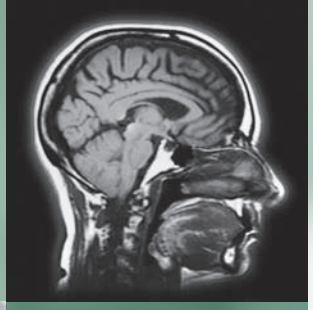
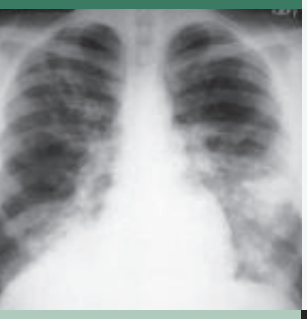
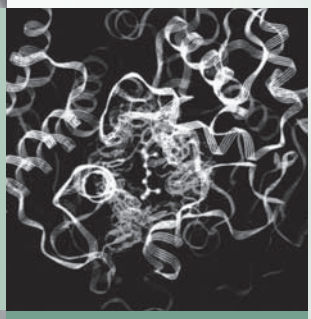


NIH Strategic Plan and Research Agenda for Medical Countermeasures Against Chemical Threats





U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

NIH Strategic Plan and Research Agenda for Medical Countermeasures Against Chemical Threats

Coordinated by the Office of Biodefense Research NIAID

April 2007

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

National Institute of Allergy and Infectious Diseases

FOREWORD

In 2003, the United States Department of Health and Human Services (HHS) asked the National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health (NIH) to ascertain the availability of medical products that could be used in a chemical terrorist attack in the United States and to develop a comprehensive research plan for the development of new medical countermeasures, that would be useful during and following such an event. For many years, the Department of Defense (DoD) has invested in a research program to develop medical and non-medical chemical defenses for the military forces. The DoD research efforts addressed the classical chemical warfare threats such as sarin, soman, VX, and mustard gas, as well as novel chemical threats to military forces operating throughout the world. With the increasing threat of terrorism, the development of medical products for a civilian chemical attack has become a high priority, but civilian-focused research is beyond the mission of the DoD. Such research more appropriately resides within HHS, which has not had a program to develop and stockpile medical products for chemical threats until recently.

This NIH Strategic Plan and Research Agenda is the culmination of NIH planning efforts to address chemical threats with NIAID serving as the main coordinating and implementation biodefense research institute. This plan complements the biodefense research strategies already developed by NIAID against biological, radiological and nuclear threats. It also takes into account the ongoing efforts of other federal agencies and departments and is consistent with current chemical intelligence threat assessments.

The success of the program outlined in this plan will depend on cooperative efforts and partnerships with other federal agencies, academia and industry, and the integration of cutting-edge research with the latest technological advances in science and medicine. Research institutes across the NIH, particularly the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Environmental Health Sciences (NIEHS), contributed to the development of the Strategic Plan and Research Agenda and will be directly involved in its implementation. Other NIH institutes will also be engaged, as appropriate. This research program was initiated through a special Congressional supplement to the NIH budget beginning in fiscal year 2006, with the full support of HHS.

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INTRODUCTION

The events of September and October of 2001 exposed the vulnerability of the United States to acts of terrorism that employ unconventional weapons and tactics. Chemical warfare agents and highly toxic industrial chemicals could be employed in an attack on a civilian population. Chemicals have long attracted the attention of terrorists, for such toxic materials represent simple weapons that could have devastating effects on the general public. Indeed in 1995, the Japanese terrorist cult Aum Shinrikyo used the nerve gas sarin, that they produced, in an attack in the Tokyo subway. Twelve civilians were killed and over 5,000 sickened.

Several threat scenarios involving chemicals include the deliberate release of illegally obtained or manufactured chemical warfare agents, the release of purchased or stolen industrial chemicals, and attacks on chemical manufacturing plants, storage sites, or transport vehicles. Moreover, the potential also exists for the malicious contamination of food or water sources with chemicals.

Several industrial accidents that caused many casualties highlight the potential impact of a terrorist attack on chemical storage sites or transport vehicles. In 1984, a methyl isocyanate leak at a Union Carbide plant in Bhopal, India killed as many as 5,000 people and injured more than 14,000. In the United States since 2002, three major chlorine gas leaks-one due to a ruptured hose, another due to the rupture of a tanker in a train accident, and the third due to an industrial fire-and caused several deaths. Recent events in Iraq with the use of chlorine gas by Al Queda have demonstrated the attractiveness of chemicals as weapons of mass destruction. Explosions in a chemical plant can also disseminate toxic materials into the atmosphere and surrounding grounds and represent an environmental health emergency.

The number and variety of different chemicals that pose a health risk to the civilian population is daunting. Terrorists could use any of the traditional chemical warfare agents, ranging from nerve gas and cyanide to pulmonary and vesicating (blister) agents (see Table). A variety of toxic industrial chemicals could be released in a terrorist attack or by accident and these chemicals could also undergo dangerous reactions following release. The Occupational Safety and Health Administration (OSHA) has identified almost 100 toxic industrial chemicals (TICs) and the Environmental Protection Agency (EPA) lists over 600 chemicals in its Toxic Release Inventory. Animal, plant, and bacterial toxins that can be synthesized are also potential chemical threats.

Previous Research on Medical Countermeasures against Chemical Threats

The United States Army Medical Research Institute of Chemical Defense (USAMRICD) has a long history of developing medical countermeasures against chemical warfare agents. However, there are significant differences between military and civilian scenarios. One key difference is the demographics of the at-risk population. The typical warfighter is a healthy young to middle-aged adult, whereas the civilian population includes a wider spectrum from the very young to the elderly. Many civilians may have pre-existing health problems, possibly increasing their risk of injury during a chemical incident. Such groups may require modified treatment courses, such as reduced dosage of standard therapies.

A chemical terrorist attack or accident may involve a larger range of dangerous compounds. As a result, the civilian-focused effort must place a high priority on rapid screening tests and encompass a broader range of chemicals. Ideally, medical interventions should be effective against more than one agent but this is not always possible. Also, these compounds may require different formulations depending on how they would be used. For example, inhalation therapies that are inappropriate for war fighters wearing

protective equipment may, nevertheless, be desirable for civilian casualties.

Until recently, the National Institutes of Health (NIH) has funded research on some of the symptoms associated with chemical exposures. These include studies on seizures, memory deficits and pulmonary edema due to other causes. The NIH has also supported research on environmental toxicology, but no research program has focused exclusively on the biodefense civilian threat posed by chemicals. A Blue Ribbon Panel and several targeted workshops on specific chemical issues assisted the NIH in the development of the medical research strategy and agenda described in this document (Appendix 1-3). This new research thrust on the development of medical countermeasures that could be used in mass casualty situations represent a new and important priority for the NIH and HHS and its commitment to protect and maintain the health of the nation.

RESEARCH STRATEGY

General Principles

This document presents an NIH strategic research plan and research agenda to improve the Nation's ability to diagnose, prevent, and treat injuries resulting from chemical attacks or accidents. The guiding principles are:

- Treatments must be appropriate for a diverse civilian population
- Treatment strategies must take into account how a toxic chemical enters the body and the time window for possible medical intervention (see table)
- Treatments must be formulated so that they can be administered easily and rapidly in a mass casualty situation
- Rapid diagnostic tests must be reliable and easily used in a mass casualty situation
- Immediate as well as long-term effects of exposure to chemicals must be understood
- Drugs should be chemically and physically stable so that they are amenable to pre-positioning and stockpiling
- Pre-treatments for first responders are desirable especially when decontamination is not possible

Overall Short-Term Goals

The NIH has identified important short-term goals based on current knowledge of chemical threats and existing medical products. These goals include evaluating promising drugs and interventions and expanding research to accelerate product development:

- Identify FDA-approved medical products with potential applications for the treatment and/or prevention of chemically-induced injury in civilian populations
- Conduct appropriate studies to document the efficacy and safety of promising medical products for use as chemical countermeasures in order to obtain FDA approval
- Develop the capacity to conduct preclinical studies with Good Laboratory Practices (GLP) and Good Manufacturing Practices (GMP) in order to meet the FDA approval requirements for an Investigational New Drug (IND) application
- Expand the current NIH research infrastructure to support clinical trials on promising medical chemical countermeasures
- Encourage pharmaceutical and biotechnology industries to engage in the development of medical products pertinent to the NIH research agenda
- Identify and validate appropriate *in vitro* and animal models for preclinical drug testing
- Establish a research network with focused projects to conduct basic, translational, and clinical research
- Develop and support collaborative research facilities that will foster inter-governmental, industrial, and academic partnerships, in full compliance with applicable chemical safety and security regulations

Overall Long-Term Goals

The NIH has also identified important long-term goals based on gaps in fundamental scientific knowledge and specific needs for medical countermeasures that are currently non-existent or at early stages of development:

- Determine how chemical agents are absorbed, distributed, metabolized, and eliminated by the human body as a means of identifying targets for intervention
- Identify the mechanisms of action of specific chemical agents and their sites of injury, down to the molecular level
- Identify effective routes of administration for promising drugs
- Identify common physiological responses to chemical exposure, such as oxidative stress and immune processes
- Investigate the healing mechanisms following chemical injury and identify novel ways to accelerate recovery processes
- Develop and validate new screening models for rapid identification of promising therapeutic and prophylactic drug candidates
- Develop rapid screening and assessment tools to improve the triage process during mass casualty events and to differentiate levels of exposure
- Develop medical prophylactic measures appropriate for use by first responders or other individuals who must operate in a chemically contaminated environment
- Identify biological markers that indicate exposure to specific chemical agents and level of exposure
- Determine the long-term chronic health effects resulting from exposure to specific toxic chemicals and establish databases for clinical, epidemiological, and laboratory information that will contribute to this understanding

RESEARCH AGENDA

I. Chemicals Affecting the Nervous System

A variety of chemicals are known to affect the nervous system. Some directly target neural signaling pathways. These include the classic nerve agents (e.g., sarin, soman, tabun and VX), organophosphate pesticides, and some animal toxins (e.g., botulinum toxin). Chemicals can also affect the nervous system indirectly. For example, metabolic poisons (e.g., cyanide) disrupt cellular respiration, which ultimately prevents the brain from getting sufficient oxygen and energy. Some vesicating agents (e.g., sulfur mustard) appear to have neurological effects as well, although the specific mechanism is poorly understood.

Neurological symptoms depend on the type of chemical, the level of exposure, and the time elapsed following exposure. Exposure to nerve agents, metabolic poisons, or high levels of sulfur mustard can trigger seizures and loss of consciousness. Other acute effects of nerve agent poisoning include muscle paralysis, cardiorespiratory depression, massive secretion from mucous membranes, eye irritation, and blurry or dim vision. Other acute effects of exposure to high doses of sulfur mustard include behavioral effects and cognitive difficulties. Nerve agents and metabolic poisons also appear to have serious long-term neurological effects, including neurodegeneration, but these have not been studied extensively.

The physical states of these chemicals are an important determinant of the countermeasure requirements. While some chemicals that affect the nervous system exist primarily in the form of a vapor (e.g., hydrogen cyanide), others are oily liquids that are very difficult to remove from the environment and extremely toxic even at miniscule levels (e.g., VX). For these persistent agents, it would be ideal to have pretreatments that can be administered to personnel who must enter contaminated sites in advance of possible exposure, with long-lasting protective effects.

Current medical countermeasures

Existing medical countermeasures target the interactions between nerve agent molecules and proteins involved in neural signaling. Neurons can communicate with each other or stimulate muscle cells by releasing a chemical called acetylcholine. Nerve agents and organophosphate pesticides bind and inhibit protein called acetylcholinesterase (AChE), which breaks down acetylcholine after a neuron has been stimulated. The acute symptoms of nerve agent and organophosphate exposure are due to excess acetylcholine continuing to stimulate nerve endings in the brain, muscles and secretory glands. Although this route of nerve excitation is considered to be the major focus for drug intervention, other neurotransmission pathways in the body that be affected by toxic chemicals may need to be separately assessed for potential intervention.

Pretreatment

The U.S. military adopted pyridostigmine bromide (PB), an FDA-approved treatment for myasthenia gravis, for the pretreatment of soman poisoning. PB competes with nerve agent by reversibly attaching to AChE prior to nerve agent exposure. PB has limited usefulness in a post-exposure situation and is only approved for use in military populations against only one of several of nerve agents that could be used in an attack.

Post-exposure treatments

Standard treatment of nerve agent and organophosphate poisoning includes a combination of atropine sulfate, the oxime 2-PAM, and benzodiazepine anticonvulsants, such as diazepam. Atropine blocks acetylcholine receptors, drying secretions and reducing smooth muscle contraction. Oximes free AChE from the chemical agent and have their most

marked effect on skeletal muscle strength. The only oxime approved for use in the U.S. against nerve agents is pralidoxime chloride (2-PAM). This oxime is also indicated as an antidote for organophosphate insecticide poisoning and to control overdosage of anticholinesterase drugs in the treatment of myasthenia gravis. The Strategic National Stockpile CHEMPACKs, which have been distributed around the U.S. for deployment in case of a chemical attack or accident, contain military "Mark I" adult autoinjectors with atropine and 2-PAM, diazepam autoinjectors, pediatric atropine autoinjectors, and multi-use vials of 2-PAM and diazepam.

These current treatments for nerve agent or organophosphate exposure have significant disadvantages. Multiple doses of atropine and 2-PAM may be necessary in order to be effective. Atropine does not relieve nerve agent effects on skeletal muscles. Oximes are ineffective once the AChE-nerve agent complex has undergone "aging," a chemical change that permanently inactivates AChE. Aging can happen within minutes of exposure to some of the nerve agents, such as soman. While diazepam is effective treatment for nerve agent seizures in about the first 40 minutes after exposure, it is less useful later. Benzodiazepine anticonvulsants also carry risks of excessive sedation, and respiratory depression. No treatments are currently available to prevent or reduce neurodegeneration resulting from prolonged seizures, anoxia, or the direct effects of chemical agents.

Diagnosis

Diagnosis following an acute exposure is generally based on clinical observations of specific symptoms. Environmental sensors may provide valuable information on probable chemical exposure. One of the greatest challenges in diagnosis is determining whether an individual exposed to nerve agent is experiencing chemically induced seizure activity in the absence of visible convulsions, since the chemicals that trigger seizures may also cause unconsciousness or paralysis. Sustained seizure activity that is uncontrolled can result in permanent brain injury and death. The standard test for seizure activity involves recording electrical brain activity from the scalp using electroencephalography (EEG). Such devices are not portable and have limited practical value in evaluating ill patients in a mass casualty situation.

Potential Countermeasures

Alternative oximes, such as TMB4, Toxogonin, and HI-6, are available in other parts of the world for the treatment of nerve agent casualties. Some of these have been or are in the process of being evaluated for use by the U.S. military, but none have been evaluated for possible use in U.S. civilian populations. Several promising new oxime candidates also have been identified and will require further development.

Proteins like butyrlcholinesterase (BChE), which have a similar structure to AChE represent another potential therapeutic approach. These can act as "bioscavengers," sequestering nerve agent molecules in the bloodstream. Plasma-derived human BChE shows some promise as a prophylactic countermeasures for military personnel, but it remains uncertain whether this product can be administered efficiently in a large enough volume to be fully effective. A few studies are underway and more are needed to determine if this, and similar bioscavenger-like proteins, could be effective for civilians after exposure to the nerve agent has already occurred. Alternative forms of BChE have been produced through genetic engineering. They appear to be effective as pre-treatments in animal models, and it may be possible to develop these into treatments for humans.

Several promising anticonvulsant drugs for the treatment of nerve agent poisoning are on the horizon. New anticonvulsant drugs that have been or are being developed for the treatment of epilepsy in pediatric and adult populations may be applicable to chemically induced injury. Alternate or more expeditious delivery routes for

anticonvulsant drugs already approved to treat seizures may also be desirable in a mass casualty scenario.

The benzodiazepine midazolam, currently FDA-approved as an intravenous sedative and anesthetic, may also be very effective in the treatment of seizures. Midazolam is being investigated to replace diazepam as the immediate anticonvulsant treatment for nerve agent-induced seizures FDA approval for the intramuscular use of midazolam to treat nerve agent-induced seizures will require a clinical trial for its effectiveness in seizure patients. Other benzodiazepines and other classes of drugs that antagonize several neuronal excitation pathways, such as the anti-glutamatergic drugs and neurosteroids, are also potential candidates to treat chemically induced seizures. These will also require preclinical and/or clinical studies.

There are also promising research avenues to address chemically induced degradation of the nervous system, or neurodegeneration. Recent studies have shown that the immunosuppressant drug cyclosporine dramatically reduced organophosphate-induced seizures and brain damage and preserved memory and learning ability in rodents. Clinical trials are planned or underway with several drugs that appear to slow or stop the process of neurodegeneration due to stroke, traumatic brain injury, and chronic nervous system diseases. Some of these drugs may be candidates to prevent chemically induced neurodegeneration.

Short-Term Goals

- Initiate appropriate clinical studies to determine the safety and efficacy of promising anticonvulsants, such as midazolam, that would lead to FDA licensure and explore use of such products in different populations
- Establish a drug development program that includes preclinical drug screening and clinical studies on potential anticonvulsant and neuroprotective therapies
- Identify and validate appropriate models for preclinical drug testing, including *in vitro* systems and animal models, to address high and low levels of exposure to nerve agents
- Expand the knowledge base on how different nerve agents are absorbed, distributed, metabolized, and eliminated by the body and on the interaction of agents with current antidotes
- Determine optimal drug formulations of the most promising medical countermeasures and safe and effective route(s) of administration
- Explore the practical use of enzyme bioscavengers that could be used to treat victims after they have been exposed to nerve agents
- Establish a collaborative research effort with DoD to develop medical countermeasures against nerve agents of greatest concern, capitalizing on current and future DoD research investments
- Develop a comprehensive medical research program that involves academia and industry in the development of specific medical countermeasures directed against nerve agents

Long-Term Goals

- Expand knowledge of the mechanisms by which chemical agents affect the nervous system and its neuroexcitatory pathways
- Expand knowledge of the physiological responses to toxic chemicals, including oxidative stress at the cellular and

molecular level and the inflammatory changes and other immune responses following chemical exposure

- Identify mechanisms and types of injury and recovery associated with specific nerve agents and the anti-seizure responses to anticonvulsants
- Identify any differences in population susceptibility to nerve agents
- Identify acute and chronic neurological effects of exposure to high and low levels of chemical agents and strategies for intervention
- Identify new rapid screening or diagnostic tools that can be used in the evaluation of individuals during and following suspected chemical exposure
- Identify specific biomarkers of injury to help identify the specific chemicals responsible for observed neurological symptoms
- Support technologies used in portable assessment devices that could prove useful in the initial evaluation and treatment of chemically-induced seizures during a mass casualty situation
- Evaluate different safe and effective routes of administration of FDA-approved anticonvulsants and other drugs
- Develop new enzyme reactivators that are broadly effective against groups of nerve agents, including those agents such as soman that makes the body refractory to treatment over time
- Develop protein catalytic bioscavengers that can bind and break down nerve agents into inert substances
- Determine the applicability and safety of specific medical countermeasures to different subpopulations in the U.S., to include those with pre-existing illnesses or taking other medications
- Evaluate approaches to eliminate and/or deactivate nerve agents from body surfaces and open wounds to prevent further absorption, exposure, and injury
- Develop appropriate animal models of acute and chronic chemically induced neurological injury that parallel the human experience
- Establish databases of clinical, epidemiological, and laboratory information that will contribute to the understanding of the mechanisms of nerve agent-induced injury and the acute and chronic effects of high and low level exposure

II. Chemicals Affecting the Respiratory Tract

Many toxic chemicals can damage the respiratory airways, with potentially life-threatening effects. Ammonia, various alkalis (e.g., bleach and sodium hydroxide), hydrochloric and sulfuric acid, vesicants (e.g., sulfur mustard) and other corrosive agents affect the upper airways, the portion of the respiratory tract that begins at the mouth and nose and ends at the larynx (voice box). Inhalation of these chemicals can cause acute inflammation, painful ulcerations, increased secretions, and difficulties in breathing and swallowing. Secondary bacterial infections may further exacerbate the initial injury. Damage to the upper airways can lead to respiratory failure and death. Exposure can also lead to long-term health problems. For example, chronic respiratory problems, such as scarring and narrowing of the trachea, have been observed in Iranians exposed to sulfur mustard during the Iran-Iraq War of the 1980s. Vesicating chemicals will be discussed in

more detail in the later section on injuries to the skin, eyes and mucous membranes.

Some industrial chemicals, including ammonia, chlorine, phosgene and perfluoroisobutylene (PFIB), can cause lower respiratory tract injuries, particularly life-threatening pulmonary edema. Pulmonary edema—the leakage of fluid into the lungs—prevents oxygen delivery to the blood, ultimately preventing oxygen from reaching the brain, kidneys and other organs. Symptoms may be immediate or delayed; chlorine causes immediate airway irritation and pain, whereas phosgene exposure may not be evident for 24 to 48 hours (see Table). People who survive a single, acute exposure generally show little or no long-term health problems, although some may eventually develop asthma or chronic bronchitis. Individuals at greatest risk are those with pre-existing heart or lung disease.

Current Countermeasures

Pretreatment and post-exposure treatment

Specific pre-treatment drugs to prevent chemical-induced lung injuries are not available. Analgesic medications, oxygen, humidification, and ventilator support currently constitute standard therapy. Hemorrhaging, signifying substantial damage to the lining of the airways and lungs, can occur with exposure to highly corrosive chemicals and may require additional medical interventions. Treatment of injuries to the lower respiratory tract is also supportive and usually includes administration of oxygen, the use of mechanical ventilation to include positive airway pressure, and bronchodilators to treat bronchospasms. Drugs that reduce the inflammatory response, promote healing of tissues, and prevent the onset of pulmonary edema or secondary inflammation may be used following severe injury to prevent chronic scarring and airway narrowing.

Diagnosis

Current diagnostic capabilities are limited. Exposure to chlorine, phosgene or any of the major alkalis is determined based on clinical signs and symptoms. No screening tests are available to identify individuals exposed to low levels of chemicals.

Potential Countermeasures

While current treatments can be administered in a controlled hospital setting, many are ill-suited for a mass casualty situation. Inexpensive positive-pressure devices that can be easily used in a mass casualty situation and drugs to prevent inflammation and pulmonary edema are needed. Several drugs that have been approved by the FDA for other indications hold promise for treating chemically induced pulmonary edema. These include β2-agonists, dopamine, insulin, allopurinol, and non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen. Ibuprofen is particularly appealing because it has an established safety record and can be easily administered as an initial intervention. Studies have shown that ibuprofen improves survival and reduces lung fluid levels in mice exposed to phosgene. Inhaled and systemic forms of β2-agonists used in the treatment of asthma and other commonly used medications, such as insulin, dopamine and allopurinol, have also been effective in reducing pulmonary edema in animal models but require further study.

Other promising drugs are in earlier stages of development. These act at various stages in the complex molecular pathways underlying pulmonary edema. Some of these potential drugs target the inflammatory response or the specific site(s) of injury. Other potential drugs modulate the activity of ion channels that control fluid transport across lung membranes or target surfactant, a substance that lines the air sacs in the lungs and prevents them from collapsing. Mechanistic information based on toxicology, biochemistry, and physiology may be instrumental in determining new targets for therapy.

Mechanistic studies may also aid in the development of new diagnostic approaches. Some chemicals generate metabolic byproducts that could be used for diagnosis, but detection of these byproducts may not be possible until many hours after initial exposure. Additional research needs to be directed at developing sensitive and specific tests to identify individuals who have been exposed to varying levels of chemicals toxic to the respiratory tract.

Short-Term Goals

- Identify and validate appropriate *in vitro* systems and animal models for preclinical testing of drugs to treat chemically induced injury to the upper and lower respiratory tract
- Identify products approved by the FDA for other indications that have potential for the treatment and/or prevention of chemically induced pulmonary edema
- Conduct appropriate studies to document safety and efficacy of commonly used anti-inflammatory drugs following acute exposure to chemicals such as chlorine and phosgene
- Assess effectiveness of current medical interventions for lung injury, as they apply to the treatment of specific chemically induced pulmonary edema
- Develop collaborations between academia, government, non profit organizations, clinical research networks and multi-research centers that are specifically focused on pulmonary edema-inducing chemical agents
- Develop a database/registry of individuals exposed to high quantities of toxic chemicals to the respiratory tract

Long-Term Goals

- Determine specific mechanisms and sites of injury to the respiratory tract, down to the molecular level, for the major chemical threat agents
- Identify the healing processes and immune responses in the respiratory tract following chemically induced injury and identify windows of opportunity for intervention
- Identify new drugs and therapeutic regimens using appropriate animal models that simulate lung injury in humans
- Identify chronic health effects associated with low and high doses of inhaled toxic chemicals and methods to prevent these effects
- Develop diagnostic tools and biological markers associated with acute lung injury
- Identify new diagnostic technologies to assess pulmonary function, lung inflammation and lung injury, non-invasively and continuously, using emerging technologies
- Identify risk factors associated with chronic effects of lung injury and develop strategies to prevent development of such chronic changes
- Encourage the development of a more portable state-of-art positive-pressure ventilatory device to be used in patients with acute respiratory distress during mass casualty events

III. Chemicals Affecting the Skin, Eyes, and Mucous Membranes

Vesicating (blister) agents, such as sulfur mustard, nitrogen mustard, lewisite, and caustic industrial chemicals can cause severe blistering and burns to the eyes, mucous membranes, skin, and upper airways, as well as chronic eye inflammation and blindness. The eyes are the organs most sensitive to these chemicals. Vesicants may also affect other parts of the body, including the respiratory tract, immune system, and bone marrow. Sulfur mustard can cause tissue damage within minutes of exposure. Physical injury from other vesicants agents may not be evident for several hours and may result in delayed recognition of exposure (see table). In such situations, the exposed individual may put others at risk of secondary contamination.

Current Countermeasures

Pretreatment

Sulfur mustard is an oily liquid and is considered a "persistent" chemical agent, i.e., it does not evaporate quickly and remains active for an extended time. Clothing, skin and, hair may remain contaminated with sulfur mustard for hours, presenting a challenge to health care providers. The military and first responders rely heavily on individual physical protection (e.g. protective masks and suits) to prevent exposure to vesicants. No medical pretreatment drugs are yet available.

Post-exposure treatment

Current treatment of vesicant injuries is largely symptomatic and supportive. Eye injuries require the use of special eye drops, antibiotics and other drugs to prevent secondary infection and steroids to limit the inflammatory response and speed the healing process. Skin wounds, especially when severe with blister formation, require specific medical attention to reduce pain, prevent infection and reduce inflammation. Debridement (removal) of a layer of the injured skin may be necessary to speed the secondary healing process.

British-Anti-Lewisite (BAL, dimercaprol) is a specific antidote for the chemical agent Lewisite and is also used for the treatment of heavy metal poisoning. BAL skin and eye ointments were developed for the military and have been shown to decrease the severity of skin and eye lesions when quickly applied.

Diagnosis

At this time, diagnosis of vesicant injury is based on clinical signs and symptoms and the detection of specific agents in the environment. There are no FDA-approved clinical laboratory tests for sulfur mustard in blood or tissue. However, compounds such as thiodiglycol (TDG) are produced in the body after exposure to sulfur mustard and can be detected in blood, urine and tissue. These compounds can be analyzed in a research setting and require the use of complex laboratory equipment such as gas chromatographic mass spectrophotometers.

Potential Countermeasures

BAL may be useful in the topical treatment of other injuries from vesicants besides Lewisite. Because of reported toxicities associated with BAL, though, this compound has not been considered to be a useful prophylactic drug. Other therapeutic compounds are needed that can prevent/reduce the redness and deep tissue damage (blisters) in a short period of time. Also needed are improved skin protectants, reactive skin protectants that can neutralize the agent, new skin and eye therapies, and improved healing techniques.

Short-Term Goals

- Compare medical countermeasures used by the DoD for the treatment

of vesicating injuries for their use in civilian populations during mass casualty situations

- Evaluate and monitor promising ophthalmic drugs developed in the DoD program and assess the applicability for civilian populations and first responders
- Identify FDA-approved skin protectants against chemical agents for potential use in civilian populations
- Identify and validate appropriate *in vitro* systems and animal models for preclinical drug testing to address caustic agents and vesicants

Long-Term Goals

- Develop novel therapeutic strategies, including reactive therapeutic compounds, to prevent blister formation and inflammatory effects in skin and eyes
- Evaluate the effectiveness of new immuunotherapeutic compounds and their applicability in the treatment of acid/alkali and mustard injuries
- Identify the specific mechanisms of action of specific chemical agents and their sites of injury to the skin, eyes and mucous membranes, down to the molecular level
- Investigate the healing mechanisms following chemical injury and identify novel ways of accelerating the recovery process
- Consider the mechanisms of action of vesicants on tissues, organs and the hematopoetic system for the development of therapeutic interventions
- Evaluate novel therapeutic strategies for acid and alkali injuries
- Identify biological markers consistent with types of chemical agents and level of exposure to such agents
- Evaluate "reactive" or "catalytic" skin protectants for use in civilian populations, such as first responders who must operate in a contaminated environment
- Evaluate decontamination approaches for patients with open wound injuries and identify novel opportunities for medical intervention
- Develop practical therapies that can be easily and safely administered to decontaminate the skin during mass causality situations

IV. Chemicals Affecting Cellular Respiration

Metabolic poisons, such as hydrogen cyanide and cyanogen chloride, inhibit cellular respiration, whereby oxygen is extracted from the blood at the cellular level and sugar molecules are transformed into energy for cells. All systems of the body are ultimately affected. The cardiovascular and central nervous systems are most strongly affected, due to their high demands for oxygen and energy and limited ability to use alternative pathways for energy production. Exposure to metabolic poisons can quickly cause seizures, respiratory failure, cardiac arrest and death. Long-term effects are poorly understood and may include gradual neurodegeneration.

Metabolic poisons can be inhaled or ingested. Exposure to high concentrations of hydrogen cyanide gas (HCN) can cause death within minutes. This narrow therapeutic window presents a formidable challenge for treatment but emphasizes the need for immediate medical intervention. Inhalation of lower concentrations of cyanide vapor or cyanide salt ingestion may result in a slower development of symptoms.

Current Countermeasures

Pretreatment and post-exposure treatment

No pre-treatment for cyanide poisoning is available and may not be practical. Since 1933, a Cyanide Antidote Kit has been marketed for use in the U.S., but, as a kit, it has never received formal regulatory approval by FDA. The Cyanide Antidote Kit includes crushable ampoules of amyl nitrite, for inhalation, and sodium nitrite and sodium thiosulfate, which are administered intravenously. The nitrites bind with hemoglobin in the blood to produce methemoglobin molecules. The methemoglobin then binds with cyanide to produce a much less toxic cyanomethemoglobin, which is eventually eliminated from the body. Sodium thiosulfate, often referred to as a sulfur donor drug, converts cyanide into non-toxic thiocyanate, which is then excreted by the kidneys.

The Cyanide Antidote Kit can be very effective, but it carries the risk of toxic side effects. High levels of methemoglobin can be lethal. Dosing is especially challenging for pediatric casualties. Individuals with pre-existing glucose 6-phosphate deficiency (G6PD deficiency) have a risk of red cell hemolysis if given sodium thiosulfate. Individuals with renal deficiency, or anemia could also suffer toxicity from the treatment. Concern has been raised over the ability to predictably quantify the amount of amyl nitrite that would be absorbed through inhalation.

Recently the U.S. Food and Drug Administration (FDA) approved Cyanokit (hydroxocobalamin for injection) for treatment of cyanide poisoning. It has not yet been determined how effective this new countermeasure would be in a mass casualty situation.

Administration of 10% (hyperbaric) oxygen is a major component in the treatment of cyanide poisoning, typically used even before the administration of any cyanide antidotes. However, the value of hyperbaric oxygen has not been determined, especially with products that form methemoglobin.

Diagnosis

Because the cyanide antidote kits can have toxic side effects, accurate diagnosis of cyanide poisoning is important. Currently, diagnosis is based on clinical evaluation, but the presenting symptoms may be confused with exposure to other agents including nerve agents, botulinum toxin, hydrogen sulfide, or carbon monoxide. No rapid diagnostic tests are available for any cyanide-containing compounds.

Potential Countermeasures

Cobinamide, one of the compounds in the biosynthesis pathway of hydroxocobalamin, is another promising drug that warrants further investigation. Cyanohydrin-forming compounds (e.g., alpha-ketoglutarate and pyruvate) and vasodilatory drugs that act similar to nitrite compounds are potential new cyanide antidotes, as are drugs that act at the cellular level, such as synthetic S crystallized rhodanese (an enzyme that promotes the conversion of cyanide to non-toxic thiocyanate). Sulfur-containing medications may also have potential benefits in the treatment of cyanide poisoning, especially those that remain in circulation for longer periods of time than sodium thiosulfate. Drugs that form methemoglobin may have an advantage, but there are significant health risks associated with high levels of methemoglobin.

Several sophisticated cyanide detection methodologies have been developed but are neither rapid nor widely available.

Short-Term Goals

- Improve understanding of the mechanisms of injury, down to the cellular level, from cyanide-containing compounds, and

identify potential targets for medical intervention

- Identify FDA-approved drugs containing sulfur that may have therapeutic value in the treatment of cyanide poisoning
- Determine optimal and novel routes of drug administration of promising compounds, to include administration through inhalation
- Identify screening tests and biological markers consistent with the identification of hydrogen cyanide and/or cyanide metabolite(s) and the level of exposure to such agents
- Identify and validate appropriate *in vitro* systems and animal models for preclinical testing of drugs that could be useful in cyanide poisoning
- Validate the use of oxygen therapy in the initial treatment of cyanide poisoning, alone or in combination with other medical countermeasures
- Understand the differences in cyanide intoxication between different age ranges and establish a treatment plan for susceptible populations

Long-Term Goals

- Conduct safety and efficacy studies with promising drugs and identify effective routes of administration that would lead to timely intervention
- Identify the major mechanisms and pathways by which sulfur donors, methemoglobin formers, and cobalt compounds counter cyanide toxicity in different systems of the body
- Expand the current NIH research infrastructure to enable preclinical and clinical studies on compounds with promising anti-cyanide activity
- Develop rapid diagnostic test and assays to identify specific biological markers consistent with cyanide exposure and the level of exposure to such agents
- Identify any long-term or chronic health effects resulting from exposure to hydrogen cyanide, the cyanide-containing salts, and/or cyanogen chloride
- Establish databases of clinical, epidemiological and laboratory information that will contribute to the understanding of the acute and chronic health effects of high and low level exposures to cyanide-containing compounds
- Review current therapeutic interventions with oxygen and assess the value of other proposed alternatives, such as the use of hyperbaric oxygen in treatment

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Table. Names & Symbols of Classical Chemical Warfare Agents with Time of Onset for Initial and Delayed Symptoms

Type	Common Name	Symbol	Time of Onset of Initial Symptoms	Time of Onset of Symptoms (skin absorption)
Nerve Agents	Tabun	GA (highly volatile)	Seconds to minutes	Within 2 hours
	Sarin	GB (highly volatile)	Seconds to minutes	Within 2 hours
	Soman	GD (highly volatile)	Seconds to minutes	Within 2 hours
	Cyclosarin	GF (highly volatile)	Seconds to minutes	Within 2 hours
		VX (lower volatility)	Minutes	Up to 18 hours
Vesicants or Blister Agents	Sulfur Mustard	H and HD	4 to 6 hours	2-48 hours
	Sulfur Mustard-T Mixture	HT	4 to 6 hours	2-48 hours
	Nitrogen Mustard	HN-1	4 to 6 hours	2-48 hours
	Nitrogen Mustard	HN-2	4 to 6 hours	2-48 hours
	Nitrogen Mustard	HN-3	4 to 6 hours	2-48 hours
	Lewisite and other arsenical vesicants	L	Immediate	Immediate
Corrosive Skin Irritant	Phosgene oxime	CX	Immediate contact effects; may cause pulmonary edema if inhaled	Immediate (when used with VX , VX absorption is enhanced)
Pulmonary (Choking Agents)	Phosgene	CG	Some irritant effects; pulmonary edema 4-48 hours post exposure	N/A
	Chlorine	Cl	Pronounced irritant effects (eyes & upper airway); pulmonary edema in 2-4 hours	Minimal
	Diphosgene	DP	Similar to CG	N/A
Blood Agents (Cellular Poisons)	Hydrogen cyanide (vapor & liquid)	AC	< 1 minute (persistence <1 hr)	N/A
	Cyanogen chloride (vapor)	CK	< 1 minute (non-persistent)	N/A

*Table based on information in (1) *The Medical NBC Battlebook*, published by the U.S. Army Center for Health Promotion and Preventive Medicine, May 2000; (2) The Textbook of Military Medicine: Medical Aspects of Chemical and Biological Warfare, Office of the Surgeon General, U.S. Army, 1997; and (3) Department of Health and Human Services CDC Emergency Preparedness & Response information bulletins. 23 Sept. 2005 (http://www.bt.cdc.gov/chemical/)

Not included in this table are other chemical agents recognized by the military, such as BZ (incapacitating agent), CN and CS (tear gas products), and DM (adamsite), a vomiting gas.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

National Institute of Allergy and Infectious Diseases

NIH Publication No. XX–XXX
April 2007
www.niaid.nih.gov