neuropsychopharmacological characteristics, fitness, and the genome of the person. One example of the genomic component of resistance was the finding that those persons whose predecessors came from areas of the globe that experienced bubonic plague were more resistant to human immunodeficiency virus (HIV) infections than persons from other areas. One explanation for this observation was that there was a common genetic factor that protected individuals against both diseases and that the plague permitted survival of such protected populations.

Progress made in biotechnology and the understanding of the genetic code of humans will enable the susceptibility of persons to disease and stress to be determined by the year 2003. Since the genetic material of the human is determined at conception, it is possible to identify and characterize genes responsible for the inherited predisposition to decreased human performance and clinical disease. By the year 2003 it will be possible to have gene-based screens and diagnostic tests for alterations in genes; to develop the informatics needed to collect, store, analyze, and integrate the resulting molecular patterns; and to obtain epidemiologic and clinical data of persons at birth. With this information it will be possible to identify every major human gene that predisposes people to disease; to use the knowledge to help persons at risk; and to deal with the psychosocial, ethical, and legal issues associated with inherited disease. A portion of the material in subsection 4.3 (Affordability—National Clinical Information System) is relevant to this subsection.

### **A. SUSCEPTIBILITY TO INFECTIOUS AGENTS**

#### **1. Genomics of the Pathogenic Organisms**

The genome of many pathogenic organisms on the AG list has been characterized. Within the genome there are sequences of nucleic acids that enhance the pathogenicity of the organisms. These sequences are virulence genes and PAIs. The PAIs and virulence genes may allow the bacteria to adhere more firmly to mammalian cells or to otherwise enhance the survival and multiplication potential of the bacteria in the host (human or animal). The

sequence of the PAIs in pathogenic *E. coli*, for example, is similar to sequences of cell proteins (adhesins) on the external surface of cells and to those used in cell-cell binding. The knowledge of the PAIs, virulence genes, and sequences unique to each of the pathogenic organisms allow rapid detection of these agents in samples of tissue (including blood) from infected patients.

The ability to amplify and sequence nucleic acid fragments from infected tissues has given rise to a new approach in the understanding of emerging pathogens. Until the past decade it has been necessary to culture tissue samples to recover and identify the infectious agent. This requirement meant that appropriate culture media and conditions for culture had to be known. With the polymerase chain reaction (PCR) technology and with a gene data bank of infectious organisms, it is now possible to obtain very small samples of tissue and biological agent. The nucleic acid component of the agent can be amplified and matched to other known agents. This technology has been used to identify a bacterium involved etiologically in Whipple's disease. In a related technology, "representational difference analyses" (RDA), samples of healthy and diseased tissues from a single subject are taken and the genomic material from the healthy tissue subtracted from that of the diseased tissue. This method has been used to identify Kaposi Sarcoma HV (KSHV), a virus responsible for Kaposi sarcoma in patients infected with HIV. The known genes can also be used in the construction of multi-array sensors used to detect pathogenic agents in the military or medical environment.

The knowledge of the genomics of bacteria, viruses, and fungi permits rapid identification of infectious materials, allows the development of new immunogens without injecting material that has a potential to cause infection, and allows the development of new antibiotic and antiviral compounds. It permits the identification, by PCR and RDA, of pathogenic organisms not previously recognized and is expected to provide evidence of new microbial genera. See *Science*, 282: 219221, 1998.

## **2. Genomics of Personnel as Related to Disease or Toxicant Susceptibility**

Large, population-based studies are being conducted to evaluate disease risks associated with the combined effects of genetic status and environmental exposures, including those related to lifestyle and diet. Using minute quantities of DNA in cells obtained from a simple mouth rinse, blood, or tissue, it is possible to detect gene mutations, the functions or effects of which may point the way to environmental, nutritional, hormonal, and other factors that contribute to diseases in humans. As more information about human genes becomes available, there will be opportunities to test the importance of newly discovered genes not only for their relation to susceptibility, but also for clues to environmental agents that affect health and performance. The tools to examine these complex interactions between genetic susceptibility and environmental exposures are being developed for studies that could greatly advance our understanding of how inheritance, lifestyle, and environment combine to cause disease. This knowledge will lead to new strategies for disease prevention.

The development, function, and behavior of humans have been shown to involve genetic and environmental elements. In recent research efforts, biomedical science has been giving attention to inherent differences among individuals and groups of persons. These differences, at the genetic level, are collectively called genetic polymorphisms (GPs), and can affect the way that individuals and groups respond to various physical, chemical, and biological stresses. GPs generally manifest themselves as differences among individuals with regard to their ability to metabolize drugs and other substances and to their susceptibility to disease and other stressors. As a general rule, each human population is estimated to possess 3–10 genes that affect its susceptibility to disease or toxicants.

Some GPs can be identified only by phenotyping the individuals, i.e., by examining blood or other tissues for the presence or absence of specific enzymes or receptors. Other GPs may be identified by looking at specific DNA sequences in the cells or at RNA products.

Polymorphisms can manifest themselves as:

- The presence or absence of a specific enzyme that metabolizes xenobiotics;
- Differing relative concentrations of a specific enzyme, with associated differences in levels or rates of metabolism;
- Modified enzyme/gene product with a different level, or spectrum of activity than the wild type;

- The presence or absence of a specific gene product that controls a vital body function; and
- Differences in the ability of a gene to be induced to produce a product.

The polymorphisms can manifest themselves as differences in enzyme activity, differences in cell receptors, and differences in response to stress or injury. Different polymorphisms confer increased or decreased sensitivity to various external insults. These polymorphisms do not confer absolute resistance or sensitivity to an insult, but affect the probability that the individual (or group) with that polymorphism would be more or less sensitive to the disease/damage. For example, the presence or absence of various cytochrome P450 and GST isoforms will increase or decrease the susceptibility of that individual to different types of smoking or chemical-related cancers, whereas other isoforms would increase the susceptibility for contracting the disease. Genetic polymorphisms and environmental factors interact in the development of resistance or susceptibility to disease.

The human genome project will inform the medical community about the specific genes related to the development of disease, the susceptibility to shock following traumatic injury, and the susceptibility of individuals to intense stress associated with exposure to temperature extremes, intense noise, sleep deprivation, and infection.

In the next decade it is likely that polymorphisms that affect performance, sensitivity to biological and chemical agents and specific drugs, and sensitivity to environmental conditions and situations will be identified. The individual genotype will affect sensitivity to biological and chemical agents, susceptibility to infection by specific organisms, activation or detoxification of chemical agents, and modulation of chemical or biological agent exposure. Examples include P450 and glutathione S-transferase (GST) polymorphisms that are associated with resistance or susceptibility to smoking-induced cancers; cell surface major histocompatibility (HLA) molecules that confer resistance or sensitivity to infection by specific microorganisms; and acetylase variants that rapidly or slowly metabolize (to activate or inactivate) certain toxins. GPs also affect the response of individuals to drugs that are important in the prophylaxis of disease and treatment of injury or fatigue. For example, polymorphisms for rapid or slow metabolism of drugs can lead to a propensity for adverse reactions, decreased drug efficacy, or to the need to use lower doses to achieve the desired effect. A correlation between genetic background and human performance will provide a capability to determine where, on the spectrum of susceptibility or resistance, personnel may be most suited for tasks.

### ***3. Global Surveillance of Infectious Diseases***

There are three components to the surveillance database: endemic and epidemic disease; emerging and re-emerging diseases, particularly of viral etiology; and antimicrobial drug resistance.

There are several agencies that gather data on worldwide endemic disease. These include the Center for Disease Control (CDC), World Health Organization (WHO), and Pan-American Health Organization (PAHO). The military services, through organizations such as Naval Medical Research Units (NAMRU) and Walter Reed Army facility, have interests in collating data on endemic disease. A comprehensive database of such information can function as a clearinghouse for defense and public health requirements, as well as an early warning system for outbreak of infectious diseases, whether caused by organisms endemic to an area or disseminated by terrorist or nation/state entities. The information would serve to alert pharmaceutical firms and the defense community to increase production requirements of vaccines and antibiotics.

The database includes

- Information gathered from agencies currently involved in monitoring disease;
- Genomic sequences of viral, bacterial, and fungal pathogens;
- Genomic sequences of pathogenicity islands of AG agents and other relevant organisms; and
- Antigenic epitopes characteristic of AG agents and other relevant organisms.

Multi-array sensors consisting of probes for the relevant genomic sequences or epitopes could then be constructed and used in the surveillance system.

**B. NONLETHAL WEAPONS EFFECTS**

Military peacekeeping, humanitarian efforts, and missions other than war have become increasingly common. In such operations, many dangers exist to the troops, yet the use of lethal force is often not justified or acceptable.

***Bioeffects and Nonlethal Weapons***

Bioeffects include any effect an internal or external stimulus has on part or all of a biological organism. Examples of bioeffects include DNA mutation, loss of equilibrium, stimulation or inhibition of sensory input, emotional response, nausea, fear, increase in heart rate, behavior avoidance, cellular damage, altered metabolism, confusion, loss of consciousness, convulsions, and death. They can be as innocuous as a recognition of a pleasant odor or as harmful as stopping of the heart. Bioeffects specialists include medical doctors, physiologists, psychologists, behavioral scientists, veterinarians, anatomists, neuroscientists, biologists, epidemiologists, theoreticians and others, all concerned with the effects of any stimulus (biological, chemical, or physical) on part or all of a biological organism.

Policy acceptability is a topic in which bioeffects have two major roles. The first role of bioeffects concerns the policy that antipersonnel NLWs should “minimize permanent injury.” The second role of bioeffects in setting NLW policy concerns the long-term medical consequences of exposure to the NLWs for everyone exposed, including the operator, the target, and bystanders. If occupational exposure standards exist for the particular agent being used, as they do for many types of noise, radiation, and chemicals, then these standards should be followed when possible. If the exposures are sufficiently novel that no health standards exist—for example, certain types of directed energy—then standards need to be developed.

***The Variability of Human Responses and the Probabilistic Nature of Bioeffects***

Because of biological variability there will always be uncertainty in predicting the biological responses to non-lethal weapons. This is true for target, operator, and bystander effects. Even among a consistent population of humans, such as a group of young adult males, there will be a variability in responses to the same stimulus. When the variance of the population increases, for example, by adding persons of differing sizes, ages, weights, frailty, health, and sex, so will the variability of the population response to most NLWs. Therefore, biological responses to nonlethal weapons are probabilistic.

***Acoustic Energy as a Nonlethal Weapon***

In his work *Life of Marcus Crassus*, Plutarch described the use of bells and drums as a psychological NLW. More recently, rock music was used to annoy Manuel Noriega in Panama. Current ideas for NLWs use high-intensity infrasound. A special pressure chamber, the infrasound test device (ITS), has been constructed to examine the effects of infrasound at different frequencies on both anesthetized and awake subjects. The utility of acoustic energy as an NLW is likely to be defined in five years.

**LIST OF TECHNOLOGY DATA SHEETS  
4.1. ETIOLOGICAL FACTORS**

Genomics ..... 4-7

## DATA SHEET 4.1. GENOMICS

<b>Developing Critical Technology Parameter</b>	<p>The technologies required for sequencing the human genome and the genome of pathogens are the same. Accurate knowledge of, and the ability to determine, modify, and use, the base sequence of the human genome will reveal sequences that increase or decrease susceptibility to specific pathogens. Although the entire human genome is expected to be characterized by 2002, the identification of susceptibility/resistance genes in specific populations will require a longer period. A small portion (25 nucleotides) of the entire sequence of one susceptibility/resistance gene is likely to be useful in designing a detector element.</p> <p>Determination of the base sequence of PAIs/virulence factors in the genome of biological pathogens enables differentiating pathogens from non-pathogens and thereby allows rapid detection of biological agents and design of countermeasures. The majority of these sequences should be determined by 2005. A single biological agent may contain one to five such pathogenicity factors. The total set of pathogenicity factors for all biological agents may be as low as 100 since multiple organisms share similar sequences. A small portion (25 nucleotides) of the entire sequence of 1 PAI is likely to be useful in designing a detector element.</p>
<b>Critical Materials</b>	None identified.
<b>Unique Test, Production, Inspection Equipment</b>	None identified.
<b>Unique Software</b>	The database of the genomes of biological agents and generic human genome is available on several commercial software systems. Various display systems are accessible directly. Although the polymorphism of disease-resistant/susceptible genes in differing populations has yet to be determined, initial findings indicate that resistance to HIV may be correlated with prior exposures of populations to plague.
<b>Major Commercial Applications</b>	<p>The same genomic sequences that confer susceptibility/resistance to biological agents affect the health of the U.S. population. Immune-compromised populations are more susceptible to infection, and hospitalized individuals are subject to nosocomial infections. The medical and pharmaceutical industries are driving this technology.</p> <p>The same pathogens that pose threats as biological agents also cause disease in the general population. Immune-compromised populations are more susceptible to these organisms, and patients in hospitals are subject to nosocomial infections with the same agent. Contamination of food during processing involves several of the identified biological agents. For these reasons the medical, pharmaceutical, and food industries are driving this technology.</p>
<b>Affordability</b>	The large investment by commercial sectors identified above results in lower costs to the defense sector.

### **BACKGROUND**

The genetic code of biological agents is the determinant of infectivity of the agent and identifies those gene products in the infectious organism responsible for pathogenicity. The genetic code of the human, livestock, and agricultural grains determines the susceptibility of each target to infectious agents.

## SECTION 4.2—DEFEAT OR MANAGEMENT OF BIOLOGICAL AND CHEMICAL ATTACK

### *Highlights*

- Enhanced protection achieved by super-antigens, synthetic immune or antibody systems, vaccines, antibiotics, and antivirals.
- Preventing secondary organ target infection following viral exposure is now a realization.
- Multi-array sensors detect B/C agents by genomic and immunogenic probes.
- A process has been initiated to training first responders to B/C incidents and attacks.

### **OVERVIEW**

The etiological basis of infectious disease in otherwise physically fit persons is exposure to sufficient amounts of pathogen or toxin that will overcome natural or induced protection against such agents. Traumatic injury or environmental toxicants (chemical or physical) may increase susceptibility to pathogens. The protection of persons from illness and the management of illness involve the determination of the causative factors, then the administration of appropriate medications and nutrition, and isolation of those individuals likely to transmit illness and compromise group function. For infectious disease the identification of the infectious organism and appropriate antivirals and antibiotics for the organism is important. The majority of infectious diseases affecting military personnel is associated with organisms in the environment of the deployed soldier. From a historical perspective, disease resulting from the intentional release of biological agents is the exception. Emerging and re-emerging viruses and bacteria, increased drug resistance in the general population associated with the increased use of antibiotics, and increased deployment of forces to third world countries where nutritional standards and sanitary conditions are wanting increase the risk of exposure to infectious disease.

#### **A. ENHANCED PROTECTION AND TREATMENT OF PERSONNEL PRIOR TO AND IMMEDIATELY FOLLOWING EXPOSURE**

These technologies include materials that may be provided to personnel before deployment (e.g., vaccines), physical equipment used at the time that a biological or chemical agent is encountered [face masks, mission-oriented protective posture (MOPP) gear, aeroprecipitation of the agents], treatment of exposed persons entering a contaminated area (antibiotics, antivirals). The physical protection of persons from biological agents requires the use only of respiratory and eye protection filter systems, while that for chemical agents requires MOPP gear. The physical protection from biological agents is embodied by the filters that remove particles from the air flow system to the person. One potential new physical method of protection against biological and chemical agents is aeroprecipitation.

#### ***Biologically Based Protection***

New technologies are in development that will afford biological protection against biological agents. These include novel unconventional vaccines, antibiotics, antitoxins, superantigens, immune modulating viruses, synthetic immune systems, synthetic antibody-like drugs, chemical agent neutralizing drugs, and antiviral drugs that interdict viral disease after a person is exposed to viral agents.

#### ***Vaccines***

Vaccines that protect against a subset of the biological agents are currently available, but vary in efficacy and time required to achieve protection after exposure. Methods to increase the rate at which immunological protection can be achieved are described below.

## ***Antibiotics***

The development of sulfa drugs in the 1930s and of penicillin and others in the 1940–1970s was a major gain in the protection of persons following exposure to infectious bacteria. The use of antibiotics remains the primary mode of treatment of infectious disease of bacterial etiology, even as new problems emerge as a result of the broad distribution of these drugs. Drug-resistant organisms have become a significant concern in the treatment of bacterial infection in immuno-compromised persons [e.g., with nutrition difficulties, acquired immune deficiency syndrome (AIDS), and transplant recipients]. Associated with the rise of drug resistance is the increase of nosocomial infections in patients entering hospitals. The rise in drug resistance is observed as new pharmaceuticals are developed. The use of combinatorial chemistry, multivalent drug regimes, and rational drug design based on knowledge of the immunogenic and genomic properties of infectious agents are three approaches used to interdict disease from bacterial agents.

## ***Antitoxins***

Active or passive immunization or the administration of toxin binding agents are two methods of protection in the time period immediately following toxin exposure.

The above strategies may not apply in certain circumstances because (1) antibiotic-resistant organisms are relatively easy to produce; (2) not all pathogens produce toxins; (3) while vaccines are available for many pathogens, they have limited effect against active disease; (4) conventional vaccines can take several weeks to produce using the hybridoma-based technologies; and (5) vaccine development for a novel, unknown pathogen requires isolation and culture or generation of a large library of genomic DNA of the putative pathogen.

New approaches for the development of antiviral, antibacterial, and antifungal materials include the following:

- Development of super-antigens to achieve rapid immune responses;
- Synthesis of antibody-like drugs constructed through combinatorial approaches;
- Development of immune modulating constructs that increase production of immuno-modulators in affected persons;
- Development of compounds that block the entry of viruses into secondary target sites, the replication of viruses in the secondary sites, and the packaging of the viral materials into mature viruses.

These approaches are flexible in that they could be developed very rapidly with minimal laboratory requirements and in self-contained modular units.

*Super-antigens* (Section 3, Biological Technology). Enhanced prophylaxis can be achieved by use of active vaccination against biological agents or infectious agents endemic in deployed areas. Vaccination with super-antigens or advanced adjuvants (i.e., improved antigen presentation) can up-regulate the immune system provide protection in a 4-day period rather than the usual ten days after vaccination. The enabling technologies include genomic sequencing of all known threat agents and infectious disease organisms; multi component, multivalent vaccination systems to upregulate the immune system; and development of immune response modifiers, including interferons and interleukins, having the potential to enhance immune response under crisis situations. The sequencing of PAIs can reduce the total number of vaccines needed.

*Immune modulating viruses.* Retrovirus coding for interleukin 12 (IL-12) or interferon gamma (IFN-g) could be administered directly to the lungs as an aerosol. This would enhance the immune response in the location of agent delivered by inhalation, i.e., the lungs. This method is currently under development and proof of principle may be achieved within a year. This strategy may be most useful during early infection.

*Synthetic immune systems.* These systems involve the delivery of retroviruses containing a pseudo-gene coding for an oligonucleotide derived from a SELEX-based method (see below). Gene therapies for cancer and various disease states characterized by a mutation-associated dysfunction of a key enzyme or receptor (for example, cystic fibrosis) have been used experimentally for the last five years. Genes coding for immunomodulators could also be used. The main reason for this approach is that large-scale oligonucleotide synthesis is not readily achieved, and in any case repeated administration would have to be performed to ensure efficacy. Since the body would express the

retroviral gene construct continuously, a single dose would provide protection for an extended period of time. An alternative approach could use a phage-based selection system (Gao et al., *Proc. Natl. Acad. Sci.*, 94, 11777–82, 1997). The approach in principal is similar to SELEX; however, selection and enrichment occur directly through phage expression and selection without PCR enrichment steps. Both technologies are extremely robust, do not require extensive participation by the host immune system, and can be developed very rapidly with minimal laboratory equipment.

*Synthetic antibody-like drugs.* One promising strategy utilizes a PCR-based technology called SELEX (“Systematic Evolution of Ligands by Exponential Enrichment,” Gold et al., *Proc. Natl. Acad. Sci.*, 94, 59–64, 1997). Very specific DNA fragments can be made against a pathogen in a very short period of time. The pathogen does not have to be cultured or strictly isolated from surrounding infected tissue. The fragments bind to the pathogen very tightly and can be made to include other elements that either alert the immune system to the pathogen or inactivate the pathogen directly. This technology is very robust but is also quite new.

*Chemical agent neutralization.* The SELEX- and phage-based synthetic immune systems can be used to prepare a person for exposure to a wide array of intoxicants. A major hurdle to be overcome would be the construction of appropriate transcription control elements based on the presence of an array of intoxicants because it would not be desirable to have the response systems turned on unless the intoxicants were present in sufficient concentration.

### ***Interdiction of Viral Entry, Replication, and Maturation in Secondary Target Cells***

For the virus to attack secondary target sites successfully it must enter the cell, the nucleic acid may travel to the nucleus for replication, and then the newly synthesized viral nucleic acid must be coated by the viral protein capsid. Cysteine protease inhibitors can block entry of the virus to cells, inhibitors of cytoplasmic nuclear transport can inhibit the second step, and inhibitors of molecular chaperones can inhibit the nucleic acid-viral protein coat interaction. Finally, mature viral particles may only be released following initiation of apoptotic event. Compounds that inhibit apoptosis may protect the patient from rapid development of clinical signs.

Recent studies indicate that the development of compounds that inhibit specific hemagglutinins and neuraminidases may protect individuals from virulent influenza viruses, a major cause of illness. There are virulent and avirulent influenza viruses. Hydrolytic enzymes play a major role in the infectivity of influenza viruses. The virulent type replicates in all organs, while the avirulent type only replicate in gut and respiratory tract. Hydrolytic cleavage of hemagglutinin is required for virulence. Hemagglutinin (HA) of virulent organisms cleaved in all organs, but HA of avirulent cleaved only in gut and respiratory tract.

New sets of antibiotics that inactivate PAIs may have utility in individual and group protection. These antibiotics can be antisense materials or chemicals similar to traditional antibiotics. It is important to develop antibiotics that have not been used in the general population to preclude the further development of drug resistance in the population.

### ***Assessment of Drug Toxicity on Microchips***

All the above technologies involve the development of new drugs to be administered to affected persons. Two major expenses in drug development are (1) the determination of the efficacy of the drug in protecting persons from biological or chemical agents, and (2) determining whether the novel drugs have adverse side effects. A new technique is emerging that will allow initial screening of a drug’s actions on a microarray of DNA or peptide fragments. In this method, living cells are exposed to the drug of interest and the altered expression of genes is analyzed on the microarray. Because many of the drugs that are developed have undesirable side effects and because these side effects involve increased expression of specific proteins, the treated cell can be monitored for overexpression of messenger ribonucleic acid (mRNA) for the undesirable proteins. This would provide a critical step in reducing costs of drug development. The method has been described in Friend et al., in *Nature Medicine*, 4: 1293, 1998.

### ***Aeroprecipitation***

Aeroprecipitation technologies can be used to defend against the dispersal of biological agents as aerosols. The net electrostatic charge on the particles can be used to cause aggregation of the infectious agents, thereby reducing the

number of particles that may affect the target population. The other physical properties of dispersed aerosols facilitate developing countermeasures that result in aggregation or precipitation of the biological agents shortly after dispersal.

## **B. DETECTION AND IDENTIFICATION OF BIOLOGICAL OR CHEMICAL AGENTS**

Some chemical and biological agents may not result in an overt clinical presentation until days or weeks after an attack. It is possible to envision a scenario where a number of intoxicants and biological agents may be present because of endemic disease rather than because of an intentional release of weaponized agent. In either case a subset of the exposed population may suffer due to genetic predisposition.

Biopolymer-based sensors are available to detect and identify infectious agents, chemical agents, and biomarkers. Until the mid 1980s the majority of sensors depended on macroscale systems that utilized changes in optical density or changes in enzyme reactivity when a biological agent or chemical agent entered the field of the sensor. The optical density and enzyme reactivity changes were relatively nonspecific for agents, and the sensors therefore had utility as detectors but not identifiers of specific agents. With the advent of monoclonal antibody (MAb) and PCR technology it became possible to recognize specific infectious biological agents by the proteins on their surface (MAb) or by their genomic material (PCR). It became possible to identify toxins or chemical agents by the use of MABs or receptors that specifically interacted with the agent. A new technology has arisen that permits miniaturization of the sensor through the production of multi-array sensors. The multi-array sensor recognizes either surface antigens or genomic sequences on a single detector surface. Upon interaction between the immobilized antibody or complementary genomic sequence on the sensor surface with the biological or chemical agents an optical/electrical signal is generated. The multi-array sensor may contain 1,000 detector elements on a single 4-cm<sup>2</sup> surface.

Another new technology permits the rapid synthesis of microscale amounts of chemicals. This technology is a fusion of microfluidics and chip technology (see Robert Service, *Science*, 282: 399–401, 1998). The apparatus has dimensions of 5 × 8 cm and can synthesize or sequence small amounts of DNA for inclusion as genomic probes on a multi-array sensor. This new technology will have a major impact on affordability because almost all of the processes are automated and therefore require many fewer technicians. See also Biological Technology, Section 3.

A second general technology for assessing whether a population has been exposed to a biological or chemical agent is a probe that would identify an endogenous biomarker (see subsection 4.3) at concentrations below that at which any pharmacological effect becomes evident. The detection of low molecular weight chemical molecules will probably be more tractable than the identification of high molecular weight compounds or microorganisms.

Probes/detectors for known chemical agents:

- May be implanted to measure blood levels or the appearance of the chemical or a secondary product; or
- Can be attached to clothing or respirators to measure ambient levels.

Probes/detectors for known biological agents comprise several types:

- High-affinity bio- or immuno-chemical probes for specific antigens or cell products can be used to monitor body fluids and lavages for the presence of specific biomarkers of infection.
- High-efficiency probes can be used to monitor ambient air for specific microorganisms.
- Sensors that identify specific toxins/soluble infectivity factors/cell-surface invasive elements can provide advance warning and enable appropriate protective responses.
- Sensors that identify the body's early response markers to pathogens or toxins can be used to provide warning and initiate responses.

One system for early detection of an extreme physiological stress or infection is an artificial antibody/antitoxin-producing cell: an implanted reservoir containing specific antibodies, antitoxins, or antibiotics that are connected to implanted sensors. This sensor will identify specific molecules entering the circulation (or lungs or other tissues) and trigger the reservoir to release its contents and also transmit an outside signal to inform others of the exposure. This could lead to remote triggering of reservoirs in individuals who have not yet encountered the insult, but are potentially at risk.

## ***Sensors for Biological and Chemical Agents***

Sensor systems are discussed below and in Biological Technology, Section 3.

- a. *Synthetic reporter systems.* Recent approaches in combinatorial chemistry permit the placement of thousands of unique protein or DNA fragments onto a microchip (multi-array sensor). Such a device could be used to identify intoxicants in urine, saliva, lung lavage, etc., or to identify organic markers of oxidative stress (for example: nitrotyrosine) or the presence of transcription factors related to stress. Nucleic acid sequences about 20 nucleotides long and complementary to the nucleic acid of pathogenic agents may be immobilized on these sensors and serve as probes for biological agents. These systems are likely to be extremely robust and technologically feasible.
- b. *Cell-based reporter systems.* Biological or chemical agent exposure could be identified by observing the changes in gene expression occurring in cells. Genes involved in cellular death (apoptosis), DNA damage (p53, p21, RB), and response to oxidant stress (NF-kappa-B, c-jun, OX-1, HSP-70) are up-regulated early during stress. The transcription of these genes can be identified with a fluorescent or electrochemical reporter system.
- c. *People-based reporter systems.* A similar approach as that suggested in (a) above could also be used to monitor people. In this scenario the increased synthesis of biomarkers of infectious disease, chemical, or stress exposure will be observed in peripheral blood cells. The cost of observing gene regulation is currently high in terms of number of personnel, time, and machine-maintenance cost.

## ***C. TRAINING OF HEALTH PERSONNEL FOR INCIDENTS OR ACCIDENTS INVOLVING BIOLOGICAL AGENTS***

During the past decade the acquisition and management of chemical and biological warfare weapons have become a concern to the international community. The low cost of obtaining and weaponizing chemical/biological agents raises concerns about the potential use of such agents by lesser developed countries (LDCs), by surrogate groups operating at the behest of nation states, and by terrorist groups.

Several panels appointed by President Clinton examined the ability of the United States and other industrialized nations to respond to the threat of use of weapons of mass destruction (WMD). The reports of these panels resulted in a set of Presidential directives that included:

- a. increased international cooperation in the area of WMD;
- b. new approaches to prevent weapon acquisition;
- c. new approaches to crisis management;
- d. development of a critical infrastructure to coordinate responses; and
- e. increased transportation security.

Items c, d, and e involve increasing public awareness (including medical professionals; hospital administrators; and law enforcement, fire department and emergency medical response teams) to the potential threat of a developing incident/accident and appropriate responses to this threat.

## ***Emergency Preparedness in CONUS–Integrated Civilian and Defense Activities***

Processes will be identified for informing residents when a release of biological agents has occurred or is imminent. Appropriate responses to the threat and ways to limit the exposure of adjacent communities to the biological agent will be developed. The critical elements of the process include the training of first responders and the development of mechanisms to control the dissemination and spread of the agent with minimal social disruption and panic following release of information to the public. The agencies involved in this task include the National Guard, Federal Emergency Management Agency (FEMA), and the Departments of Justice, Health and Human Services, and Defense (DOJ, DHHS, and DoD).

At the present time (1998), the Chemical and Biological (CB) Hotline serves as an emergency resource for first responders to request technical assistance. The Nunn-Lugar II act specifically calls for “establishment of a designated telephonic link to a designated source of relevant data and expert advice for the use of state or local officials responding to emergencies involving a weapon of mass destruction or related materials.” The Hotline’s intended users include trained emergency response personnel: emergency operators and “first responders” (the firefighters, police, and emergency medical technicians who arrive at the scene of a CB terrorist incident). Other users may include the state emergency operations centers and hospitals that may treat victims of CB agent exposure.

- The CB Hotline is staffed by trained operators servicing the phones 7 days a week, 24 hours a day. Operators use extensive databases and reference materials in addition to immediate access to the nation’s top subject-matter experts in the field of CB agents. Areas of specialty include CB agent identification, medical treatments, and information on military and civilian defense equipment.
- The CB Hotline is a joint effort of the Coast Guard, Federal Bureau of Investigation (FBI), FEMA, Environmental Protection Agency (EPA), DHHS, and DoD. The National Response Center (NRC) is the entry point for the CB Hotline. The NRC receives basic incident information and links the caller to the DoD’s and FBI’s chemical, biological, and terrorism experts. These and other federal agencies can be tapped within a few minutes to provide technical assistance during a potential CB incident. If the situation warrants, a federal response action may be initiated.
- Use the local established policies and procedures for requesting federal assistance before contacting the CB Hotline. State and local officials can access the CB Hotline in emergency circumstances by calling 1-800-424-8802.
- Chemical and Biological Defense Command (CBDCOM) Public Affairs Office \* Phone (410) 671-4345 \* Facsimile (410) 671-5297.

***Emergency Preparedness–Military Response Teams***

Following the experience of the Gulf War, the Pentagon designated a platoon-size Army force, the technical escort unit (TEU) to have specific training and equipment to permit detection and identification of biological agents in deployed and combat areas. This TEU of 182 persons from the 310th Chemical Company and the Marine Corps 375-member Chemical Biological Incident Response Force (CBRIF) respond to biological agent threats. A biological integrated detection system (BIDS) has been developed and fielded for the 310th Company. The M93A1 Fox nuclear, chemical, and biological reconnaissance system vehicle is a component of the detection system. The Army has a “Domestic Preparedness Program” intended to strengthen the ability of federal, state, and local emergency personnel to respond to BW threats. A new National Guard initiative, National Guard Rapid Assessment and Initial Detection (RAID) organization is in the formative stages.

**LIST OF TECHNOLOGY DATA SHEETS**

**4.2. DEFEAT OR MANAGEMENT OF BIOLOGICAL AND CHEMICAL ATTACK**

Biological Protection Against Biological and Chemical Agents.....4-15  
 Aeroprecipitation.....4-16  
 Bio-based Sensors.....4-17  
 Training of Health Personnel.....4-18

## DATA SHEET 4.2. BIOLOGICAL PROTECTION AGAINST BIOLOGICAL AND CHEMICAL AGENTS

<b>Developing Critical Technology Parameter</b>	Biological protection: vaccines, antibiotics, antivirals, superantigens, immune-modulating viruses, synthetic immune systems, synthetic antibody-like drugs (SELEX), aeroprecipitation.
<b>Critical Materials</b>	Biosystems that result in rapid production of antibodies in a 1–3–day period instead of usual ten days. Production of effective multivalent antibacterial and antiviral compounds by combinatorial chemistry and rational drug design. Production of non-infectious retroviruses that code for IL-2, interferon gamma, and other protective immuno-modulatory compounds. SELEX-produced oligonucleotides that bind and inactivate infectious biological agents.
<b>Unique Test, Production, Inspection Equipment</b>	Biosafety Level (BL)-4 or BL-3 laboratories.
<b>Unique Software</b>	This software is useful for the SELEX and immune vaccine and immunomodulatory protection systems. Databases of the three-dimensional structure of biological agent proteins, nucleic acids, and of the receptors for these agents on cells in the host are important for the construction of antibacterial and antiviral compounds. Such a database exists at web sites.
<b>Major Commercial Applications</b>	Novel antibacterial and antiviral compounds have broad utility in the medical and pharmaceutical industries. Nosocomial infections, outbreaks of diseases in impoverished areas and in the developed world, and evolution of drug-resistant diseases all increase the demand for such materials. These factors drive the research and transition to the marketplace.
<b>Affordability</b>	The cost of the drugs, including testing to FDA standards, is a major factor in the biological protection arena. Because the medical and pharmaceutical industries are driving the research, the cost to the defense community is mitigated.

## DATA SHEET 4.2. AEROPRECIPITATION

<b>Developing Critical Technology Parameter</b>	Development of particles with standing electrostatic charge and other properties to aggregate airborne biological agents.
<b>Critical Materials</b>	Stable particles with an appropriate electrostatic charge. Most surfaces of biological agents are electronegative due to modified sugars on the surface. These sugars are critical to binding of the agent to the target cell. Encapsulation of the B agent may result in an electropositive coating. The dissemination of oppositely charged particles having diameters of 20–100 microns over the released B agent may cause aggregation and precipitation of the organisms prior to inhalation by the target population. Current technology permits preparation of large amounts of such particles.
<b>Unique Test, Production, Inspection Equipment</b>	BL-3 or BL-4 laboratories. Turbulent flow test chambers in BL-3 or BL-4 facilities.
<b>Unique Software</b>	Software to monitor wind shear and airflow patterns following release of agent, aggregation of the agent with particles, or sonic coagulation of the agent.
<b>Major Commercial Applications</b>	Removal of pollens and fuel particles from the air.
<b>Affordability</b>	Not determined.

## DATA SHEET 4.2. BIO-BASED SENSORS

<b>Developing Critical Technology Parameter</b>	Development of multi-array sensors based on genomics/immunogenics of all biological agents or of the target population. The use of combinatorial chemical approaches to identify signatures of all biological agents.
<b>Critical Materials</b>	The identification of biological agent nucleic acid fragments (20–30 nucleotides in length) that will bind complementary sequences in an appropriately stringent manner. The production of highly specific antibodies to target antigens of the agents, or the identification of chemical materials produced by combinatorial chemistry, that bind agents and differentiate them from nonpathogens of the same bacterial/viral family. The attachment of these specific binding materials to a transducing surface that is lightweight and field hardened and has low energy requirements.
<b>Unique Test, Production, Inspection Equipment</b>	Clean rooms for preparing the sensor surface and for attaching the biopolymer probes to the transducing surface using optical, chemical, or lithographic technologies. Characterizing the product for utility in detecting biological agents in BL-3/BL-4 facility.
<b>Unique Software</b>	Multi-array sensors have been produced using optical and lithographic techniques. The current prototypes contain 100 to 400 sensor elements on a surface that is 4 cm <sup>2</sup> . The capability to produce large numbers of multi-array sensors with appropriate quality assurance/quality control (QA/QC) will be achieved by 2003. The fielded version of the multi-array sensor can be realized by 2008 or sooner.
<b>Major Commercial Applications</b>	The leading drivers in this technology are the medical, pharmaceutical, and food industries.
<b>Affordability</b>	The cost component for DoD applications will complement those of the medical, pharmaceutical and food industries and increase affordability.

### ***BACKGROUND***

Sensors can detect and identify biological or chemical agents based on the genomic, immunogenic, or chemical binding properties of biological agents or the receptor, immunogenic, or chemical-binding properties of C agents. Multi-array sensors, built on a variety of platforms, can achieve identification in minutes.

## DATA SHEET 4.2. TRAINING OF HEALTH PERSONNEL

<b>Developing Critical Technology Parameter</b>	Fluid hierarchy in communication systems between medical triage groups and first responders. The development of a fluid hierarchy will permit thoughtful responses sufficient to cope with all dimensions of a biological incident or threat in a timely and adaptive manner. Create an interface of local and federal public health resources with local security, National Guard, and military support.
<b>Critical Materials</b>	Novel communication structures, data fusion, and educational tools for rapid insertion in a crisis area.
<b>Unique Test, Production, Inspection Equipment</b>	None identified.
<b>Unique Software</b>	Training and communications systems.
<b>Major Commercial Applications</b>	Managing local outbreak of infectious disease or mass food-poisoning cases.
<b>Affordability</b>	As various interagency task teams are formed and the interdepartmental linkages are established, the incremental costs may be modest.

### ***BACKGROUND***

The rapid developments of new biomedical technologies, of information science, and of bioterrorism have given rise to a need to train health-care professionals in new approaches. There is a need for continuing education, for insertion of affordability concepts into care delivery and for integrating information science knowledge into health-care management.

## SECTION 4.3—MANAGEMENT OF TRAUMA, STRESS, AND TREATMENT

### *Highlights*

- Biomarkers will permit early detection of high-level toxicant and stress exposure.
- Biological growth factors enhance rate of wound healing and neural regeneration.
- Telemedicine promises the rapid removal and treatment of persons with traumatic injuries to enhance survival and reinsertion into units.

### **OVERVIEW**

As a result of the advances associated with the human genome project a needle-stick in the finger of a person provides a drop of blood to test for (1) signs of emerging disease, (2) unusual sensitivity to chemicals in the environment, or (3) stress. Sensitive tests look for the presence of telltale proteins that may be secreted from cells. This may be evident hours to days before clinical disease or functional decompensation becomes evident. A computer is used to connect to a database of DNA samples that can be compared to the patient's DNA. If the patient's DNA matches DNA sequences in the database that are consistent with early-stage disease or chemical sensitivity, treatment protocols can be initiated immediately. Biomarkers of cell responses to drug therapy are also now being used to rapidly screen new drugs in development for early signs of toxicity. Biomarkers of intense emotional stress have been identified. Evidence that a new drug is causing the synthesis of proteins in cells that signal cell death or dysfunction (biomarkers) can short-circuit expensive tests required to demonstrate toxicity. Because the new technologies of combinatorial chemistry and drug design produce thousands of compounds per week, it is necessary to devise tests that provide rapid indication of utility and of toxicity. Biomarkers may provide information related to both of these needs. Telemedicine technologies and novel methods to treat traumatic injury are included in this subsection.

This subsection discusses the interface between medicine and telecommunications (telemedicine) in the management of persons at a site distant from primary medical care facilities. The final portion of this subsection discusses control of internal bleeding, cell and organ transplants, and the increasing role of growth factors in wound healing and nervous system repair.

### **A. BIOMARKERS OF TOXICANT EXPOSURE AND OF PHYSIOLOGICAL STRESS**

A biomarker is an indicator of exposure of persons to particular agents, toxicants, or physiological stress. There are three types of biomarkers:

- An *exposure biomarker*—the presence of an exogenous compound or its metabolite signaling that the person has been exposed to the toxicant;
- An *effect biomarker*—the detection of an endogenous component or of a change in functional capacity of a person or other indication that an individual has been exposed to a toxicant or a biological or chemical agent or to physiological stress; and
- A *susceptibility biomarker*—a genetic indicator that an individual is particularly susceptible to specific toxicants or stresses.

The “exposure biomarkers” are typically metabolites of the toxicant and their presence in body fluids (serum, urine, saliva, and spinal fluid) usually follows an acute exposure. They may be detected minutes to hours after exposure in most cases.

The “effect biomarkers” are usually biomolecules such as proteins or hormones produced in the body of the exposed person. Examples of such “effect biomarkers” are “acute phase proteins,” “heat shock proteins” (HSP), and

epinephrine. The change in these compounds may be detected in minutes to days after exposure to the toxicant or agent.

The “susceptibility biomarkers” are usually components of the genome of the individual. Examples include the enzymes such as glutathione S-transferase (GST) and cytochrome P450 (P450) that function to detoxify compounds in the environment. Persons deficient in one of the GST isoenzymes have a fourfold higher incidence of lung cancer, if they smoke, than persons who have that subunit.

There are endogenous chemicals that are produced by the body under conditions of stress such as intense noise, temperature extremes, industrial chemical exposure, fear, and fatigue. These compounds include the high molecular weight heat shock proteins, interferons and other immunomodulating factors, acute phase proteins, and low molecular weight hormones such as adrenalin and corticosteroids. Sensors that detect changing levels of stress biomarkers can be used in distributed information systems to assign tasks and alert command about rapid changes in readiness and vigilance.

Exposing personnel to elevated concentrations of organic chemicals or industrial solvents for extended periods of time may compromise the health of a subset of the population. Acute effects may degrade the operational capability of units in which these persons function. Historical examples include the “Agent Orange” and “Gulf War Syndrome” incidents with associated morale issues and liability claims. The optimal strategy, from an occupational health standpoint, is to identify biomarkers that signal when a person is on the verge of developing clinical signs following exposure to a toxicant. Such a signal will permit the temporary removal of the affected individuals from exposure.

Isotope-dilution gas chromatography (mass-spectrometry method), has been used analyze levels of exposure of Air Force veterans who worked in Operation Ranch Hand to Agent Orange (by its dioxin contaminant). The method now provides the opportunity to analyze occupational exposures to industrial chemicals in the workplace.

### ***Sensors and Probes to Detect Changes in Biomarkers (see also the subsections on Disease Detection, Diagnosis, and Treatment)***

Sensors may be developed to identify these markers so that the psychological fitness of individuals can be monitored. The response of the body to a physiological stress, foreign chemical, or infectious agent involves the increased or decreased synthesis of specific molecules by cells/tissues in the affected person. The substance produced by the subject could be an antibody (which could take from several days to months to appear); a cellular protein or mRNA, the concentration of which is increased or decreased in response to the insult; or a hormone that is produced as an effect of, or in response to, the insult.

The measurement of biomarkers of exposure allows for prophylactic measures to be taken. The ideal system would be one that identifies the insult and initiates prophylactic or preventive measures before, or simultaneous with, any toxic response by the body.

## ***B. TELEMEDICINE***

Telemedicine is the use of electronic information and communications technologies to provide and support health care when distance separates the participants.

The technologies included in this area are multimedia medical databases, virtual reality presentations (visual, auditory, haptic), telepresence surgery, life support for trauma and transport (LSTAT), microsensors and transmitters, and sensate liners in which both coverings contain sensors.

The civilian biomedical community will utilize these technologies while providing service to remote areas and when transporting persons experiencing traumatic injury (e.g., automobile and sports accidents). The industrial sector will utilize these technologies to monitor employees working in hazardous areas.

### ***Telemedicine Applications***

The Information Age has direct impact on the medical industry, replete with robotics, telemedicine, telepresence surgery, remote manipulation, and dexterity-enhanced surgical techniques—even three-dimensional visualization

technologies. As a result, a paradigm shift has occurred in medicine, empowering surgeons and patients. Creating the operating room of the future that is capable of integrating and facilitating this infrastructure of applications is a task on the drawing boards of technology developers, research institutions, and innovators worldwide. One goal is to create an operating theater capable of freeing the surgeon from peripheral distractions during surgery, delivering information to the surgeon's fingertips, and supplying speech-recognition technologies and robotics applications to assist in the process. The primary drivers in this technology will be the medical, civil defense, and national defense communities.

### ***Telemedicine Systems***

Telemedicine technology requires a sophisticated telecommunications system that includes video, audio, and haptic interfaces from medical evacuation platforms and forward medical units to areas that may be several thousand miles away. In this process, satellite systems are involved as are continuous communications. The fielded units are anticipated to contain smart systems that can facilitate the remote information processing between experts at a distance and medics on site.

Telemedicine trials in psychiatry, home care, dermatology, radiology, cardiology, and renal dialysis monitoring have been tested successfully in the civilian health-care delivery system. Radiology has been employed extensively in this mode, utilizing transfer of images between distant sites. Neurological diagnoses and pharmacological control of seizures have been accomplished through transmission of electroencephalographic (EEG) patterns by telecommunications. Dermatological images of nonpigmented lesions have been transmitted to distant sites for diagnostic purposes.

The applications of telemedicine technologies to radiology have increased as a result of marked progress in computer-based imaging. During the past 20 years, the anatomical and functional imaging of human organs has taken a quantum leap forward. The methodology of X-rays has now been complemented by computerized tomographic (CT) systems including magnetic resonance imaging (MRI), positron emission tomography (PET), or single photon emission computerized tomography (SPECT). Organs deep within the body can now be biopsied by long, thin needles guided safely to their targets by CT or ultrasound scanning; in many cases, this capability has eliminated the need for general anesthesia and an open surgical procedure. Adaptations of MRI permit the placement of catheters within 1 mm of any region in the brain. This can allow specific delivery of materials to organs if the vascular bed of the organ is permeable to the material. In the next decade it is likely that metabolic imaging techniques will provide information about the disruption of cellular signaling pathways or specific patterns of gene expression.

Using data from the National Library of Medicine's "Visible Male" from the Visible Human Project, researchers have developed and tested imaging software that enables technicians to combine X-ray, CT scan, and MRI data to create a three-dimensional rendering of any organ in a patient, as well as the surrounding organs. By manipulating the three-dimensional image, the surgeon can see the relationship of one organ to other anatomic structures prior to surgery. This information enables the surgeon to determine the best way to conduct the operation.

The application of computer technologies to enhance and manipulate images has been illustrated most dramatically in the pictures beamed back to Earth from orbiting satellites or from interplanetary probes. Extensions of this technology have profound implications for analyzing and refining patterns detected in medical images. Neural networks are a component of some artificial intelligence technologies that can be "trained" to recognize patterns.

### ***C. NOVEL APPROACHES TO TREAT TRAUMATIC INJURY, STANCH ABDOMINAL BLEEDING, TREAT EXTENSIVE BURNS, AND PROVIDE ORGAN REPLACEMENT***

Projectile injuries to the abdomen frequently result in extensive loss of blood through hemorrhage. Consequences of hemorrhage are a marked reduction in oxygen-carrying capacity of the blood; rapid changes in blood fluid volume; and associated changes in brain, kidney, and liver function. Reperfusion of the patient with cells and/or blood substitutes is often accompanied by damage to the central nervous system and other organ systems. The generation of free radicals and associated oxidative stress are among the factors that are etiologically involved in tissue damage following traumatic injury and reperfusion.

The following are among the developing technologies that can be used to treat traumatic injury, severe hemorrhage, and their sequelae:

- Rapid detection of changes in vital signs of personnel;
- Mass casualty respirator capability;
- Tissue viability enhancers including pharmacological intervention to reduce oxidative stress, development of synthetic reperfusion fluids that have low hepato-toxicity, pharmacologic strategies to lower tissue oxygen requirements of tissues in shock;
- Stem cell and organ culture systems to increase the rate of organ regeneration and repair;
- Development of cell growth factors to enhance regeneration of damaged tissue; and
- Development of nerve growth factors to enhance rate of neural regeneration.

### ***Specific Elements of Traumatic Care***

#### ***a. Vital Signs***

Rapid detection of vital signs can be greatly enhanced by future technologies to the point that “tricorder” technology should actually exist. In its current form, the “tricorder” is a radio-frequency radiation device that will detect pulse/respiration. It has a distant life-signs scanning capability originally built for detecting vital signs through chemical warfare protective clothing, and can detect life signs through brush, structures, or collapsed buildings.

#### ***b. Mass Casualty Respirator***

Mass casualty respirator capability to sustain survivability has recently been explored. This technology consists of high-frequency ventilation capability from a central source, but with multiple stations such that overall ventilation will be sufficient for 80–95 percent of casualties.

#### ***c. Tissue Viability***

Tissue viability is dependent on cellular respiration, which in turn depends on supplying oxygen and removing wastes, and is a function of blood flow and perfusion. The availability of oxygen for tissue use is also governed by the perfusion fluid and cellular metabolic level. Blood substitutes, stroma free hemoglobin, and blood banking capability offer near-term vehicles of delivering oxygen to tissues and thus promote tissue salvage. Tissue salvage includes manipulating oxygen dissociation to allow oxygen release to hypoxic tissues. A more radical means of tissue and body salvage is an overall reduction in metabolic activity, thus decreasing oxygen demand and preserving available oxygen for tissue use.

Another mechanism likely to be available by 2003 is the use of hyperbaric oxygen (HBO). Oxygen breathed at increased pressure will follow gas solubility laws (3 vol% per atmosphere in plasma); hence, at standard treatment pressures, oxygen no longer depends on red blood cell concentration or hemoglobin. Tissue oxygen levels in compromised areas can approach or exceed levels found in normal tissue, provided there is minimal perfusion. It could also be used in conjunction with blood substitutes or volume fluids. HBO may have multiple actions. Preliminary studies demonstrate that HBO has a protective effect in reperfusion injuries. It is indicated as adjunct treatment for crush injuries, burns, cyanide poisoning, and severe carbon monoxide poisoning. Multiple studies show that HBO increases oxygen levels in compromised tissue enough to allow polymorphonucleocytes to phagocytize bacteria. This may be important in preventing infection in burn cases.

The use of antioxidants to counteract radical formation during reperfusion injury is a near-term methodology. Research into decreasing lymphocyte adhesion to vascular endothelium and consequent inflammatory reaction is key to reperfusion injury treatment. Pharmacologic means of modifying biochemical responses in reperfusion injuries are also being studied.

#### ***d. Growth Factors***

The new horizon in treating wounds is related to the understanding and development of growth hormones, cytokines, and integrins that trigger wound healing and angiogenesis. There appears to be an independent critical mechanism that involves the oxygen molecule that as of yet is not understood. The process of wound healing from a biochemical standpoint should advance quickly over the next ten years, yielding a palate of pharmaceutical enhancements to heal traumatic injuries sooner.

In stabilizing patients, surgery and antibiotics will continue to play a major role. New technologies concerning telemedicine consultation and advice (discussed in other areas of this subsection) offer to the field a means of handling more complicated cases. However, in a mass triage situation, time may be limited for this capability. In the surgical arena, scanning or similar technology should also develop over this time period to allow tissue viability determination that is independent of blood flow. Such a technology would allow the surgeon to prevent overly aggressive debridement.

#### ***e. Cell and Organ Culture and Organ Transplant***

New cellular technologies are emerging that may allow for growing stem cells, growing organs, or stimulating organ regeneration. The successful reports in November 1998 of stem cell culture from fetal tissues promises availability of cells to replace all tissues, including neural tissues. A second technology report appeared in November 1998, indicating that nuclei from mature human cells could be caused to dedifferentiate by inserting the nuclei into cytosol of cells from cattle. Such dedifferentiated cells can also behave as stem cells. Pluripotent cells have the potential to differentiate into any type of cell or organ system. This is particularly promising in spinal cord contusion or partial transection where immature neural cells act as a bridge between host nerve tissue. It also promises benefit to aging patients with neuro-degenerative diseases such as Alzheimer's disease, Parkinson's disease, and dystrophies. Another concept is an organ bank with cryogenically preserved replacement organs for transplantation. Over the next 20 years, advances in standard organ transplantation and organ storage will also develop, as well as a means of reducing organ rejection. Artificial skins, grown from cell tissue cultures, and synthetic membranes are already entering the marketplace. Continued development is certain.

The first successful cloning of an adult mammal was achieved in 1996 in Scotland using sheep. The feat was replicated in 1998 using adult mice (*New York Times*, July 22, 1998). The implication of these findings is that the nuclei of cells that have differentiated can be induced to serve as primary genetic material for future generations of animals. The nucleic acid sequence in the future generations will be identical to that of the nucleic acid in the cell nucleus used at the start, hence the future generations are clones of the primary donor. The cloning of cattle can result in a highly predictable milk yield and quality from subsequent generations and has significant economic impact. The capability to clone humans has social and ethical consequences that remain to be addressed, and the technique is therefore controversial. However, this technical demonstration also has implications for the large production of organ tissues from individuals. Although the technology is not available at this time to specifically program the generation of a liver, kidney, spleen, etc., from an adult nucleus, such directed programming is likely to appear by 2010. In this manner the donor of the nucleus may be a person who suffered extensive damage to an organ; the regrown organ may be implanted with little to no risk of tissue rejection or of infections with latent or slow viruses.

#### ***Sustain Function and Repair of the Nervous System***

The nervous system is critical for sensory perception and motor function, information analysis, and decision making. This area encompasses neural and psychiatric aspects of brain, spinal cord, and peripheral nerve function. Traumatic injury to the spinal cord is a primary concern, both because at the present time there is little clinical treatment to be offered to the patient with spinal cord transection, and as a consequence the massive loss of function will remain for the duration of the patient's life. The financial cost to relatives and to society in caring for the patient is extensive. The incidence of spinal cord injuries in the civilian sector is approximately 40 persons per million population, with the rate of spinal injuries for males 2.5 times greater than that seen in females. The costs of caring for persons in the first year following injury is approximately \$200,000, and each subsequent year has a cost of approximately \$30,000. Veterans constitute 22 percent of the spinal cord injury population.

## ***Spinal Cord Repair***

The past 15 years have seen the emergence of new technologies that may facilitate repair of hemisectioned spinal cord. Three major contributions have been (1) the recognition that placement of bridging matrices across the transected section of cord will serve as a bridge across which the nerve axons may pass; (2) placement of biological growth factors in the vicinity of the regenerating nerves appears to enhance the growth of the cut axons across the transection; and (3) biochemicals or biomimetics may be able to limit the “scar” forming growth of the glial cells, thereby removing a barrier to axonal growth across the transection.

The bridging materials that have shown efficacy in experimental animals include fibrous biopolymers, biomimetics, and synthetic polymers. The ends of the polymers are placed in each edge of the cut surface of the cord. Neuronal axons will grow along the surface of the polymer and become inserted into the spinal cord on the other side of the cut cord. Most frequently the axons penetrate only 1–3 mm, thereby limiting the regeneration of the cord.

Several proteins have shown utility in enhancing survival of neurons in spinal cord following injury and in facilitating axonal outgrowth. Included in this category are brain-derived neurotrophic factors. Other proteins have demonstrated utility in reducing edematous swelling of neural tissue following traumatic injury. Since edema is accompanied by increased cell damage and death, these compounds are considered neuroprotective. Insulin-like growth factor I is an example of a compound with protective action. Insulin-like growth factor also reduced the marked increase of neuronal nitric acid synthase, an etiological inducer of nerve damage.

In neural regions other than the spinal cord it has been shown that in humans, hypoxic damage is associated with the phosphorylation of a “mitogen-activated kinase activating death domain protein” and migration of the protein to the nucleolus of neurons. The phosphorylation is catalyzed by stress-activated kinase Jun kinase 3. The correlation of hypoxic damage of the nervous system with an enzymic event suggests that low molecular weight inhibitors may be developed that can interdict the hypoxic damage. Finally, during early development it has been shown that proteinaceous materials (GAP 43) are required for growth of retinal ganglion cell axons in the visual system. It is likely that such signaling molecules are required during neural regeneration in certain brain regions. With the advent of combinatorial chemistry it is anticipated that new classes of compounds will have applications in neuroprotection and regrowth of nerves across the lesion.

## ***Civilian Sector Relevance***

Penetrating abdominal wounds often accompany automobile and motorcycle accidents and gunshots. The same technologies used to treat military personnel are applicable to the victims of vehicular and gunshot incidents.

## ***D. SYSTEMS TO DETECT VITAL SIGNS AND REMOTE DETECTION OF LIFE FORMS***

Microneural bionics, microchips designed to translate sensory input and mimic nerve efferent signals, are used to treat patients with lost hearing or vision. Current use in otolaryngology allows hearing in children who are born with hearing deficits. Ophthalmologic uses have been demonstrated in recently blind individuals, allowing light perception. It is not inconceivable that similar technology may not only restore some sensory deficits from injured warfighters, but could be developed to allow one to recognize nonhuman sensory input (infrasound, ultraviolet, and infrared spectrum) or enhance normal sensory perception.

## ***E. EVIDENCE-BASED MEDICINE AS RELATED TO AFFORDABILITY***

Medicine as practiced in 1998 is based on the interpretation by a clinical care giver (e.g., physician) of clinical signs and symptoms through a process of differential diagnosis. The database of information available to the physician is derived from information provided by a patient, experimentation in clinical trials, personal experience, scholarly reading of the literature, continuing medical education, and informational briefings. In these situations, the data available is relatively large and the physician relies in large part on that which can be processed in a period of minutes. The processing of this information is a function of recall ability, access to current information, state of readiness, and vigilance. The degree to which the physician can monitor patient compliance with prescribed medication and therapy varies with the clinical setting, diagnosis, and cost of follow-up.

The availability of new computer-based systems and interfaces with the physician and other care givers can facilitate establishment of a database warehouse and provide a coherent format for taking patients' medical histories. It also offers the ability to track distribution of medication; "ticklers" regarding upcoming visits; and responses to medication, including allergic reactions. The new technologies offer the opportunity to obtain evidence-based information and provide evidence-based management if the number of subjects is sufficiently large. They also provide the basis for developing a data chip that will contain the medical history and deployment history of each individual.

"National Clinical Information System (NCIS)," has been developed in an effort to achieve information acquisition, retrieval, presentation, and management.

One of the outcomes expected with NCIS is the determination of most useful treatment modalities and management of patients. To improve health-care delivery, a system must incorporate new technology and knowledge. Associated with the new information and technology is the need to change the culture and behavior of physicians and health-care providers as well as the behavior of patients. The approach requires a medical component to examine technology effectiveness. A management focus examines treatment tradeoffs and must invest in most effective outcomes.

Care management (evidence-based management), focuses on:

- Component-based care delivery;
- Eliminating inappropriate physician variation (diagnostic testing, pharmaceuticals); and
- Developing and adopting breakthrough methods (e.g., outcome driven, technology enabled).

The new model for health-care delivery should identify the role of the physician, establish a system responsible for patient adherence, and determine outcomes accountability. All these points based on large  $N$  of patients, large number of physicians, geographical distribution, and interaction with Blue Cross/Blue Shield cooperative arrangement. These large  $N$  values allow one to look at statistical outcomes of each treatment paradigm.

### ***Issues Related to Affordability***

One critical point is the rapid change in technologies that will become available to physicians and health-care professionals in the next two decades. The utilization of these new technologies can improve health-care delivery. In those cases where new diagnostic modalities and pharmaceuticals improve treatment outcome, new standards for appropriate medical care in the 21st century will emerge. These technologies may also provide an ever-increasing capability to produce new compounds that affect human behavior and performance. The issue of affordability rises to the surface because the new pharmaceuticals and diagnostic tools are likely to be expensive. Past experiences suggest that what is not affordable at time  $a$  may be at time  $b$ . The factor of affordability in the military community relates to the actual cost of the new item, the benefit achieved by the patient in terms of time away from the task, the compromise in function if treatment is not initiated, and the number of persons affected. These considerations lead to three action items:

- Provide incentives for new technologies so they can be adapted;
- Measure affordability as related to outcome; and
- Real cost effectiveness will increase in biotechnology and informatics because of rapid growth of fields and affordability not necessarily correlated with best business practice.

Many of these items have parallels to the TacMedCS discussed in Section 4, Overview, above.

**LIST OF TECHNOLOGY DATA SHEETS**  
**4.3. MANAGEMENT OF TRAUMA, STRESS AND TREATMENT**

Biomarkers of Toxicant Exposure and Stress.....4-27

Telemedicine .....4-28

Treat Traumatic Injury, Abdominal Bleeding, Burns, and Provide Organ Replacement.....4-29

### DATA SHEET 4.3. BIOMARKERS OF TOXICANT EXPOSURE AND STRESS

<b>Developing Critical Technology Parameter</b>	Identification of exposure biomarkers, effect biomarkers, susceptibility biomarkers that serve as indicators of toxicant or stress thresholds. The biomarkers should have sufficient capability to detect traits and exposure levels that would predispose affected individuals to clinical symptoms. A single biomarker change may indicate a doubling of the risk of that individual to a toxicant or environmental stress; a set of biomarker changes may indicate that an individual's performance is reduced to 20 percent of his or her normal state.
<b>Critical Materials</b>	Compounds that bind or materials that respond to such biomarkers and can be used to transduce such a binding event to an optical, electrical, or auditory output. Non-invasive monitors of physiological responses including heart rate, eye blink, and interbeat interval.
<b>Unique Test, Production, Inspection Equipment</b>	None identified.
<b>Unique Software</b>	Database of biomarkers for toxicants or stress.
<b>Major Commercial Applications</b>	Monitoring fitness for duty in critical work environments (transportation personnel including airline pilots, railroad engineers, and surgeons/anesthesiologists).
<b>Affordability</b>	The technology is anticipated to be of low cost.

#### **BACKGROUND**

Early detection of biological effects on individuals exposed to low-level toxicants can permit initiation of protective actions. This will increase vigilance, readiness, and fitness for duty of affected persons. Biomarkers of exposure and of susceptibility will permit early warning and management of persons.

### DATA SHEET 4.3. TELEMEDICINE

<b>Developing Critical Technology Parameter</b>	Multimedia medical databases, portable virtual reality presentations (visual/auditory/haptic), telepresence surgery, life support for trauma and transport, microsensors and transmitters, sensate liners. The telemedicine visual, auditory, and haptic devices will enable medics to interact in real time with physicians located miles away and perform critical surgical procedures under guidance.
<b>Critical Materials</b>	Telecommunication system with visual, auditory, and haptic interfaces on medical evacuation platforms, on-line satellite communications, and computer technologies that enhance and manipulate images.
<b>Unique Test, Production, Inspection Equipment</b>	None identified.
<b>Unique Software</b>	Visible Human Project of NLM and similar databases . Software packages that interface MRI, CT scan, PET SPECT, and X-ray data sets. Software that encodes auditory, visual, and haptic information; uploads to and downloads from satellites; and reconstructs such information on-line.
<b>Major Commercial Applications</b>	Rural health-care delivery in the United States and abroad. Medical and nursing education.
<b>Affordability</b>	The databases are currently on line. The identification of trained medical personnel may be costly. The system of evidence-based management in health care, may serve as one model.

#### **BACKGROUND**

The treatment of and recovery from traumatic body injury is dependent upon the time interval between injury and health care. Care delivered in the first 30 minutes following injury markedly improves recovery because the effects of blood loss and subsequent shock may be mitigated.

**DATA SHEET 4.3. TREAT TRAUMATIC INJURY, ABDOMINAL BLEEDING,  
BURNS, AND PROVIDE ORGAN REPLACEMENT**

<b>Developing Critical Technology Parameter</b>	Device for rapid detection of vital signs, tissue viability assessor, growth factors, organ replacement from culture, neural regeneration.
<b>Critical Materials</b>	Radio-frequency radiation system that detects pulse/respiration. High-frequency ventilation system. Hyperbaric oxygen supply system. Growth factors including nerve growth factor, fibroblast growth factor, interleukins, insulin-like growth factor, and pluripotent stem cells.
<b>Unique Test, Production, Inspection Equipment</b>	Equipment to validate purity of growth factors and differentiation of stem cells.
<b>Unique Software</b>	None identified.
<b>Major Commercial Applications</b>	Emergency medical trauma care.
<b>Affordability</b>	Current care for patients with neurological damage is very costly. The technologies described here are modest in comparison.

***BACKGROUND***

The treatment of and recovery from traumatic body injury is dependent upon the time interval between injury and health care. Care delivered in the first 30 minutes following injury markedly improves recovery because the effects of blood loss and subsequent shock may be mitigated.

## SECTION 4.4—TACTICAL MEDICAL COMMAND AND CONTROL

### *Highlights*

- TacMedCS manages care from field through treatment.
- Medical care, medical informatics, and medical communication are integrated.

### **OVERVIEW**

Medical command and control is the integration of disparate technologies including electronics, communications, information systems, and trauma care. It is evolving into a system providing both specific medical information as well as procedures that have utility across all services. The consequences of the advances in this technology have profound dual-use applications. These include emergency services, occupational medicine, rural health-care delivery, and disaster response. These broad applications will make the technologies more affordable.

Associated with these shifts are changes in the medical response strategies to locate and treat wounded, provide accurate diagnosis/triage, and evacuate to an optimum treatment facility. The new technologies available to the corpsman will enable more accurate information about the wounded soldier, a more complete selection of options to treat the patient, rapid communication with forward medical units to prepare them for receiving the patient, evacuation options, and additional procedures to stabilize the patient. This paradigm requires three elements of information management: accurate information, real-time information, and data integration.

The technologies available to the corpsman and other health-care providers in the combat arena are described in subsections 4.1, 4.2, and 4.3. The information technologies supporting the medical technologies and assets are discussed below.

### ***Tactical Medical Coordination***

A Tactical Medical Coordination System (TacMedCS) has been developed. TacMedCS is a multicomponent system for efficient management of patients and their associated clinical/identification information from the field through evacuation to definitive treatment.

TacMedCS has three components:

- Patient ID/clinical data chip (component 1);
- Hand-carried data input/transmission device (component 2); and
- Operations area command and control suite (component 3).

*Component 1 (EPROM chip)* contains identification and pertinent clinical history; data transmitted when interrogated by a Component 2 device; and stores limited treatment information. Component 1 automatically measures and records vital signs, past/present medical history including biomarkers and other clinically important information.

*Component 2 (handheld reader/transmitter/recorder)* interrogates the EPROM chip using an RF signal; transmits GPS-derived location and clinical data to the command and control suite; stores data internally for later download; writes data back to the patient EPROM chip; and has the potential to utilize different formats for storing information (barcode). A future component 2 is likely to contain capability for transmitting real-time images, auditory displays, and matrixed information to component 3.

*Component 3 (clinical command and control center)* provides command and control real-time data coordination and management, along with patient tracking and status monitoring (includes visual display). Component 3 is staffed with high-level medical experts and is remote from the combat situation. Its function is to advise the corpsman

regarding the most appropriate short-term treatment, recommend procedures for transfer of the patient, prepare the receiving facility for the arrival of the patient, and initiate care.

The TacMedCS is patterned after the Tactical C4I and overnight delivery services currently available nationwide. The system utilizes adaptable, off-the-shelf technology in a unique combination. The new system provides real-time data integration and coordination, patient identification, and immediate information concerning clinical status, evacuation, and treatment choices. It is adaptable and conforms to contemporary C4I requirements.

Leading-edge tactical medical command and control is a newly developing area of expertise. It relies on innovations in information gathering and processing, structured medical hierarchy, and integrated communication systems. The early stage of development has provided many opportunities for innovation.

**LIST OF TECHNOLOGY DATA SHEETS**  
**4.4. TACTICAL MEDICAL COMMAND AND CONTROL**

Medical Informatics .....4-33

## DATA SHEET 4.4. MEDICAL INFORMATICS

<b>Developing Critical Technology Parameter</b>	A tactical medical coordination system comprising a patient ID/clinical data chip, a hand-carried data input/transmission device, and an operations area command and control suite.
<b>Critical Materials</b>	EPROM chip with ID and pertinent medical history; a component that interrogates the EPROM chip with an RF signal, transmits GPS location and clinical data to command suite, and stores data as barcode; a component to coordinate/manage data in real time, track the patient, and monitor status.
<b>Unique Test, Production, Inspection Equipment</b>	Validate EPROM chip and data storage system for reliability.
<b>Unique Software</b>	None identified.
<b>Major Commercial Applications</b>	Control of astronaut data systems. Rural health-care delivery. Home care delivery to persons with chronic illness requiring daily or more frequent monitoring of status (i.e., renal dialysis).
<b>Affordability</b>	The system is relatively low cost in the current configuration.