
# Interactions of Drugs, Biologics, and Chemicals in U.S. Military Forces

Robert G. Petersdorf, William F. Page, and Susan Thaul, Editors, Committee to Study the Interactions of Drugs, Biologics, and Chemicals in U.S. Military Forces

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Robert G. Petersdorf, William F. Page, and Susan Thaul, *Editors*

Medical Follow-up Agency
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The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The serpent adopted as a logotype by the Institute of Medicine is a relief carving from ancient Greece, now held by the Staatlichemuseen in Berlin.

# COMMITTEE TO STUDY THE INTERACTIONS OF DRUGS, BIOLOGICS, AND CHEMICALS IN U.S. MILITARY FORCES

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# Preface

At the request of the Department of the Army, the Medical Follow-up Agency of the Institute of Medicine established a committee to review the available medical and scientific information on the interactions of drugs, biologics, and chemicals. The committee was asked to consider this topic further, specifically regarding U.S. military personnel, who are exposed to numerous drugs, biologics, and vaccines throughout their basic training and prior to and during deployment.

The committee met in Washington, D.C., on four separate occasions: September 5–6, 1995, and March 5–6, May 1–2, and June 18, 1996. During the first two meetings the committee heard testimony from officials of the U.S. Army, the Food and Drug Administration, the Centers for Disease Control and Prevention, and the British Ministry of Defence. This report sets forth the results of the committee's deliberations.

The committee is deeply appreciative of the testimony and written material submitted by the various agencies and of the work of the Medical Follow-up Agency. In particular, the committee thanks Richard Miller, William Page, Carol Maczka, Erin Bell, Pamela Ramey-McCray, and Nancy Diener for staff support. The committee also thanks Michael Hayes and Michael Edington for editorial review.

Robert G. Petersdorf, *Chair*

# Contents

# Executive Summary

## BACKGROUND

The U.S. Army Medical Research and Materiel Command is addressing the increasingly contentious issue of the effects of exposures to drugs, chemicals, and biologics and their possible interactions. U.S. troops receive a number of routine immunizations, and when they are deployed they may be given antimalarial drugs, anti-biological warfare drugs and vaccines, and additional vaccines to protect them against indigenous diseases. They may be further exposed to a number of chemicals, such as permethrin or *N*,*N*-diethyl-*m*-toluamide (DEET), and to environmental contaminants and warfare by-products; some personnel will also be using individually prescribed and over-the-counter medications. Although the adverse effects of most single products have been relatively well studied (for example, in the data submitted to the Food and Drug Administration [FDA] for approval of a new drug), it is largely unknown whether their combined use may provoke unanticipated interactions. For the purposes of this report, agents are said to interact if the presence of one agent affects an exposed individual's reactivity to other agents.

The U.S. Army contracted with the Institute of Medicine to address the issue of the interactions of drugs, chemicals, and biologics. The Institute assembled a committee of experts in pharmacology, drug safety assessment, immunology, vaccinology, epidemiology, biostatistics, occupational health, environmental health, toxicology, and biomedical administration. The names of potential committee members were sought from a variety of sources, and the final committee roster was approved by the chairman of the National Research Council.

Using a broad range of sources, the committee informed itself on this topic. The committee reviewed the available scientific literature and heard testimony from officials of the U.S. Army, the FDA, the Centers for Disease Control and Prevention (CDC), and the British Ministry of Defence (a list of presenters can be found in the Appendix).

## THE COMMITTEE'S CHARGE

The committee was asked to address the following questions:

1. What are the drugs, biologics, and chemicals that U.S. military forces currently receive as prophylactic-preventive agents, and what additional prophylactic-preventive agents are planned?
2. What does the published scientific literature tell us about the health effects of combinations of these prophylactic-preventive agents in the U.S. military, in other human populations, or in model systems (e.g., animal, in vitro, and computer)?
3. Do the experiences of the militaries of other nations shed any light on issues #1 and #2?
4. If there are important gaps in our knowledge, where are they and how would they best be filled?
5. Should, and in what way, the Army modify or expand its development and utilization strategies to ascertain possible interactions of prophylactic-preventive agents?
6. Should the Army undertake any new programs to provide information on drug, biologic, and chemical interactions?

## SCOPE OF THE PROBLEM

The number of potential drugs, chemicals, and biologics to which military personnel may be exposed is quite large (see Chapter 2), and a complete study of their interactions would by necessity involve examination of all their possible combinations. For example, in the case of 25 agents, there are $2^{25} - 1$ (or 33,554,431) combinations. To reduce the problem to a more manageable level, the committee advocates a categorical approach to the study of interactions. This approach would categorize interactions into three classes—Known, potential, and unknown—so that different strategies may be applied to each class. Known interactions are those for which there is documented evidence of risk in humans; potential interactions are those that are known from animal studies, or that can be anticipated or predicted on the basis of the individual properties—for example, target organ toxicities—of the agents in putative combinations; and un

known interactions that are those that cannot be anticipated on the basis of current knowledge. Once the interactions are categorized, specific strategies can be put into place for their study. Table E-1 summarizes the categorical approach.

## CATEGORICAL APPROACH

The committee recommends that a matrix approach be used to identify interactions for which data from studies with experimental animals are lacking. Such an approach, if it is designed appropriately, will help to identify commonalities between agents that may predispose these agents to interactions. The matrix approach is an iterative one; as agents are added or deleted from the matrix or entries are modified, the matrix must be updated and reexamined for potential interactions. In some instances interactions may not be identified by examining the matrix. For example, DEET will enhance the dermal penetration of some chemicals and thus facilitate the interaction. Alternatively, since there is no one method that can be used to identify and predict all possible interactions, the committee proposes the use of a tiered approach for conducting prospective animal studies. By this approach, potential hazards can first be identified in appropriately chosen in vitro studies. Studies can then be extended to in vivo animal models, choosing appropriate species and experimental designs.

TABLE E-1 Categorical Approach

| Interaction Type | Recommended Approaches |
|---|---|
| Known | • Avoid unless benefit outweighs risk<br>• Use surveillance to monitor outcomes and implement appropriate intervention<br>• Study in depth |
| Potential | • Use matrix approach to predict or identify the interaction<br>• Conduct studies (in vitro, animal, or human volunteer)<br>• Use surveillance |
| Unknown | • Put in place surveillance systems to detect sentinel events and do follow-up studies<br>• Do prospective screening studies of important combinations |

The committee emphasizes that this approach is just one practical method that can be used to grapple with a difficult subject; there are no completely fail-safe methods. Even if it were possible to study all combinations of agents in epidemiologic or animal model systems, it is unlikely that such a strategy would work. Many confounding factors would be encountered in epidemiologic studies; for example, host susceptibility factors such as age, race, sex, and comorbid conditions could affect the results. In the case of experimental studies, although

randomization minimizes the effects of confounding variables, there remain the problems of multiple comparisons and sample size considerations.

## AVAILABLE LITERATURE

Despite the existence of more than 10,000 publications on drug interactions in the medical literature, the epidemiology of these interactions is poorly understood. Only a very small percentage of all of the scientific literature on interactions has resulted from epidemiologic investigations. The remainder of the literature primarily comprises pharmacokinetic or pharmacodynamic studies with humans and animals, case reports, review articles, animal studies, or in vitro studies. Thus, the existing literature provides very little information about how often drug interactions actually occur in humans or how often they produce clinically meaningful adverse effects. Similarly, the medical literature pertaining to biologics and chemicals does not provide adequate information on the interactions of all three agents. The committee's own Medline search did not turn up any additional notable articles related to its charge, although some articles of interest may be found in the reference list.

## USES OF AUTOMATED MULTIPURPOSE DATABASES FOR EPIDEMIOLOGIC SURVEILLANCE

The categorical approach to the study of interactions advocated in this report presumes that a large proportion of interactions will be unknown. Therefore, a comprehensive strategy for studying such interactions must depend on surveillance. This requires both alerting mechanisms to signal that unanticipated health effects may have occurred and the gathering of confirmatory data to estimate the incidence of these events and to determine if they were due to some particular exposure. Alerting mechanisms include case reports as well as broad monitoring programs designed to search for changes in rates of clinically important events. Such efforts also encompass the analysis of accidents or so-called natural experiments. In contrast, confirmatory data collection and analysis will be more focused on specific hypotheses. Such confirmatory data may be obtained from cohort studies or case-control studies, as well as randomized experiments and intervention studies, which include cessation of use studies.

Automated multipurpose databases are increasingly being used for epidemiologic purposes, including surveillance. Examples of such multipurpose databases used in epidemiologic studies of drug effects include those assembled from the records of health maintenance organization enrollees, Medicare or Medicaid populations, military or U.S. Department of Veterans Affairs cohorts, or some other defined populations. Such databases are considered to be popula

tion-based if the information that they contain is derived from some underlying population in the statistical sense, specifically, some group of known size and composition from which statistical samples might be drawn.

In carefully designed studies, multipurpose databases offer a number of advantages: the ability to conduct studies of uncommon health events or of understudied but well-defined populations, the minimization of study costs, a reduction in the amount of time needed to conduct a study, and the opportunity to study a large number of people. However, studies based on multipurpose data sets are affected by a number of potential problems, including completeness and the quality of the data.

Although no perfect surveillance systems exist, much can be learned from the currently available databases. The report briefly describes Army and U.S. Department of Defense (DoD) surveillance activities that are in current use or in development, as well as other sources of material from which to assemble multipurpose databases. In addition, the report also briefly discusses relevant U.S. Department of Veterans Affairs databases and two other nonmilitary systems— the Vaccine Adverse Event Reporting System, managed jointly by CDC and FDA, and FDA's medical products reporting program, MEDWatch— that can provide useful information.

The surveillance tools currently available to the military comprise a series of linkable automated databases. Opportunities for creating automated multipurpose databases have already been seized; the Army Medical Surveillance Activity and the Uniformed Services Prescription Database Project are two examples. Additional opportunities to create linked databases remain, a fact recognized in the planning for the triservice Defense Medical Epidemiology Database.

In general, the strength of these large databases is their outcomes data, and their limitation is their exposure data, with prescription drug data being the exception. Data on the use of nonprescription drugs are not available, and vaccine data are not captured in an automated system. Moreover, no chemical and environmental exposure databases like the ones described above exist, although such databases are being created after the fact (see Chapter 5).

## STUDY AND MANAGEMENT OF INTERACTIONS

Multipurpose automated databases with person-based *exposure* information are largely undeveloped. However, future plans for a person-based deployment database and unit-based environmental exposure databases hold some promise. It will be necessary to design such databases carefully to permit linkages between person-based and unit-based information. Person-based *outcomes* databases are much further developed than are exposure databases, and expanding outcomes database coverage (for example, adding conditions to the Reportable

Disease Surveillance System) and increasing linkages among them are relatively easy next steps that would make their information even more useful. Aside from good surveillance mechanisms, some relatively small prospective studies—for example, comparing outcomes before and after deployment—could provide supporting data; however, the amount of support will be directly related the soundness of design and statistical power of such studies. In addition, recent developments in the design and analysis of animal toxicity studies have markedly increased their effectiveness in identifying interactions, and these developments should be used.

Not all of these activities can be carried out at once, and the Army will have to set priorities for its future actions; a cost-benefit analysis may prove fruitful to determine priorities. In advance of this process, the Army will need to take careful stock of all its pertinent ongoing activities. Additionally, the effective study and management of interactions will depend on the productive communication and coordination among those responsible for product development, preventive medicine surveillance, and all others who will be involved with the exposures of U.S. military personnel to drugs, biologics, and chemicals and their potential interactions.

## FINDINGS AND RECOMMENDATIONS

### Findings

1. Military personnel, especially when they are deployed, are exposed to a large number of drugs, biologics, and chemicals to which their civilian counterparts in the United States are not exposed. None of the information gathered on additional planned prophylactic-preventive agents had a substantial impact on the committee's deliberations.
2. The published scientific literature on the interactions of militarily relevant drugs, biologics, and chemicals does not provide an adequate basis for assessing the degree of safety; the committee, however, did not find any basis for extraordinary concern.
3. Discussions held with liaisons from the medical divisions of the Canadian and British militaries indicated the international need for increased information and research regarding interactions.
4. The diversity and number of agents precludes not only the testing of all possible combinations for interactions but also the development of systems that could be used to identify and predict with confidence all possible interactions that could result in increased toxicity.
5. Operational requirements may necessitate the use of combinations of agents of known or potential toxicity. The committee understands that it is DoD

policy to ensure that the benefits outweigh the risks when these combinations of agents are used.

6. Many programs are under way within the military in the areas of drug and vaccine design and development, research on the effects of those agents that are administered to military personnel or to which military personnel are known to be exposed, and the development of surveillance systems and related databases that could be used in epidemiologic studies. However, many of the surveillance systems are incomplete, and databases that contain related, relevant information have not been linked to date. Most important, a coordinated effort among the services to link the relevant programs is lacking.

## Recommendations

1. A focused strategy for evaluating and managing the effects of interactions needs to be developed. This strategy should also be suitable for new agents. The proposed approach involves the characterization of interactions into three broad categories:

a. *Known:* those interactions for which there is documented evidence of risk in humans;
b. *Potential:* those interactions that are known from animal studies or that can be anticipated or predicted on the basis of the individual properties of the agents in putative combinations; and
c. *Unknown:* the interactions of combinations of agents that cannot be anticipated on the basis of current knowledge (this is the largest class).

2. For agents with known interactions, if exposure cannot be avoided, surveillance measures should be implemented and focused studies should be undertaken to identify ways to minimize risk levels.
3. Potential interactions might be predicted by use of a matrix based on target organ toxicity, pharmacokinetics, and pharmacodynamics. High-priority potential interactions should be investigated in a tiered process involving in vitro, animal, human volunteer, and epidemiologic studies.
4. For agents with unknown interactions, three strategies are recommended.

a. The first strategy is to develop, enhance, and implement surveillance systems to monitor both exposure combinations and health outcomes. Surveillance systems for exposures should include data regarding drugs, biologics, and other deployment-site-specific chemicals. Surveillance systems for health outcomes should be expanded to capture additional sentinel events (using notifiable conditions) and could be used to support focused prospective studies, provided they are of sufficient sample size, to compare specific health measures before and after deployment.

b. The second strategy is to conduct a battery of in vitro and in vivo experimental studies to investigate a core set of exposures anticipated for most deployed troops.

c. When outcomes of interest are identified, they should be investigated with carefully designed epidemiologic studies of disease-exposure relationships. The committee recommends further that efforts be better coordinated within and among all those military units and branches involved with the development of these systems.

5. Programs within the Army and DoD that involve product development, preventive medicine (including the development of surveillance systems and integrated databases), clinical medicine, and the medical defense against biological and chemical warfare weapons should be closely coordinated. An advisory committee should be established to help identify and use existing and future research tools for the purposes of anticipating, studying, and minimizing harmful interactions.

# 1

# Introduction

## BACKGROUND

The U.S. Army Medical Research and Materiel Command is addressing the increasingly contentious issue of the effects of exposures to drugs, biologics, and chemicals and their possible interactions. U.S. troops routinely receive a number of vaccines, and when they are deployed they may be given antimalarial drugs, anti-biological warfare drugs and vaccines, and additional vaccines to protect against indigenous diseases. They may be further exposed to sundry chemicals, such as permethrin or *N*,*N*-diethyl-*m*-toluamide (DEET), environmental contaminants, and warfare byproducts; some personnel will also be using individually prescribed and over-the-counter medications. Although the adverse effects of most single products have been relatively well studied (for example, in the data submitted to the Food and Drug Administration [FDA] for approval of a new drug), it is largely unknown whether and how their combined use may provoke unanticipated interactions. For the purposes of this report, agents are said to interact if the presence of one agent affects an exposed individual's reactivity to other agents.

The U.S. Army contracted with the Institute of Medicine to address the issue of the interactions of drugs, chemicals, and biologics. The Institute assembled a committee of experts in pharmacology, drug safety assessment, immunology, vaccinology, epidemiology, biostatistics, occupational health, environmental health, toxicology, and biomedical administration. The names of potential committee members were sought from a variety of sources, and the final committee roster was approved by the chairman of the National Research Council.

Using a broad range of sources, the committee informed itself on this topic and then deliberated to reach consensus recommendations. The committee reviewed the available scientific literature and heard personal testimony from officials of the U.S. Army, the FDA, the Centers for Disease Control and Prevention (CDC), and the British Ministry of Defence (a list of presenters can be found in the Appendix).

## THE COMMITTEE'S CHARGE

The committee was asked to address the following questions:

1. What are the drugs, biologics, and chemicals that U.S. military forces currently receive as prophylactic-preventive agents, and what additional prophylactic-preventive agents are planned?
2. What does the published scientific literature tell us about the health effects of combinations of these prophylactic-preventive agents in the U.S. military, in other human populations, or in model systems (e.g., animal, in vitro, and computer)?
3. Do the experiences of the militaries of other nations shed any light on issues #1 and #2?
4. If there are important gaps in our knowledge, where are they and how would they best be filled?
5. Should, and in what way, the Army modify or expand its development and utilization strategies to ascertain possible interactions of prophylactic-preventive agents?
6. Should the Army undertake any new programs to provide information on drug, biologic, and chemical interactions?

## SCOPE OF THE PROBLEM

The number of potential drugs, chemicals, and biologics to which military personnel may be exposed is quite large (see Chapter 2), and a complete study of their interactions would by necessity involve examination of all their possible combinations. For example, in the case of 25 agents, there are $2^{25} - 1$ (or 33,554,431) combinations. Even if it were possible to study all combinations of agents in epidemiologic or animal model systems, it is unlikely that such a strategy would work. Many confounding factors would be encountered in epidemiologic studies; for example, host susceptibility factors such as age, race, sex, comorbid conditions, and other effect modifiers could affect the results.

With exposure to drugs, biologics, and chemicals being such common occurrence in the military, it is critical to know whether coexposure to two or

more of these agents yields a different health effect than what would be expected by adding each separate effect. Reports of drug interactions began to appear in the medical literature in the 1940s when *para*-aminobenzoic acid was found to reduce the renal tubular excretion of salicylates (Gilman et al., 1990). Since then, many drug interactions have been discovered. There have also been major advances in the understanding of the mechanisms and pharmacokinetic principles of drug interactions.

However, little or no information exists on interactions among drugs, biologics, and chemicals. The committee's own Medline search did not turn up any notable articles related to its charge other than the few noted below. Additionally, discussions with liaisons from the Canadian and British militaries provided no additional insight regarding interactions.

Nonetheless, this does not mean that interactions have not been the subject of separate study in the disciplines of pharmacology, toxicology, statistics, and epidemiology. The committee has, indeed, drawn briefly on material from each of these disciplines as necessary. As an aid to the reader who would like to pursue further discipline-specific findings, the committee offers the following short discussion.

There is a vast literature on drug-drug interactions; for example, standard compendia can be used to identify potentially interacting drug combinations (Hansten and Horn, 1993; Tarto, 1995). However, the bulk of the more than 10,000 publications on drug interactions in the medical literature primarily comprises pharmacokinetic or pharmacodynamic studies with humans and animals, case reports, review articles, animal studies, and in vitro studies. Thus, the existing literature provides very little information about how often drug interactions actually occur in humans or how often they produce clinically meaningful adverse effects. Although epidemiologic methods have demonstrated strong utility in the detection and quantitation of drug reactions in general, they have not been applied often in the study of interactions. There are also no meaningful estimates of the importance of drug interactions as a clinical problem (Jankel and Speedie, 1990; Jankel and Fitterman, 1993).

The existing literature also provides some information on the potential for interactions among certain biologics to which military personnel may be exposed. With regard to vaccine interactions, Grabenstein (1990) reviewed interactions between vaccines, vaccines and immunoglobulins, and vaccines and other drugs. Similar to drug interactions, vaccine interactions can lead to potentiated or diminished effects, enhanced or impaired elimination, or other metabolic or pharmacologic effects. Vaccines, for example, have been shown to affect the metabolism of other drugs, possibly by interfering with human liver cytochrome P450 isozymes (Kramer and McClain, 1981). More recently, Gizurarson (1996) summarized the known and suspected vaccine-vaccine and vaccine-drug interactions.

The toxicology literature on interactions is considerable, although such work is more apt to be indexed under "complex mixtures" than "interactions," per se. One recent review article is by Mauderly (1993), who cites a more detailed treatise, the NRC report on complex mixtures (NRC, 1988). It is worth noting that major research efforts directed toward the study of complex mixtures date back to the mid-1970s. Studies of the effects of tobacco smoke and of engine exhaust provide examples of studies of complex mixtures. Toxicologists generally have a much broader range of study tools than investigators who are limited to studying humans, but this advantage is offset by the disadvantage that data not derived from human sources must be extrapolated to humans, with varying degrees of uncertainty. Nevertheless, the considerable advantages of toxicological studies led the committee to recommend their use in addition to studies of humans (see Chapter 5 and Chpater 6).

Statistics and epidemiology each have made their contributions to the study of interactions. Over the years, statisticians have developed a considerable body of work on the subject of interactions. The statistical term *interaction* denotes a departure from additivity in some (linear) mathematical model of exposure and response, and thus much of the statistical literature on departure from additivity in models is pertinent. In Chapter 5, the committee has made particular mention of newly developed statistical techniques for the study of interaction.

Epidemiology provides at least two definitions of the term interaction, one the more traditional "statistical" definition above and the other arising from the counterfactual model of effects (see Greenland, 1993). The committee has operated using the more traditional definition of interaction in this report. Epidemiologists have rightly emphasized the practical difficulties in assessing interactions. For example, the power to detect interactions in epidemiologic settings is typically much less than the power to detect single-factor effects, and the impact of measurement errors on interactions is not nearly as well studied as is the impact of measurement errors on main effects. Given the difficulty in studying interactions using epidemiologic data, some have recommended that "design and analysis is best focused on accurate estimation of the entire dose-response surface relating incidence to covariates, rather than on isolated aspects of this surface, such as statistical interaction." (Greenland, 1993, p. 64)

## REPORT FOCUS

To reduce the problem to a more manageable level and as an organizing framework for this report, the committee advocates a categorical approach to the study of interactions. This approach would categorize interactions into three classes—known, potential, and unknown—so that different strategies may be applied to each class.

In the remainder of the report, Chapter 2 discusses the current prophylactic agents given to military personnel, Chapter 3 briefly describes the surveillance tools currently available to the military, Chapter 4 presents the strategy for identifying and dealing with the various types of interactions, Chapter 5 addresses in greater detail the study and management of the various types of interactions, and Chapter 6 contains the committee's findings and recommendations. A glossary of technical terms and acronyms is also provided.

# 2

# Current Prophylactic Agents

In the course of a career in the military, personnel are exposed to a variety of biologics, drugs, and chemicals. These include vaccines to stimulate immunologic protection against natural and biological warfare infectious disease threats, chemoprophylactic drugs against infectious diseases and chemical warfare agents, and skin repellents or uniform-impregnating agents for protection against insect vectors. Troops are also exposed occupationally to myriad environmental agents. In addition, individuals will inevitably be using a variety of prescribed and over-the-counter medications. The remainder of this chapter describes military use of preventive or prophylactic agents, those subject to direct military decision-making and provision.

The list of vaccines and other prophylactic agents used by the military is constantly changing. As new agents become available, their efficacies are determined and evidence of their disease risk is established. Preventive medicine guidelines used by the military, including medical guidelines for travel, are similar to those developed for the civilian sector (such as the Centers for Disease Control and Prevention and the Advisory Committee on Immunization Practices), with modifications dictated by the peculiarities of the military environment. The military depends heavily on a group of civilian medical consultants, the Armed Forces Epidemiological Board, which has been advising the medical leadership of the U.S. Department of Defense (DoD) since World War II.

## BASIC PREVENTIVE SERIES

In general, military recruits currently receive the following on entering active duty:

- poliovirus vaccine, live oral trivalent type 1, 2, and 3;
- measles and rubella virus vaccine live or measles, mumps, and rubella virus vaccine live;
- meningococcal polysaccharide vaccine (groups A, C, Y, and W-135);
- tetanus and diphtheria toxoids (adult), which they receive every 10 years thereafter;
- influenza virus vaccine, which they receive yearly thereafter;
- penicillin G benzathine (Bicillin) (or erythromycin for penicillin-sensitive individuals) for prophylaxis for streptococcal disease during training at several basic training camps.

Some differences in policy exist between services because of different disease experiences or because of different operational requirements (Table 2-1). For example, adenovirus vaccine is given to all male Army, Navy, and Marine recruits, but it is not given to Air Force or Coast Guard recruits, because it is not considered a serious threat in the Air Force or Coast Guard. Similarly, because early overseas deployment is highly likely for Navy and Marine Corps personnel, they are given typhoid vaccine and yellow fever vaccine during recruit training and every 3 years and 10 years thereafter, respectively.

Because of occupational exposure, hepatitis B virus, varicella-zoster virus, plague, or rabies virus vaccines may be added for selected individuals. Reserve component personnel usually receive oral poliovirus vaccine, diphtheria-tetanus toxoid, and influenza virus vaccines.

## AGENTS USED DURING DEPLOYMENTS

The list of agents added to the routine preventive series described above is dependent on the deployment scenario: the climate, the state of socioeconomic development of the nation(s) to which troops will be deployed, the known or suspected natural disease threats, and the existence of biological or chemical warfare agents. The members of some alert units (ready to be deployed) receive a number of the vaccines listed below to maintain immunity, because they are at continuous risk of rapid deployment to areas of increased disease threat. The following list, which is not necessarily exhaustive, represents examples of some agents currently used (including investigational new drugs [INDs]).

### Temperate Climate, Developing Country

- hepatitis A virus vaccine or immune globulin,
- hepatitis B virus vaccine (normally only Army in the Republic of Korea),
- typhoid vaccine (injectable or oral),
- tick-borne encephalitis vaccine if local threat exists (IND), and
- self-treatment for traveler's diarrhea, which may be prescribed (ciprofloxacin, loperamide).

### Tropical Climate, Developing Country

- hepatitis A vaccine or immune globulin,
- typhoid vaccine (injectable or oral),
- yellow fever vaccine, every 10 years,
- meningococcal polysaccharide vaccine (groups A, C, Y, and W-135), every 5 years,
- Japanese encephalitis vaccine,
- rabies virus vaccine (generally only Special Forces receive preexposure prophylaxis),
- plague vaccine (Vietnam only),
- mefloquine, doxycycline, or chloroquine (malaria),
- primaquine (relapsing malaria),
- doxycycline for leptospirosis or scrub typhus prophylaxis, and
- self-treatment for traveler's diarrhea, which may be prescribed (ciprofloxacin, loperamide).

Injectable cholera vaccine is available to the military, but it is given exclusively to those personnel going to countries whose health authorities require cholera immunization for entry. See section below on IND vaccines for comments on oral cholera vaccine.

### Desert Climate, Developing Country

- hepatitis A virus vaccine or immune globulin,
- typhoid vaccine (injectable or oral),
- meningococcal polysaccharide vaccine (groups A, C, Y, W1-35), every 5 years,
- self-treatment for traveler's diarrhea, which may be prescribed (ciprofloxacin, loperamide),
- mefloquine, doxycycline, or chloroquine in oasis and riverine areas, and
- primaquine in oasis and riverine areas.

### Some Potential Responses to Biological Warfare Threat

- anthrax vaccine adsorbed,
- ciprofloxacin self-medication (for anthrax),
- smallpox vaccine,
- plague vaccine,
- tularemia vaccine (IND), and
- botulinin toxoid (IND).

### Potential Response to Chemical Warfare Threat

- Pyridostigmine bromide (IND): 30-mg tablets are taken daily every 8 hours for a maximum of 14 days. Service members start or discontinue use on order from the commander when nerve agents, particularly soman (GD), are a threat.

### Agents Used in Climates Where Tick-Borne Diseases Have Been Identified

- DEET skin repellent and
- permethrin uniform impregnant.

TABLE 2-1 Vaccinations for Military Personnel

| Immunizing Agent | Army | Navy | Air Force | Marine Corps | Coast Guard |
|---|---|---|---|---|---|
| Adenovirus type 4 and 7 vaccines | B | B | G | B | G |
| Cholera vaccine | E | E | E | E | E |
| Hepatitis A virus vaccine | G | G | C, D | G | G |
| Hepatitis B virus vaccine | F, G | F, G | F, G | F, G | F, G |
| Influenza virus vaccine | A, B, X | A, B, R, | A, B, R | A, B, R | B, C, G |
| Japanese encephalitis virus vaccine | D | D | D | D | G |
| Measles virus vaccine | B, F | B, F | B, F | B, F | B, G |
| Meningococcal vaccine (groups A,C,Y, and W-135) | B, D | B, D | B, D | B, D | B, G |
| Mumps virus vaccine | F, G | B, F, G | F, G | B, F, G | G |
| Oral poliovirus vaccine | B, D, R | B, R | B, R | B, R | A |
| Plague vaccine | D, F | F | F | F | F |
| Rabies virus vaccine | F | F | F | F | G |
| Rubella vaccine | B, F | B, F | B, F | B, F | B |
| Tetanus-diphtheria toxoid | A, B, R | A, B, R | A, B, R | A, B, R | A, B |
| Typhoid vaccine | C, D | C, D | C, D | C, D | D |
| Varicella-zoster virus vaccine | F, G | F, G | F, G | G | F, G |
| Yellow fever vaccine | C, D | A, R | C, D | A, R | B, C, E |

NOTE: A = all active-duty personnel; B = recruits; C = alert forces; D = when deploying or traveling to high-risk areas; E = only when required by host country for entry; F = high-risk occupational groups; G = as directed by applicable Surgeon General or Commandant, Coast Guard; R = reserve components; and X = reserve component personnel on active duty for 30 days or more during the influenza season.

SOURCE: U.S. Army Regulation 40-562, November 1, 1995.

# 3

# Surveillance Tools Currently Available to the Military

The approach to the study of interactions advocated in Chapter 4 presupposes that a large proportion of all interactions will be unknown and unpredictable. Therefore, a comprehensive strategy for studying such interactions must depend on surveillance. This requires both alerting mechanisms to signal that unanticipated health effects may have occurred and confirming mechanisms to estimate the incidence of these events and to determine if they were due to some particular exposure. Alerting mechanisms include case reports as well as broad monitoring programs designed to search for changes in rates of clinically important events. Such efforts also encompass the analysis of accidents or so-called natural experiments. In contrast, confirmatory data collection and analysis will be more focused on specific hypotheses. Such confirmatory data may be obtained from cohort studies or case-control studies, as well as randomized experiments and intervention studies, which include cessation of use studies. Animal studies should also be considered, either as preliminary or concomitant investigations, to help establish biological plausibility (see Chapter 5).

Automated multipurpose databases are increasingly being used for epidemiologic purposes, including surveillance. Such databases are typically assembled by combining patient-level information from two or more separate files originally developed primarily for nonresearch purposes. Through record linkage, it is possible to create these person-level longitudinal files on a general or

ad hoc basis. Examples of such multipurpose databases used in epidemiologic studies of drug effects include those assembled from the records of health maintenance organization enrollees, Medicare or Medicaid populations, military or Department of Veterans Affairs cohorts, or some other defined populations. Such databases are considered to be population-based if the information that they contain is derived from some underlying population in the statistical sense, specifically, some group of known size and composition from which statistical samples might be drawn. The utility of multipurpose databases for epidemiologic studies largely depends on the ability to assemble such files through linkage of individual person-level records and the quality and the completeness of the information recorded in such files.

In carefully designed studies, multipurpose databases offer a number of advantages: the ability to conduct studies of uncommon health events or of understudied but well-defined populations, the minimization of study costs, a reduction in the amount of time needed to conduct a study, and the opportunity to study a large number of people. However, studies based on multipurpose data sets are affected by a number of potential problems, including completeness and the quality of the data. It is worth reiterating that data collected for administrative purposes are not necessarily suited to research purposes. In such instances, careful editing and cautious use of these data can help to minimize the effects of their limitations.

Although there are no perfect surveillance systems, much can be done with currently available databases. This chapter describes Army and DoD surveillance activities that are under way or in development, as well as other sources of material from which to assemble multipurpose databases. There are also brief discussions of two nonmilitary systems—the Vaccine Adverse Event Reporting System (VAERS) and MEDWatch—that can provide useful information.

## CURRENT MILITARY SURVEILLANCE SYSTEMS

The Army Medical Surveillance Activity, the Defense Medical Epidemiology Database, and the Uniformed Services Prescription Database Project (USPDP) are the three automated multipurpose database systems currently in development that can be used to monitor adverse health events and their potential causes. This section briefly describes these databases, their developmental histories, and their potential uses for studying the interactions of drugs, biologics, and chemicals, as well as plans for further development of surveillance systems.

### Army Medical Surveillance Activity

The Army Medical Surveillance Activity is a multipurpose database whose component parts include the following: the Reportable Disease Surveillance System, the U.S. Army HIV Data System (USAHDS), the Acute Respiratory Disease Surveillance System (ARD), the U.S. Army Hospitalization Surveillance System (Individual Patient Data System [IPDS]), the Deployment Medical Surveillance System, and the Defense Manpower Data Center. Because each component database collects data on an individual person basis and because each database record is identified by Social Security number (SSN), the data in all of these systems are potentially linkable.

### Reportable Disease Surveillance System

Much like the data gathering system for the *Morbidity and Mortality Weekly Report* of CDC, the Reportable Disease Surveillance System (RDSS) is a worldwide automated system that collects relevant information on a specified list of morbidity endpoints (reportable diseases—see list below). Data are gathered by Preventive Medicine Service personnel at U.S. Army installations. The individual case reports, including SSNs, are coded so that updated local, daily, weekly, and monthly reports can be generated by the Army Medical Surveillance Activity. Reportable diseases occurring among inpatients and nondeployed personnel are more likely to be reported than are those occurring among military personnel who are deployed for training or duty or who are being treated on an outpatient basis.

**Notifiable Conditions Reported Through the Army Medical Surveillance System, January 1995**

Amebiasis
Anthrax
Arboviral fever, unspecified
Asbestosis
Botulism (adult)
Botulism (infant)
Brucellosis
Campylobacteriosis
Carbon monoxide intoxication
Chancroid
Chemical agent exposure
Chlamydia
Cholera
Coccidioidomycosis
Cold weather injury (CWI)
CWI, unspecified
CWI, frostbite
CWI, hypothermia
CWI, immersion type
Granuloma inguinale
Dengue fever
Diphtheria
Ehrlichiosis
Encephalitis
Fatality, trainee
Fatality, occupational
Giardiasis
Gonorrhea

Guillain-Barré syndrome
Haemophilus influenzae, invasive
Heat exhaustion
Heat stroke
Hemorrhagic fever
Hepatitis A, acute
Hepatitis B, acute
Hepatitis C, acute
Hepatitis,unspecified
Herpes simplex
Influenza, unspecified
Influenza,type A
Influenza, type B
Kawasaki syndrome
Lead poisoning
Legionellosis
Leishmaniasis, unspecified
Leishmaniasis, cutaneous
Leishmaniasis, mucocutaneous
Leishmaniasis,visceral
Leishmaniasis, viscerotropic
Leprosy
Leptospirosis
Listeriosis
Lyme disease
Lymphogranuloma venereum
Malaria,unspecified
Malaria, falciparum
Malaria, malariae
Malaria, ovale
Malaria, vivax
Measles
Meningitis, bacterial
Meningitis, viral
Mercury intoxication
Mumps (adults only)
Mycobacterial infection
Pertussis
Plague
Pneumococcal pneumonia
Poliomyelitis
Psittacosis
Q fever
Rabies, human
Radiation, ionizing
Radiation, nonionizing
Relapsing fever
Reye's syndrome
Rhabdomyolsis
Rheumatic fever
Rift Valley fever
Rocky Mountain spotted Fever
Rubella
Salmonellosis
Schistosomiasis
Shigellosis
Smallpox
Syphilis, unspecified
Syphilis, primary/secondary
Syphilis, latent
Syphilis, tertiary
Syphilis, congenital
Tetanus
Toxic shock syndrome
Toxoplasmosis
Trichinellosis
Trypanosomiasis, African
Trypanosomiasis, American
Tuberculosis, multidrug-resistant
Tularemia
Typhoid fever
Typhus fever
Urethritis, nonspecific
Vaccine adverse event
Varicella, adult only
Yellow fever

### U.S. Army HIV Data System

USAHDS acquires and maintains the data for the Army's human immunodeficiency virus (HIV) testing program. This system reports the dates and results of tests, as well as medical information. USAHDS also maintains the registry of all individuals with confirmed cases of HIV infection, documents clinical evaluations at Army medical treatment facilities, and supplies database support to the Army/Navy Serum Repository.

### Army/Navy Serum Repository

All personnel are tested for HIV before entry into active duty and before overseas deployments, but no less often than every 2 years for active duty personnel when they are not on deployment status. Reservists are tested for HIV every 5 years. The unused sera from each HIV test are maintained in the Army/Navy Serum Repository. The availability of these serum samples is an important resource for research because the serum samples are identified by SSN and are thus linkable to all other identifiable data. They may be used in case-control as well as cohort studies, for example, analyzing predeployment and postdeployment serum samples to document various types of exposures.

### Acute Respiratory Disease Surveillance System

The information for the ARD Surveillance System is collected only from the Army basic training centers. The data consist of counts of hospital admissions for ARD, throat culture results, and group A beta-hemolytic streptococcus-positive throat culture results. A weekly report tracks admissions for ARD and a surveillance index indicates the percentage of hospital admissions for ARD that are caused by group A beta-hemolytic streptococci. Data are aggregated at the unit level and are thus not directly linkable to other individualized data. However, because individual hospitalizations are also captured in the IPDS (see below), the data can be linked via the IPDS.

### Individual Patient Data System (Hospital Records System)

IPDS is an administrative database maintained under the U.S. Army Patient Administration Systems and Biostatistical Activity. Hospitalization discharge information on all military personnel, dependents, and retirees is maintained in this system, which includes up to 10 coded procedures and 8 coded diagnoses per discharge. Information is coded using the International Classification of Disease, Ninth Revision (ICD-9), and entered into the database from hard-copy records; information from hospitals in areas where personnel are deployed is coded and entered into the system on a delayed basis. Plans are under way to automate a tracking system (Army's Patient Accounting and Reporting Real-Time Tracing System) for in-theater hospitalizations throughout the Army. This system is now operational in Bosnia. Outpatient information is not included in this database.

### Deployment Medical Surveillance System

The Deployment Medical Surveillance System maintains rosters of deployed forces for all major deployments. It has the potential to link the information on deployment cohorts with the medical event databases listed above. Using this system, one could, for example, compare deployed troops with matched controls and provide a link to their Army/Navy Serum Repository samples. Since deployed personnel and those receiving outpatient treatment may be missed in the reportable disease database, however, this linkage may not capture all the relevant health events.

### Defense Manpower Data Center

Complete Army population data (demographic and occupational data) are linked with the Deployment Medical Surveillance System by SSN in a relational database by the Army Medical Surveillance Activity.

### Data Reported in the Army Medical Surveillance Activity

As of March 1996 the following data were stored on-line in a database available through the Army Medical Surveillance Activity.

### Personnel Data (1985 to March 1996)

Army Active Duty, Reserves, and National Guard

Individuals $n$ = 3,398,778

Serum samples $n$ = 8,227,156

Military Entrance Processing Stations (recruits)

Individuals $n$ = 4,402,470

Serum samples $n$ = 3,970,757

USAHDS

Individuals $n$ = 5,680

Clinical evaluations $n$ = 16,658

### Medical Events (Morbidity Information)

Reportable Disease Surveillance System

Years on-line 1994–1995

Total reports $n$ = 11,862

Army/Navy Serum Repository

Total sera banked $n$ = 17,134,763

Individual Patient Data System (IPDS—Active Duty, Army)

Years on-line 1989–1995

Total discharges $n$ = 756,214

## Strengths and Limitations of the Current Army Medical Surveillance Activity

The Army Medical Surveillance Activity has the typical strengths and weaknesses of an automated multipurpose database, which are described in the last part of this chapter. The particular strengths of the Army Medical Surveillance Activity and the proposed Defense Medical Epidemiology Database (described below) include the following: a variety of outcomes databases that are all linkable by SSN; components that are, by and large, already on-line and working; currently generated weekly and monthly reports from the Reportable Disease Surveillance System; and relatively easy addition of surveillance endpoints to the list of reportable diseases.

The particular weaknesses of the Army Medical Surveillance Activity include the fact that the system is not yet incorporated throughout DoD (although plans for a Defense Medical Epidemiology Database are in progress), and few exposure data are available. In addition, no outpatient data are available in an automated system, and data for reservists not on active duty are generally not included in any of the databases discussed. Specifically, no automated systems collect baseline data on exposures or outcomes before deployment or follow-up data after deployment. This deficiency makes medical surveillance of the reservist population almost impossible, save for short-term surveillance when these personnel are on active duty. Given the general plan to reduce the number of active duty forces, necessitating an increased reliance on reservists, the inability to conduct surveillance activities among reservists is a substantial limitation for the study of interactions.

## Future Plans for the Current Army Medical Surveillance Activity

Other sources of information that may be incorporated into the Army Medical Surveillance Activity include the following: disability data, active duty Army hospitalizations at Navy and Air Force medical treatment facilities, and reportable diseases for Air Force and Navy personnel. In addition, health risk appraisal data are being incorporated into the system.

Plans to create a triservice surveillance system are under way. Another potential strength would be linkage to the USPDP (described below), which plans

to forge links with hospital, outpatient, and claims databases, in addition to collecting prescription drug information.

### Defense Medical Epidemiology Database

The Defense Medical Epidemiology Database will integrate the Army Medical Surveillance Activity with the epidemiologic capabilities of the Air Force and Navy to create a triservice surveillance system. There will be Internet access to triservice reports, and data will be available through the Defense Medical Epidemiology Network. SSNs will provide the means to a common linkage within and across service-specific databases.

### Uniformed Services Prescription Database Project

USPDP is an automated multipurpose database of comprehensive prescribed drug information that serves the military health service system. Although many of its components are in place, some are still under development. The purpose of USPDP is to analyze the distribution of medications to troops and all DoD health care beneficiaries and to analyze the uniformity and consistency of the prescription benefit provided.

As of July 15, 1996, the database contained 28,493,924 records on the prescriptions filled for 2,058,010 participants over a 25-month period at 31 Army and Navy medical treatment facilities. Sixty-two percent of the prescriptions were new, with the remainder being refills. The mean age of the recipients was 32.6 years, and 49 percent of the recipients were female. Limiting the analysis to active-duty personnel, the 10 most common medications, ranked by therapeutic class and based on the prescriptions filled at 22 Army USPDP sites, are listed in Table 3-1.

### Strengths and Limitations of USPDP

The particular strengths of USPDP include the ability to describe drug use rates and characteristics and to examine health policy changes, drug safety, and drug effectiveness. The limitations of this system include the lack of immunization data, an inability to define a temporal association between exposure and outcome by using only the information in the database, the lack of information on other potential confounders such as smoking, and an inadequate sample size for studying very rare events.

TABLE 3-1 Medications of Active-Duty Soldiers

| Rank | Medications for Males ($n$ = 171,638) | Medications for Females ($n$ = 29,309) |
|---|---|---|
| 1 | Nonsteroidal anti-inflammatory drugs | Antibiotics, oral |
| 2 | Antibiotics, oral | Contraceptives |
| 3 | Analgesic-antipyretic agents | Nonsteroidal anti-inflammatory drugs |
| 4 | Decongestants | Analgesic-antipyretic agents |
| 5 | Antihistamines | Vitamins |
| 6 | Cough remedies | Decongestants |
| 7 | Steroids, topical | Antifungal agents, vaginal |
| 8 | Muscle relaxants | Antihistamines |
| 9 | Dermatologic, other | Iron therapies |
| 10 | Ulcer/gastroesophageal reflux therapy | Cough remedies |

### Future Plans for USPDP

Future plans for USPDP include the following: expansion of the system to include the Air Force medical treatment facilities and all of the remaining Army and Navy sites, performance of analyses standardized by time, inclusion of mail service prescriptions, and the gathering of additional data on prescriptions filled for deployed personnel. In addition, plans to link the hospitalization, ambulatory visits, and CHAMPUS (civilian-provided health care for military health care beneficiaries) claim databases are being developed.

A proposal has been submitted to expand the current system into a Universal Pharmacy Patient Profile. This would be a computerized system maintained by all pharmaceutical dispensers that will enable pharmacists to detect any potential drug interactions among current and newly prescribed medications across the entire military health service system, as well as provide a universal, automated record of the prescriptions that have been dispensed to an individual. In addition to including all of the medical treatment facilities, the Universal Pharmacy Patient Profile would create an electronic profile in a central database and would be accessible on-line by military and civilian pharmacies.

## U.S. DEPARTMENT OF VETERANS AFFAIRS AUTOMATED DATABASES

Although they are not strictly applicable to the study of interactions among deployed military personnel, the databases of the U.S. Department of Veterans

Affairs (VA) provide an important capability: the study of long-term health effects by linking military and veteran records. A number of the relevant databases are briefly discussed here.

One of the VA's larger automated health databases is the Patient Treatment File, which is analogous to the Army's IPDS. An automated record is created for every inpatient discharge from a VA medical center. Each record contains the individual's SSN and is thus linkable to the military database records. Although only about 12 to 17 percent of veteran hospitalizations occur within the VA system (Ahuja, 1994), this amounts to roughly 1 million episodes per year.

As is the case with the Army, no automated VA outpatient database exists. However, plans for such a system are under way, and an automated database is to be created starting October 1, 1996. As with inpatient episodes, relatively few veterans' outpatient visits (15 to 20 percent) occur in a VA setting (Ahuja, 1994), but again, the amount of data is large: more than 20 million outpatient visits per year.

The VA's Veterans Benefits Administration administers two databases that are potentially useful in epidemiologic studies. The Compensation and Pension file includes records of all veterans currently drawing compensation for a military service-connected disability. Although these veterans number some 2 million, the automated medical information available about them is limited; for example, diagnoses are recorded using VA-specific codes rather than International Classification of Disease codes.

The Beneficiary Identification and Records Locator Subsystem (BIRLS) is an automated administrative database that identifies all veteran beneficiaries (and, as of the early 1970s, all veterans) and gives the location of their VA claims folders, which contain the paperwork related to any claims for veterans benefits. Of particular interest is the fact that BIRLS contains a date of death for deceased veterans, and, because reporting of death to the VA is quite complete (Page et at., 1995; Page et al., 1996), this produces an opportunity to use BIRLS to follow up on all-cause mortality. In addition, death certificates are generally located in the claims folders of the deceased individuals, so that cause-specific mortality can be determined by using death certificates requested from the claims folder. However, the SSN is not always available for every BIRLS record, although it should be available for all recent records.

### Strengths and Limitations of VA Databases

The strength of the VA databases for the study of interactions lies in their linkability to military records (via SSNs), which in turn provides opportunities to create automated multipurpose databases for long-term follow-up. In addition, the individual databases contain large numbers of records. Their main

limitation is their incomplete coverage of the veteran population, although less so in the case of mortality information.

## CURRENT CIVILIAN SURVEILLANCE SYSTEMS

Two civilian surveillance systems are relevant to the study of interactions: VAERS and the FDA medical products reporting system (MEDWatch). The DoD Directive on Immunizations and Chemoprophylaxis (Army Regulation, 1995) requires that adverse events related to vaccines be reported to VAERS; there is no corresponding regulation for reporting to MEDWatch.

It is important to emphasize that neither system contains records that are directly linkable to military databases because neither system's records contain SSNs. This sharply restricts the utility of these databases for follow-up studies of military populations. Instead, both VAERS and MEDWatch can serve as alerting mechanisms, uncovering potential interactions that could be further studied in the military system. Reporting of adverse military events to MEDWatch is not currently required but would materially strengthen that system.

### Vaccine Adverse Event Reporting System

VAERS was established in 1990 to collect reports of adverse events following vaccination with licensed products. This system is managed jointly by CDC and FDA.

#### Objective of and Data in VAERS

The objective of VAERS is to aid in the detection of previously unrecognized reactions to vaccines, to detect any increases in known reactions, to identify preexisting conditions that may promote reactions, and to determine whether particular vaccine lots result in an unusual number or types of reported adverse events.

The primary data included in VAERS are date of birth, description of adverse event, outcome, date of vaccination, date of onset of adverse event, and all vaccines administered. Additional information includes patient recovery, test results and laboratory data, other vaccinations within four weeks of the reported vaccination, other medications taken at the time of vaccination, any illness at the time of vaccination, and preexisting conditions.

Most of the reports in VAERS are for children under 10 years of age. A summary of the information for reports for adults is provided in Table 3-2

(many of the vaccines listed in Table 3-2 are those that are administered to military personnel).

### Source of Information and Follow-up in VAERS

The information is supplied by the following four sources:

- Manufacturers, 39 percent
- Patient or parent, 2 percent
- Health care professional, 25 percent
- State health coordinator, 34 percent.

All deaths that are reported to the system are investigated by FDA physicians. Serious events are followed-up by VAERS contractors for recovery status, and selected cases are reviewed in depth by FDA physicians. Less serious events are occasionally investigated if unusual manifestations or complications appear.

### Strengths and Limitations of VAERS

VAERS is most useful for identifying rare and previously unrecognized reactions to vaccines, particularly newly marketed vaccines, and for monitoring the safety of individual vaccine lots. By directive (Army Regulation 40-562, 1995), adverse vaccine events among military personnel are to be reported to VAERS; typically, reporting to VAERS is performed by preventive medicine personnel.

VAERS is a passive system; therefore, underreporting, reporting bias, and the lack of a denominator (i.e., the total number of persons exposed or vaccines administered) create analytic challenges for epidemiologic studies. The estimation of true rates of vaccine-induced serious adverse events and the detection of small to moderate differences in the capacity of individuals to react to different vaccine lots are not feasible with the VAERS system. Establishment of causal relationships between vaccines and most types of adverse events is rarely feasible from the data.

## MEDWatch: The FDA Medical Products Reporting Program

MEDWatch was established in June 1993 to gather information on serious adverse events following the administration of drugs and biologics and on problems with medical devices regulated by FDA (Kessler, 1993). This system is managed by FDA.

TABLE 3-2 VAERS Reports in Adults

| Vaccine | No. of Reports |
|---|---|
| Hepatitis B virus | 8,168 |
| Influenza virus | 4,447 |
| Tetanus, diphtheria | 2,307 |
| Mumps, measles, rubella | 1,336 |
| Pneumococcus | 1,196 |
| Other | 2,380 |
| Total reports | 19,135 |

NOTE: Multiple vaccines may be named in a single report. VAERS = Vaccine Adverse Event Reporting System.

### Objective of and Data in MEDWatch

The objectives of MEDWatch are to facilitate the voluntary reporting of serious adverse events and problems with drugs, biologics, and medical devices; to continue monitoring the safety of new drugs and devices; and to aid in the detection of previously unrecognized reactions.

The form used in MEDWatch is one page long, and the following primary data are included in this system: patient information (age, sex, and weight), adverse event, date of adverse event, description of adverse event, other relevant patient history, results of relevant tests, description of suspect medication or device, and reporter information. The patient's identity, if provided, is held in the strictest confidence by FDA. The reporter's identity may be shared with the manufacturer unless requested otherwise. However, the reporter's identity is not released to the public.

### Source of Information in MEDWatch

The information to MEDWatch is supplied directly by physicians, pharmacists, nurses, and any other professionals working in health facilities or industries where drugs and medical devices are used and manufactured. This is in contrast to VAERS, which receives the majority of its reports from manufacturers (who are mandated to submit any reports that they receive from the medical community and from patients).

### Strengths and Limitations of MEDWatch

As with the VAERS system, the strengths of MEDWatch include the ability to detect a large number of serious adverse events whose similarities would normally remain undetected and the ability to recognize reactions that were not previously observed in newly marketed drugs. Limitations include the fact that this is a passive system, which can lead to underreporting, reporting bias, and the inability to determine a denominator (i.e., the total number of persons exposed or drugs administered). The ability to estimate the true rates of drug-induced serious adverse events and to establish a causal relationship is extremely limited with this passive system.

### Postmarketing Pharmaceutical Surveillance

The FDA's involvement in postmarketing drug surveillance includes: monitoring approved drug use, monitoring the occurrence of serious adverse drug events associated with the use of approved drugs, and initiation of selected epidemiologic studies to estimate risk or test specific hypotheses (Arrowsmith-Lowe and Anello, 1994). Drug manufacturers are required to report adverse drug events that they are aware of, largely through spontaneous reporting from physicians and pharmacists, to the FDA (Kessler, 1993). In addition to conducting analyses of reported adverse drug events, the FDA supports a number of cooperative agreements to provide it with access to data on the safety of pharmaceuticals, including vaccinations. In general, the FDA's approach to postmarketing surveillance requires a variety of data sources, including the use of large, linked databases. However, it is noteworthy that the FDA lacks regulatory authority to require postmarketing or Phase 4 studies for approved drugs. The efforts of the FDA are often augmented by studies performed on a voluntary basis by pharmaceutical companies and, in some cases, academic and health care delivery organizations.

## SUMMARY OF STRENGTHS AND LIMITATIONS OF CURRENT SURVEILLANCE TOOLS

The surveillance tools currently available to the military comprise a series of potentially linkable automated databases (Grabenstein et al., 1992). Opportunities for creating automated multipurpose databases have already been seized, with the Army Medical Surveillance Activity and the USPDP being two examples. Additional opportunities to create linked databases remain, a fact recog

nized in the planning for the triservice Defense Medical Epidemiology Database.

In general, the strength of these large databases is their outcome data, and their limitation is their exposure data, with prescription drug data being the exception. Data on the use of nonprescription drugs are not available, and vaccine data are not captured. No chemical and environmental exposure databases like the ones described above exist, but in some instances such databases are being created after the fact (see Chapter 5).

Although the availability of computerized diagnoses has been considered a strength of the automated databases described above, there is an accompanying, underlying weakness as well. The process of coding medical information in itself can change that information. Frequently, sentinel events will be harder to recover from a system once they have been coded. For example, the process of coding can inappropriately group together medical conditions, combining, say, 3 sentinel cases and 30 unimportant cases in a single general category. Although this does not preclude the use of automated diagnosis information as an alerting mechanism, it makes meaningful surveillance much more difficult. Because newly discovered interactions are not likely to mimic exactly previously described disease, and may indeed have unique presentations, the successful use of surveillance data to monitor interactions depends on problem recognition as well as reporting. Once a decision has been made to follow up some series of sentinel events, it may well be necessary to secure additional information on such cases by returning to hard-copy records for the appropriate level of detail. Finally, medical coding conventions lag behind developments in medical science and practice, so that the diagnoses that one may wish to retrieve from a system may not yet be available in coded form.

Given the inherent difficulties in identifying and confirming unknown interactions, the use of surveillance tools cannot ensure success. However, the current surveillance systems—with an expanded list of reportable conditions, additional linking of databases, and additional sentinel data from relevant civilian systems—can provide sentinel-event reporting for further investigation by the military. Furthermore, they represent one of the few practical ways to approach the problem of interactions.

# 4

# Strategy for Identifying and Dealing with Interactions

Although the committee clearly sees the value of investigations of the entire dose-response surface, that is, of all the responses to all the combinations of all the agents to which military personnel might be exposed (see discussion in Chapter 1), the virtually infinite number of interactions of the many drugs, biologics, and chemicals makes it practically impossible to study and define all of them at once. Because of this it is not feasible to predict and eliminate all potentially adverse interactions. Therefore, the committee urges that studies be focused on those interactions that are likely to occur, that may compromise military unit or individual effectiveness, or, although rare, that may cause severe consequences. Although numerous schemes to categorize such interactions can be devised, the committee chose to categorize interactions in three ways: (1) those which are *known* from properly conducted and documented human investigations; (2) those which may be *potential* because of the individual characteristics of the agents, such as their known target organ toxicities, pharmacokinetics, or mechanisms of action in animals or other nonhuman systems; and (3) those which, given the present state of understanding, are *unknown.*

The committee proposes using these three categories to facilitate study, discussion, and action. To place various combinations of agents into one of the categories, the committee proposes constructing and then using a matrix (described later in this chapter). Finally, the committee proposes planning a research agenda in tiers, by category, using surveillance, toxicology, and epidemiology tools and approaches. Table 4-1 illustrates the varied research

approaches based on the three categories. Chapter 5 gives details of the tiered approach.

## KNOWN INTERACTIONS

Only a relatively small number of the total number of possible interactions of various agents have been studied. Examples include protein binding displacement interactions (Udall, 1974); the interaction of acetaminophen and ethanol (McClain et al., 1980); and the role of the hepatic cytochrome P450 enzyme system in metabolizing compounds, thereby modulating their pharmacokinetics or organ toxicities (Levy and Bajpai, 1995). An example of military medicine drawing on current knowledge of interactions in its decisions is its procedures concerning vaccines. Live vaccine is not given soon after the administration of another live vaccine because of known interference with effectiveness; multiple live vaccines are given either concurrently or separated by more than 30 days.

Various strategies have been devised to alert decisionmakers to known interactions and to reduce the risk of such interactions. However, it is reasonable to assume that military operational requirements may necessitate the use of those substances that are known to result in increased toxicity on the basis of a significant positive risk-benefit ratio. For example, troops in the Balkans during the spring-summer season wore permethrin-impregnated uniforms and topically applied DEET to exposed skin when tick-borne encephalitis posed a significant hazard. In such instances, surveillance to detect, minimize, or prevent progressive toxicity should be established.

TABLE 4-1 Categorical Approach

| Interaction Type | Recommended Approaches |
|---|---|
| Known | • Avoid unless benefit outweighs risk<br>• Use surveillance to monitor outcomes and implement appropriate intervention<br>• Study in depth |
| Potential | • Use matrix approach to predict or identify the interaction<br>• Conduct studies (in vitro, animal, or human volunteer)<br>• Use surveillance |
| Unknown | • Put in place surveillance systems to detect sentinel events and do follow-up studies<br>• Do prospective screening studies of important combinations |

## POTENTIAL INTERACTIONS

Some potential interactions, although not yet defined, can be suspected on the basis of similar target organ toxicities, toxicokinetic patterns, pharmacokinetics, or pharmacodynamics. Building on its understanding of the literature on interactions, in which agents X and Y have been shown to manifest common toxicities, toxicokinetics, or mechanisms of action, the committee recommends the development and use of a matrix system to identify potential but untested interactions. Examples of such matrices are provided in Table 4-2 and Table 4-3. The outline of the matrix is formed by listing the drugs, biologics, and chemicals to which troops may be exposed on one axis and listing known target organ toxicities, mechanisms of action, and toxicokinetic properties on the other. Then, for each row and column, the particular properties of the agent are entered. For example, fluoroquinolones and acetylcholinesterase inhibitors both express neurotoxic effects.

Once the matrix has been generated, one may look down the columns and identify commonalities between agents that may predispose them to interact. For example, the common neurotoxicities of permethrin and DEET suggest that they may interact (Table 4-2).

Table 4-3 demonstrates how a matrix could operate in assessing various classes of agents (e. g., antiparasitic or antidiarrheal agents) for overlapping sites of action or toxicities. When fully developed, these cross-comparison matrices should permit a more focused approach to the consideration of the potential interactions of multiple agents. For example, agents that express neurotoxic effects, such as fluoroquinolones and the acetylcholinesterase inhibitors (i.e., pyridostigmine) or Japanese encephalitis virus vaccination (Piesner et al., 1996), might be suspected of demonstrating interactive neurotoxicities. Moreover, new knowledge about the liver cytochrome P450 isozymes, enzymes involved in the metabolism of chemicals, may enable prediction of such interactions.

The matrix approach described in this chapter would serve as a screening step. Determining that toxic interactions between combinations of agents actually occur requires appropriate in vitro, animal toxicity, human volunteer, or epidemiologic studies for validation. Identification of potential interactions using available methodologies, including the matrix, could prompt the initiation of assessment programs (see Chapter 5). Once alerted to potential interactions, decisionmakers can prioritize studies of the potential interactions that could cause severe health consequences or impair troop effectiveness, or studies of the agents to which large numbers of individuals will be exposed. Continued improvement and updating of such a matrix is expected to further enhance its utility and validity.

The committee emphasizes that this approach is just one practical method that can be used to grapple with a difficult subject; there are no completely fail

safe methods. Even if it were possible to study all combinations of agents in epidemiologic or animal model systems, it is unlikely that such a strategy would work. Many confounding factors would be encountered in epidemiologic studies; for example, host susceptibility factors such as age, race, sex, and comorbid conditions could affect the results. In the case of experimental studies, although randomization minimizes the effects of confounding variables, there remain the problems of multiple comparisons and sample size considerations.

Finally, although epidemiologic studies are more likely to involve exposures of humans to mixtures of chemicals or other toxic agents and could thus provide a more reliable basis for risk assessment than toxicologic studies with animals, epidemiologic data are rarely available for the specific mixtures of agents and exposure situations of interest. Thus, the committee proposes an additional series of prospective animal toxicity studies (Chapter 5).

## UNKNOWN INTERACTIONS

Despite a thorough literature review and the development and use of a matrix such as the one proposed by the committee, unpredictable interactive toxicities are certain to occur. The unpredictable and severe toxicities of thalidomide, benoxaprofen, temafloxacin, and FIAU/FIAC (Fialuridine) used as single agents provide such examples (Strom, 1994). Even less predictable toxicities should be expected when complex mixtures of agents are used together. Early identification of such unusual or unpredictable events will require the use of a variety of toxicologic and epidemiologic tools. The surveillance tools that are required to investigate hitherto unknown interactions and that are currently available to the military were described in Chapter 3. Chapter 5 expands the discussion to specific toxicology and epidemiology approaches.

TABLE 4-2 Organ Toxicities, Pharmacodynamic, and Pharmacokinetic Properties of Drugs, Biologics, Chemicals, Recreational Substances, and Environmental Factors to Which Deployed U.S. Military Personnel May Be Exposed

| Class of Agent | Specific Agent | Site of Action or Toxicity | Pharmacodynamic or Pharmacokinetic Characteristics |
|---|---|---|---|
| Smokes, obscurants | Diesel fuel | Airways | |
| | Fog Oil | Airways | |
| | Red phosphorous | Airways | |
| | Hexachlorethane | Airways | |
| | Zinc chloride | Airways | |
| | Titanium dioxide | Airways | |
| Riot control agents* | CN (mace) | Mucous membranes (eyes, nose, mouth, lung), skin | |
| | CS (*O*-chlorobenzylidene malonitrile) | Mucous membranes (eyes, nose, mouth, lung), skin | |
| Chemical warfare weapons* | *Nerve agents:* GA (tabun), GB (sarin), GD (soman), GF, VX | CNS, lung | Cholinesterase inhibitor (butyrylcholinesterase, acetylcholinesterase) |
| | *Vesicants:* HD (distilled mustard), HL (mustard-lewisite mixture), HT (mustard-T mixture) | Skin, airways, eyes, CNS (poorly defined) | DNA alkylation and cross-linking in rapidly dividing cells |
| | *Cyanide:* AC (hydrogen cyanide), CK (cyanogen chloride) | CNS, heart | Binds to $Fe^{3+}$, inhibits cytochrome, prevents intracellular oxygen utilization |
| | *Pulmonary agents:* CG (phosgene), PFIB (perfluoroisobutylene: pyrolysis of Teflon) | Lung | Acylation of cells at alveolar-capillary membranes with pulmonary edema |

| | | | |
|---|---|---|---|
| Biologics/ vaccines | *Live-attenuated vaccines, routine*<br>Adenovirus types 4 and 7<br>Measles, mumps, rubella<br>Poliovirus, oral<br>Typhoid<br>Varicella-zoster virus (Vaccina virus)<br>Killed vaccines, routine Tetanus, diphtheria<br>Hepatitis A and B viruses<br>Influenza virus<br>Menigococcal (groups A, C, Y, and W-135)<br>Area of operation-specific vaccines, killed Cholera<br>Japanese encephalitis<br>Plague<br>Rabies<br>Yellow fever<br>Tick-borne encephalitis<br>Biological weapon vaccines<br>Anthrax<br>Botulinum<br>Immunoglobulins<br>Serum immune globulin<br>Hepatitis B virus Ig<br>Rabies IG | None recognized<br>None recognized<br>CNS<br>None recognized<br>Skin (liver)<br>Skin<br>None recognized<br>None recognized<br>None recognized<br>None recognized<br>None recognized<br>Anaphylaxis (rare), CNS<br>None recognized<br>None recognized<br>CNS<br>None recognized<br>None recognized<br>None recognized<br>CNS<br>None recognized<br>None recognized | Paralysis, 1:2,000,000<br>Varicella-zoster virus-like rash (5%); Reye syndrome occurs with varicella-zoster virus infection and aspirin; not reported with vaccine, but warning to avoid aspirin for 2 weeks after vaccination<br>Large intravenous doses, aseptic meningitis |

| | | | |
|---|---|---|---|
| Drugs, commonly used, prescription | NSAIDS | CNS, renal, gastrointestinal | Dizziness, headache (>3%), aseptic meningitis (<1%) |
| | Antibiotics, oral | Multiple organs, depends on specific agent | Induce cytochrome P450 enzymes |
| | Analgesics | Airways | Blocks absorption of some oral antibiotics |
| | Decongestants | Liver, skin | Induce cytochrome P450 enzymes |
| | Antihistamines | None at usual dosage | |
| | Contraceptives, oral | None at usual dosage | |
| | Vitamins | Liver | |
| | Iron | | |
| | Antifungal agents (oral) | | |

| | | | |
|---|---|---|---|
| Drugs, area of operation, for prophylaxis (P) or therapy | *Antimalarial agents* | CNS, hematologic | GABA inhibitors, liver failure |
| | Chloroquine (P) | Hematologic, | Induce cytochrome P450 enzymes |
| | Primaquine (P) | CNS, cardiac, central cholinergic system | Concentrated in fat; acute CNS toxicity |
| | Mefloquine (P) | CNS, cardiac | Induces cytochrome P450 enzymes |
| | Halofantrine | Cardiac, CNS | Pseudocholelithiasis |
| | Doxycycline (P) | Skin, liver, CNS | |
| | Quinine, quinidine | Ototoxicity, CNS | |
| | Artemisins | Cardiac | |
| | *Antidiarrheal agents* | CNS, musculoskeletal, liver | |
| | Fluoroquinolones (ciprofloxacin) | Skin, CNS | |
| | Trimethoprim-sulfamethoxazole | Skin | |
| | Loperamide | Liver | |
| | Atropine sulfate-diphenoxylate (Lomotil) | None recognized | |
| | | Liver | |
| | | Renal | |
| | *Antifungal agents* | None recognized | |
| | Topical | CNS, skin | |
| | Azoles (oral) | Skin, CNS | |
| | *Antiviral agents* | Liver, hematologic | |
| | Acyclovir | CNS, liver | |
| | Ribavirin (intravenous) | CNS | |
| | *Antiparasitic agents* | CNS | |
| | Metronidazole | Skin | |
| | Trimethoprim-sulfamethoxazole | Skin | |
| | Mebendazole | Skin, liver | |
| | Praziquantel | Skin, CNS | |
| | Ivermectin | CNS, skin | |
| | Permethrin cream | CNS, skin | |
| | *Antibacterial agents* | Skin, liver | |
| | Penicillin V (oral) | Skin, liver | |
| | Amoxicillin (oral) | | |
| | Cephalexin (oral) | | |
| | Erythromycin (oral) | | |
| | Trimethoprim-sulfamethoxazole (oral) | | |
| | Clindamycin | | |
| | Metronidazole (oral) | | |
| | Ceftriaxone (intramuscular, intravenous) | | |
| | Doxycycline (oral) | | |

| | | | |
|---|---|---|---|
| Drugs, anti-biological warfare | Fluoroquinolone (ciprofloxin) | CNS, musculoskeletal, liver | |
| Drugs, chemical warfare prophylaxis and treatment | Pyridostigmine | Nervous system | A cholinesterase inhibitor |
| | Atropine | Skin (decreased sweating) | An anticholinergic agent |
| | Pralidoxime chloride | — | Breaks the nerve agent–enzyme bond |
| | Diazepam | CNS | Anticonvulsant |

| | | |
|---|---|---|
| Recreational drugs | Caffeine (coffee, soft drinks) | CNS |
| | Nicotine (smokeless tobacco) | CNS |
| | Alcohol | Liver |
| Occupational exposures | Noise | Ototoxicity |
| | Carbon monoxide | Ototoxicity |
| | Exercise | Musculoskeletal |
| | Heat | Musculoskeletal, CNS, liver |
| | Cold | Skin, musculoskeletal |
| Insect repellants | DEET | CNS |
| | Permethrin | CNS |

NOTE: CNS = central nervous system; Ig = immunoglobulin; NSAIDs = nonsteroidal anti-inflammatory drugs; and GABA = -aminobutyric acid.

*Identified using standard military terminology for chemical agents (see Chemical Casualty Care Office, 1995).

**TABLE 4-3** Potential Interactions of Drugs, Biologics, Chemicals, Recreational Substances, and Environmental Factors

| | Chemical Agents | | | | | |
|---|---|---|---|---|---|---|
| Site of Action, Toxicity | Smokes, Obscurants | Riot Control Agents | Nerve Agents | Vesicants | Cyanide | Phosgene, PFIB |
| Nervous system (central, peripheral) | | | + | ? | + | |
| Ototoxicity | | | | | | |
| Mucous membranes, conjunctiva | | + | | + | | |
| Airways, lungs | + | + | + | + | | + |
| Cardiac | | | | | + | |
| Cutaneous, skin | | + | | + | | |
| Hepatic | | | | | | |
| Renal | | | | | | |
| Musculoskeletal | | | | | | |
| Hematologic, lymphoid | | | | | | |
| Immunologic | | | | | | |
| Gastrointestinal | | | | | | |
| Reproductive, endocrine | | | | | | |

NOTE: PFIB = perfluoroisobutylene (Teflon pyrolysis); NSAIDs = nonsteroidal anti-inflammatory drugs; beta-lactams are penicillin and cephalosporin; "+" denotes that the specified agent is active at the specified site. "?" denotes that the association of agent and site is ill-defined.

**TABLE 4-3** *Continued*

| | Vaccines | | | | |
|---|---|---|---|---|---|
| Site of Action, Toxicity | Live Attenuated, Routine | Killed, Routine | Area-of-Operation Specific | Biological Weapons-Specific | Immuno-globulins |
| Nervous system (central, peripheral) | + | | + | | + |
| Ototoxicity | | | | | |
| Mucous membranes, conjunctiva | | | | | |
| Airways, lungs | | | | | |
| Cardiac | | | | | |
| Cutaneous, skin | + | | | | |
| Hepatic | + | | | | |
| Renal | | | | | |
| Musculoskeletal | | | | | |
| Hematologic, lymphoid | | | | | |
| Immunologic | | | | + | |
| Gastrointestinal | | | | | |
| Reproductive, endocrine | | | | | |

**TABLE 4-3** *Continued*

| | Commonly Used Prescription Drugs | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Site of Action, Toxicity | NSAIDs | Anti-biotics | Anal-gesics | Decon-gestants | Antihista-mines | Contracep-tives, Oral | Vitamins | Iron | Antifungal, Agents, Oral |
| Nervous system (central, peripheral) | + | + | | | | | | | |
| Ototoxicity | | + | | | | | | | |
| Mucous membranes, conjunctiva | | | | | | | | | |
| Airways, lungs | | | | | + | | | | |
| Cardiac | | | | | | | | | |
| Cutaneous, skin | | + | | | | + | | | |
| Hepatic | | + | | | | + | | | + |
| Renal | + | + | | | | | | | |
| Musculoskeletal | | + | | | | | | | |
| Hematologic, lymphoid | | + | | | | | | | |
| Immunologic | | | | | | | | | |
| Gastrointestinal | + | + | | | | | | | |
| Reproductive, endocrine | | | | | | + | | | + |

**TABLE 4-3** *Continued*

| | Antimalarial Agents | | | | | | |
|---|---|---|---|---|---|---|---|
| Site of Action, Toxicity | Chloroquine | Primaquine | Mefloquine | Halofantrin | Doxycycline | Quinine | Artemisins |
| Nervous system (central, peripheral) | + | + | + | + | + | + | |
| Ototoxicity | | | | | | + | |
| Mucous membranes, conjunctiva | | | | | | | |
| Airways, lungs | | | | | | | |
| Cardiac | | + | + | + | | | + |
| Cutaneous, skin | | | | | + | | |
| Hepatic | | | | | + | | |
| Renal | | | | | | | |
| Musculoskeletal | | | | | | | |
| Hematologic, lymphoid | + | + | | | | | |
| Immunologic | | | | | | | |
| Gastrointestinal | | | | | | | |
| Reproductive, endocrine | | | | | | | |

**TABLE 4-3** *Continued*

| | Antidiarrheal Agents | | | | Antiviral Agents | |
|---|---|---|---|---|---|---|
| Site of Action, Toxicity | Fluoroquinolones | Trimethoprim-sulfamethoxazone | Loperamide | Lomotil | Acyclovir | Ribavirin |
| Nervous system (central, peripheral) | + | + | | | | |
| Ototoxicity | | | | | | |
| Mucous membranes, conjunctiva | | | | | | |
| Airways, lungs | | | | | | |
| Cardiac | | | | | | |
| Cutaneous, skin | | + | + | | | |
| Hepatic | + | | | + | | |
| Renal | | | | | + | |
| Musculoskeletal | + | | | | | |
| Hematologic, lymphoid | | | | | | |
| Immunologic | | | | | | |
| Gastrointestinal | | | | | | |
| Reproductive, endocrine | | | | | | |

**TABLE 4-3** *Continued*

| | Antiparasitic Agents | | | Insert Repellants | |
|---|---|---|---|---|---|
| Site of Action, Toxicity | Metroni-dazole | Meben-dazole | Praziquante | Permethrin | DEET |
| Nervous system (central, peripheral) | + | | + | + | + |
| Ototoxicity | | | | | |
| Mucous membranes, conjunctiva | | | | | |
| Airways, lungs | | | | | |
| Cardiac | | | | | |
| cCutaneous, skin | + | | | | |
| Hepatic | | + | + | | |
| Renal | | | | | |
| Musculoskeletal | | | | | |
| Hematologic, lymphoid | | + | | | |
| Immunologic | | | | | |
| Gastrointestinal | | | | | |
| Reproductive, endocrine | | | | | |

**TABLE 4-3** *Continued*

| | Antibacterial Agents | | | Nerve Agents | | |
|---|---|---|---|---|---|---|
| Site of Action, Toxicity | Beta-Lactams | Erythro-mycin | Clinda-mycin | Pyridostig-mine | Atropine | Pralidoxime |
| Nervous system (central, peripheral) | | | + | + | | |
| Ototoxicity | | | | | | |
| Mucous membranes, conjunctiva | | | | | | |
| Airways, lungs | | | | | | |
| Cardiac | | | | | | |
| Cutaneous, skin | + | + | + | | + | |
| Hepatic | | + | | | | |
| Renal | | | | | | |
| Musculoskeletal | | | | | | |
| Hematologic, lymphoid | | | | | | |
| Immunologic | + | + | | | | |
| Gastrointestinal | | | | | | |
| Reproductive, endocrine | | | | | | |

**TABLE 4-3** *Continued*

| | Miscellaneous Agents | | | | |
|---|---|---|---|---|---|
| Site of Action, Toxicity | Caffeine | Nicotine | Alcohol | Noise | Carbon Monoxide |
| Nervous system (central, peripheral) | + | + | | | |
| Ototoxicity | | | | + | + |
| Mucous membranes, conjunctiva | | | | | |
| Airways, lungs | | | | | |
| Cardiac | | | | | |
| Cutaneous, skin | | | | | + |
| Hepatic | | | + | | |
| Renal | | | | | |
| Musculoskeletal | | | | | |
| Hematologic, lymphoid | | | | | |
| Immunologic | | | | | |
| Gastrointestinal | | | | | |
| Reproductive, endocrine | | | | | |

# 5

# The Study and Management of Interactions

This chapter suggests procedures and research strategies that can be used by the military to investigate potential interactions (based on the matrices proposed in Chapter 4), manage known interactions, and conduct the necessary research to identify and study unknown interactions. The suggested procedures and research strategies involve the use of civilian systems that are already in place, the increased computerization of military and VA records to monitor both exposures and outcomes, increased linkages between databases, and careful design and conduct of experimental and epidemiologic studies.

## KNOWN INTERACTIONS

The completed matrices, described in Chapter 4, will display known interactions. These adverse health effects then can be avoided or studied to identify ways to minimize them. Although the best way to manage known adverse interactions would be to avoid them, in practice this often proves to be unattainable because (1) the mechanisms for avoidance that are in place are less than perfect, (2) there may be environmental factors beyond human control, and (3) there may be circumstances in which the benefits anticipated from the use of particular combinations of agents significantly outweigh the risks.

Mechanisms of avoidance currently in place include “Dear Dr.” letters alerting physicians and pharmacists of adverse interactions and notices from the FDA and drug manufacturers. Patients can also be alerted by reading the fact sheets for prescribed drugs. In addition, most pharmacies in the United States

today use computerized systems to keep records. Drugs with known adverse interactive effects are flagged in these systems so that when a prescription for one of these drugs is filled, the pharmacist is alerted to check for concomitant use of the other drugs that are known to interact with that drug adversely. The fact that these mechanisms are not fail-safe is documented in a recent report (Thompson and Oster, 1996) describing the concomitant or overlapping prescription of terfenadine, a nonsedating antihistamine, with macrolide antibiotics or the imidazole antifungal agent ketoconazole.

Just as in the civilian sector, it behooves the military to develop systems that can be used to avoid or minimize the prescription of drugs with known interactions. The Uniformed Services Prescription Database Project (USPDP) (see Chapter 4) provides a system that could be used to flag known drug interactions within the military pharmacy system. To be useful during military deployments, prescribed drugs must also be entered prospectively into the computerized system so that interactions can be identified during deployment. Adding biologics, including vaccines, immunoglobulins, and immune diagnostic agents (e.g., tuberculin skin tests), to the database, as the USPDP has proposed, would produce a multipurpose tracking system by allowing drug-drug and drug-other agent interactions to be flagged.

In some instances the use of drugs with known interactions cannot be avoided during military deployments. In these instances of unavoidable exposures to known interactions, the military should carefully study the exposure-effects relationships so that adverse effects can be minimized in the future.

Systematic postdeployment studies of known interactions will provide the necessary data to determine how to minimize adverse effects in training situations and possibly in future deployments. Those surveillance systems in use or in development within the U.S. military (e.g., the Individual Patient Data System, the Army Medical Surveillance Activity, the USPDP, etc.; see Chapter 4) can be used to accomplish this task.

## POTENTIAL INTERACTIONS

Potential interactions (see Chapter 3) that are identified as high priorities for study can be actively investigated in experimental in vitro and in vivo systems as well as with experimental and observational studies with human volunteers. The procedures for investigation could be, in general, similar to those used by regulatory agencies (e.g., FDA and the Environmental Protection Agency [EPA]). To conserve resources, a tiered approach would be useful. For example, identification of a potential hazard can first be accomplished in appropriately chosen in vitro systems. Studies can then be extended to in vivo animal models with appropriate species and experimental designs.

Depending on the information uncovered, the experimental designs of animal toxicity studies may vary from simple to increasingly complex studies to address the issues of dose-response relationships as well as the suitability for extrapolation to the assessment of risk in humans. If early experimental studies of a combination show clear toxicity or reduced efficacy, the agents in the combination can then be considered to have a known adverse interaction (see below), and their simultaneous use should be avoided if possible. If they are used in military operations, individuals taking them should be monitored, if necessary. If early experimental studies show minimal toxicity and little or no decrease in efficacy with the use of the combination, human volunteer studies similar to early phase drug development trials (e.g. FDA Phase I drug development trials; 21 CFR 312.21) may be warranted.

The procedures for studying potential interactions proposed by the committee are expensive. Realistically, only high-priority interactions can be studied as described above. Other combinations of agents that could interact but that need to be used by the military should be monitored by the same procedures recommended for monitoring known interactions (see below).

To demonstrate the utility of the tiered approach, the study conducted by Abou-Donia et al. (1996), which investigated the interaction of pyridostigmine bromide (PB), DEET, and permethrin, is used as an example. In that study, neurotoxicity was produced in chicken hens exposed to these agents individually or simultaneously (exposure for 5 days/week for 2 months to 5 mg of PB per kg of body weight per day in water, given orally, 500 mg of DEET neat per kg/day given subcutaneously, and 500 mg of permethrin in corn oil per kg/day given subcutaneously). At these dosages exposure to single compounds resulted in minimal toxicity. Combinations of two or more agents produced greater neurotoxicity than that caused by individual agents.

Although the findings of the study by Abou-Donia et al. (1996) are interesting, certain issues must be further investigated before such information can be applied directly to the assessment of risk in humans. For example, the dose-response relationship must be defined, since only one dosage was used. One of the chemicals studied, permethrin, was given subcutaneously at 500 mg/kg/day in corn oil. According to a recent National Research Council report (1994a) entitled *Health Effects of Permethrin-Impregnated Army Battle-Dress Uniforms,* the estimated exposure dose to a soldier in the Persian Gulf War was $6.8 \times 10^{-4}$ mg/kg/day. This represents a 7,352,941-fold lower dose than that used in the study of Abou-Donia et al. (1996). A reasonable question is, would an interaction be seen at realistic human exposure levels?

Applying the committee's tiered approach (see below), the study of AbouDonia et al. (1996) should be expanded and repeated to include a range of doses, preferably including doses low enough to be representative of human exposure levels. Once such dose-response relationships are defined, the information can

be used to help interpret the results of retrospective studies with soldiers deployed in the Persian Gulf War.

## UNKNOWN INTERACTIONS

Given the array of substances (some predictable, some not) to which deployed military personnel are exposed, unanticipated adverse effects are likely. It is to the military's advantage to identify these so that the agents' use can be minimized to the extent possible. The research elements needed to identify unanticipated adverse effects include an enhanced emphasis on toxicological screening studies focused on interactions and an increased surveillance in epidemiologic settings. With regard to surveillance, the identification of sentinel cases may indicate rare reactions to single agents as well as unpredictable or unusual interactions among multiple compounds. Such sentinel cases may be severe and may well provide unique insights into the pathobiologic properties of the various agents and their interactions. If identified, sentinel cases should be subjected to thorough investigation to elucidate the nature and meaning of the interaction.

### Toxicologic Screening

#### Experimental Approach

In toxicology, *interaction* is a general term that has been applied to toxicity test results that deviate from the additive behavior of the dose or the response expected on the basis of the dose-response curves obtained for individual agents. The term *synergism* is used when the results are greater than would be anticipated from the simple addition of doses or responses. *Antagonism* is a situation in which the response is less than that which would be predicted on the basis of a simple addition of doses or responses. *Potentiation* has been used to characterize synergistic effects that occur when one component of the mixture has no effect by itself but is capable of enhancing the effect of a second component in the mixture. *Additivity* is used for the situation in which the combined effect of the components of a mixture is equal to the sum of the effects of each agent given alone. Furthermore, one chemical may enhance or antagonize the effect of another chemical in a simple mixture but exhibit different effects in a complex mixture or when given by different routes, and it is well recognized that chemicals with different modes of action may exhibit nonadditive interactions.

Although epidemiologic studies are more likely than toxicologic studies with animals to involve exposures of humans to mixtures of chemicals or other

toxic agents and could thus provide a more reliable basis for risk assessment, epidemiologic data are rarely available for the specific mixtures of agents and the exposure situations that are of interest. Moreover, although laboratory animal studies are not infallible, the principle set forth by the International Agency for Research on Cancer and endorsed by the U.S. Office of Science and Technology Policy (1985) is that "in the absence of adequate data on humans, it is reasonable, for practical purposes, to regard chemicals for which there is sufficient evidence of carcinogenicity in animals as if they presented a carcinogenic risk in humans." Therefore, in this section of the report, a general approach and rationale for conducting animal toxicity studies with a core mixture of compounds (i.e., the major drugs, biologics, and chemicals that are to be given to deployed U.S. military personnel) are proposed.

The assumption that doses of different agents can be treated as roughly additive in producing a response appears to be reasonably consistent with the experimental evidence on the joint actions of chemicals in mixtures (National Research Council, 1994b), and the low incidence of synergism in the EPA Database on Toxic Interactions supports the use of the assumption of additivity in mixtures. Fewer than 3 percent of the 331 studies in the database (which contains data on more than 600 chemicals) showed clear evidence of synergism (U.S. Environmental Protection Agency, 1988). A similar low incidence of synergistic responses was observed by a committee of the National Research Council (1988) and by Krishnan and Brodeur (1991). However, most of these studies examined the interactions of only two compounds, and few of them examined long-term effects.

Ideally, for the most complete assessment of the potential interactions of drugs, biologics, and chemicals in U.S. military forces, a process such as the following should be adopted. Different regions of the world should be characterized according to weather and geographic conditions; ecosystems; abundance of plant, animal, and microbial species; prevalence of diseases; possible anthropogenic pollutants; and other environmental conditions. Within each region, a list of the potential dangers that military personnel might face regarding possible exposures to warfare agents, chemicals, environmental and physical stresses, diseases, pests, prophylactic drugs, biologics, and so on should be compiled and analyzed. Then, under the climatic conditions of each of these regions, animal studies should be carried out to detect at least the four major toxicity categories (i.e., immunotoxicity, developmental and reproductive toxicity, neurotoxicity, and carcinogenicity).

However, to conserve resources and as a starting point, the committee suggests the following prototype experiment with the understanding that more specific scenarios may be incorporated into the experimental design of subsequent studies as needed. At a minimum, the following combination exposure scenarios should be studied for each of the toxicities mentioned above:

1. the complete combination: drugs, biologics, and chemicals whose use is anticipated;
2. drugs whose use is anticipated;
3. biologics whose use is anticipated;
4. chemicals to which exposure is anticipated; and
5. controls.

The doses of each entity to be used in animal studies should be the anticipated level of exposure to the soldiers (on a milligram-per-kilogram, millimole-per-kilogram, or units-per-kilogram basis), which would be the baseline study dose, plus two other dose levels (10 times and 100 times this baseline dose).

This recommendation may be considered a first tier screening for possible adverse health hazards. Any toxicologic interaction detected within any of the groups should be a warning flag to DoD, and a decision must be made with respect to the risks and benefits involved in using the agents. Beyond this first tier, any additional studies should be on a case-by-case basis, guided by the recommendations of an expert panel of investigators.

Some of the conventional toxicity testing protocols may not be applicable in these studies because they are either too expensive and resource-intensive or not sensitive enough with respect to toxic responses, or both. Therefore, there is a need for continuing refinement and improvement of experimental toxicology methodologies by using the latest advances in molecular biology and genetics and in computer sciences. For example, to deal more effectively with interactions, investigators can use and integrate state-of-the-art advances in (1) computational technology; (2) physiologically based pharmacokinetic and pharmacodynamic modeling; (3) model-directed, unconventional, focused, mechanistically based, short-term toxicology studies; and (4) other mathematical and statistical modeling tools.

An advance in the pharmacokinetic and pharmacodynamic modeling of chemical carcinogenesis is the expression, in terms of fundamental cell cycle kinetics and within the framework of a linear multistage model for cancer of events, of the character of the biological processes governing cell replication and cancer (El-Masri et al., 1996; Thomas et al., 1996). Physiologically based pharmacodynamic (PBPD) modeling can be and has been used to produce reasonable estimates of cancer incidences in exposed animals. To achieve this objective, the PBPD model will have to integrate the events of cellular injury, death, and division as well as mutational events in the cells that will lead to an increased rate of cellular proliferation. Other aspects of the PBPD model will have to delineate the events of the tissue in the resting state or under accelerated growth conditions, such as in neonatal animals or following chemical injury. Many of these biological processes also can be described in the model in terms of cell cycle kinetics.

The cell cycle portion of the model describes the events that lead the cells from one phase to the other. These cellular phases are the G0 (resting phase), G1 (a gap or pause after stimulation in which some biochemical activities are occurring), S (synthesis phase, particularly DNA synthesis), G2 (a second gap), and M (mitosis phase). The number of cells in each phase can be described by mass-balance equations. The mass transfer of cells from one phase to the other is related to the residence time of the cells in each phase. The mathematical construction of this cell cycle model can be incorporated into the PBPD model to reflect such events as the possible mutational effects of the chemicals and cell proliferation rates under a variety of conditions. Current developments in immunohistochemical staining as well as molecular biology techniques with factors (e.g., oncogenes, cytokines, and tumor suppressor genes) that are reported in the literature to influence the rates of various stages of the cell cycle may prove to be fruitful in the possible prediction of cancer in humans by allowing much more efficient experimental animal models. By comparing cell cycle kinetics in preneoplastic clones of cells (e.g., liver foci in Ito's system or foci in SHE cell transformation assays) and in surrounding normal cells, mechanistically based biomarkers may be identified, and these biomarkers can be used to demonstrate more sensitively the carcinogenic potentials of chemicals or chemical mixtures (El-Masri et al., 1996; Thomas et al., 1996).

Work can be done to improve animal models so that they might flag compounds that are human health hazards. Preventive measures then may be implemented. Work can also be done to develop more efficient, less costly, state-of-the-art experimental and computer model systems, which will also help to raise warning flags. Use of these experimental and computer model systems in conjunction with epidemiologic investigations will form a powerful approach to identifying and minimizing future potential health problems. Current research advances are such that the methodologies, animal models, and systems presently used will be continually challenged, improved, and refined. Therefore, it is important to be flexible and to be prepared to adopt the latest advances in biomedical research to improve and refine the preventive measures described in this report.

### Data Analytic Approach

In addition to animal toxicity studies, careful data analysis is also needed. Recent advances in statistical methodology, discussed below, allow for the efficient detection of interactions by making use of data from studies with single agents. These advances help to characterize quantitatively earlier qualitative work based on the interpretation of isobolograms.

In the simplest case of two agents, each of which produces a single response, one can plot in two dimensions the set of doses (x, y), where x is the dose of Agent 1 and y is the dose of Agent 2, that produces identical responses. The line connecting this set of doses is an isobole, and its graph is an isobologram (see Figure 1 in Machado and Robinson, 1994). Thus, an isobologram is analogous to a topographic map, in which identical responses correspond to identical elevations. In the simple two-agent case, the two-dimensional plot of isobolograms permits a simple, qualitative interpretation: a straight line is indicative of an additive effect of the two agents, that is, no interaction. A convex isobologram is evidence that the response from the combination of the two agents is less than the sum of their responses, which is an antagonistic interaction. A concave isobologram is evidence that the response from the combination of the two agents is greater than the sum of their responses, which is a synergistic interaction.

Combinations of more than two agents must be studied in higher-dimensional space, where lines become surfaces and straight lines become planar surfaces. In 1981, Berenbaum quantified and generalized the isobologram to higher dimensions and used it to detect and characterize interactions of a combination of drugs or chemicals, showing that the contours of the constant response of the dose-response surface are planar if the components of the combination have an effect that is additive. In direct analogy to the two-agent case, if the observed response to the combination is statistically greater than that predicted under additivity, it is concluded that a synergistic interaction has taken place. For increasing dose-response relationships, if the observed response to the combination is statistically less than that predicted under additivity, it is concluded that an antagonistic interaction has taken place. If there is no statistical difference between the response predicted under additivity and the response observed upon exposure to the combination, it can be concluded that the components of the combination do not interact. The logic of the approach outlined above was used by Finney (1964), Berenbaum (1985), and Kelly and Rice (1990), among others, to detect and characterize interactions involving combinations of agents.

The real strength of this approach is that relatively few data are required to implement it. Under the assumption of additivity, in particular, the estimated dose-response surface can be calculated from the dose-response curves for the single agents; such data are likely to be available as a result of earlier product development research. One then needs only to collect additional data on the results of exposure to the combination of interest at the specified doses of the constituents.

The required single-agent dose-response data are likely to include multiple control groups, one for each agent under study, especially if these data were collected from several studies. Ideally, such control data can be used to estimate

the background rate of response, although an important consideration is their proper inclusion in the analyses. If all of the single-agent control data are collected simultaneously, there should not be any problem combining them. However, when single-agent data are found in the literature or are collected at points in time that are remote to the time of collection of the combination data, then the problem is similar to the historical control problem discussed by Prentice et al. (1992). In extending earlier approaches, Gennings and Carter (1996) used a single parameter for the background (control) rate and developed a methodology that can be used to detect and characterize interactions by incorporating this parameter into the additivity model three different ways: as a fixed-effects parameterization, as a random-effects approach following Prentice et al. (1992), and as an approach involving the use of estimating equations (Liang and Zeger, 1986).

With suitable preclinical models, the methods described above can be extended from animal toxicology studies to human studies, permitting the design and analysis of prospective studies that can test directly the existence of interaction effects when evaluating the potential health consequences of exposure to combinations of drugs, vaccines, and chemicals. Again, it is possible that many of the single-agent data are already available as a result of the research done in evaluating the individual agents. Even if the existing single-agent data are not adequate, the approach outlined above is still efficient in that the experimental effort required is greatly reduced to the generation of single-agent dose-response curves and the responses at particular fixed-dose combinations. In the case of five agents, each to be studied at four doses plus the control level, for example, the number of experimental groups to be evaluated for response is 26 (i.e., $5 \times 5$ plus the one combination dose). In contrast, the complete set of experiments ($5^5$) requires the evaluation of response among 3,125 experimental groups.

If no interaction (departure from additivity) is detected by the above analyses, there may be no need to study the combination of agents further. If an interaction is detected, however, further studies may need to be done to identify which set of agents is responsible for the departure from additivity. Even if this is the case, the number of additional experiments should be less than the number of all possible combinations (see Narotsky et al., 1995, for an example of a full $5 \times 5 \times 5$ factorial study of three chemical compounds analyzed to detect the presence of all two-way and three-way interactions).

The approach for detecting interactions outlined above is directly applicable to the study of a particular complex mixture of biologics, chemicals, and drugs, as advocated earlier. Let $B$ represent a given combination of biologics, let $C$ represent a given combination of chemicals, and let $D$ represent a given combination of drugs. The complex mixture is represented by $B + C + D$. One set of experiments designed to provide data to be analyzed by the methodology described above determines responses to the following sets of exposures:

Control, $B + C + D$, 10 ($B + C + D$), 100 ($B + C + D$);
Control, $B$, 10$B$, 100$B$;
Control, $C$, 10$C$, 100$C$; and
Control, $D$, 10$D$, 100$D$.

The first set of exposures yields the combination agent data, and the next three sets yield the single-agent data for $B$, $C$, and $D$, respectively (National Research Council, 1988).

The methodology described above applies only to the class of linear models. Generalization of the methodology to include nonlinear models, often used in the assessment of risk to human populations, should be encouraged.

Despite the advantages of the above approach, it is not a fail-safe method for detecting all interactions. Therefore, it is necessary to use surveillance systems to supplement the information gathered by the above strategy.

## Surveillance

This section describes approaches to monitoring exposures, identifying adverse health events, and investigating disease-exposure relationships in military personnel. The suggested monitoring (described below) requires the development of large databases that can be expanded and used for many years. The process used to develop the database for the USPDP provides a model for database development and expansion. First, a small pilot study was done at one site to identify and solve the problems that arise in collecting and cataloging the data of interest. Then the pilot project was slowly extended. This same process of starting small with stepwise expansions seems to provide efficiency in the development of useful databases.

Gutthann and Garcia-Rodriguez (1993) provide an example of the use of a large linkable database to study the adverse health effects of combinations of drugs in a civilian setting. Using the databases from the Saskatchewan Health Plan, they studied the risk for hospitalization for liver injury associated with the interaction of nonsteroidal anti-inflammatory drugs and other hepatotoxic drugs and found that concomitant current exposure to two or more drugs increased the risk above what would be expected from the sum of the individual risks.

### Identifying and Recording Exposures

1. The first goal for monitoring exposures in deployed personnel is to have computerized records to identify personnel who were deployed and their dates of deployment and return. The location during deployment should be available at the unit level. A personnel location database (geographical identification sys

tem [GIS]) is being developed by DoD retrospectively for those deployed during the Persian Gulf War. The GIS will identify the location of each unit during that deployment. Efforts should be made to generate such a database prospectively in future major deployments so that appropriate studies can be done in a timely fashion. Such a database must be linkable to other exposure and outcome information.

2. Computerized records of environmental exposures should be developed when the situation warrants. Currently, the military is assembling data from the Persian Gulf War for a database to be linked with the personnel location database. This database includes environmental and meteorological data (e.g., air quality data in the area of the oil fires) that were collected during the conflict. Because major environmental exposures such as oil fires are difficult to predict, the military should develop contingency plans to call in a deployable technical team to do environmental monitoring in a timely fashion. The computerized software should be developed in advance so that the data generated by such a technical team can be linked to the personnel location database (as described above in item 1).
3. Automated field records indicating the drugs and biologics given to each individual should be developed. USPDP can be extended to deployment situations if the prescriptions filled and the vaccines administered to each individual can be electronically recorded in the field.
4. Occupational exposures can be categorized for study using the current classification system, the military occupational specialty (MOS). A computerized database with MOS data on individuals throughout their service lives must be linkable to other exposure and outcome data. The MOS is a general name of the assigned duty—for example, truck driver or medical officer. As with many occupational categorization systems, the MOS does not always correspond to the actual tasks that an individual may be doing and does not allow one to quantify the occupational exposures that the individual may experience. However, the MOS can serve as a general classification for job assignments, as long as its limitations fire known and stated.
5. Personal exposures during deployment, such as use of nonprescription medication, tobacco, alcohol, recreational drugs, and personally purchased pesticides, may be important health determinants, but exposures to these substances are difficult to assess. A minimal strategy for collecting data on these exposures is to have an anonymous postdeployment questionnaire that is administered to a random sample of the returning deployed troops. If general identifier data such as age, race, sex, reserve, or active-duty status are also collected, the general levels of such exposures can be assessed for specific subsets of the deployed forces. Some important exposures might not be anticipated—for example, the flea collars that were worn by some Persian Gulf War military personnel during their deployment. Preventive medicine officers in the field should be alerted to

the need to systematically identify and record any such exposures and estimate their frequency of use. Contingency plans should be made to determine when expert advice should be called in to determine whether such an unanticipated exposure should be disallowed.

Although the above discussion of exposure monitoring is directed toward existing or planned data collection efforts and databases, one should not ignore the possibilities for developing better epidemiologic databases on exposure. Biomarker data, for example, hold out the possibility of providing more refined measures of exposure. The Army/Navy Serum Repository should be considered as an important source of specimens from which such biomarker data might be developed.

### Monitoring Outcomes

1. Monitor sentinel events. This can be done by expanding the military Reportable Disease Surveillance System (RDSS) (see Chapter 3 for description of RDSS). Just as CDC compiles a list of reportable diseases, the military monitors a similar (but not identical) list of diseases in the RDSS (see list of notifiable diseases in Chapter 3). The committee recommends that, as an aid in identifying adverse effects of interactions, the Armed Forces Epidemiology Board and its experts identify appropriate additional diseases and conditions that should be reported. The additional conditions should cover the categories of expected toxicities identified in the matrix analyses described in Chapter 3.

For example, the category neurologic toxicity might include neurologic diseases like multiple sclerosis; the category immunological toxicity might include immune-suppression-related diseases like herpes zoster, autoimmune-related diseases like systemic lupus and thyroid disease, and hypersensitivity-related diseases; the category liver toxicity might include acute liver injury; the category nephrotoxicity might include acute renal failure, and so on. Available empirical data can be used to help identify appropriate additions. For example, the events reported to the Vaccine Adverse Event Reporting System (VAERS) in the civilian sector can be surveyed and may suggest items such as marked hair loss as well as specific diseases. Prior DoD studies can also be reviewed to identify potential sentinel events that should be added to the notifiable diseases list. Because decreased effectiveness is one of the potential adverse effects of vaccine-vaccine interactions, increased incidence of any diseases that should be prevented by the vaccination program should also be monitored. In addition, when new, separate vaccines are administered simultaneously, serologic studies should be undertaken to measure antibody responses.

Drug data can also be monitored for prescriptions specific to particular diseases. Such drug-related illnesses could include agranulocytosis, aplastic ane

mia, Stevens-Johnson syndrome, toxic epidermal necrolysis, and anaphylaxis. For example, inhaled steroids are prescribed almost exclusively for asthma, so an increase in their use might reflect either an increased prevalence or increased severity of that disease.

Experts can review the data periodically, evaluate apparent increases, and recommend investigation when warranted. This recommendation requires little new development, can be implemented by expanding systems already in operation, and should be activated in the near future.

2. Design small prospective studies to collect data before and after deployment to monitor immunologic, neurobehavioral, endocrinologic and reproductive, and genetic changes associated with deployment. Comparisons of the results of these studies to similar studies of nondeployed forces could provide reassuring data if relatively sensitive markers showed no adverse effects associated with deployment. If effects are seen, they would help direct future research. Such studies could be done with relatively small samples at relatively low costs. The immunologic testing could all be done with the sera for HIV testing obtained from all deployed personnel before their deployment and with a single blood sample obtained after the deployment (and with sera obtained at two comparable time periods for nondeployed forces) to measure markers of immune suppression, autoimmunity, and hyperreactivity. Neurobehavioral testing could be done with a battery of tests, including computerized tests of cognitive functioning, measures of balance and vision, and tests of peripheral nerve function. Mutagenesis could be monitored by genetic analyses of lymphocytes with the same blood sample collected for immunologic measures. Endocrinologic and reproductive biomarkers could include reproductive and thyroid hormone measures and semen analyses. Linkage to the Army/Navy Serum Repository could provide an opportunity to obtain data on serum biomarkers. In addition, detailed data on symptoms at baseline and after deployment for deployed and comparison groups would be useful. A carefully designed questionnaire could be developed to collect detailed data on such symptoms as headaches, tiredness, weakness, rashes and other skin effects, joint pain, muscle aches, sensitivity to odor, and feelings of depression and hopelessness. It could be used periodically to test several groups of military personnel so that baseline data on the occurrence of such symptoms and the changes in such symptoms over time would be available.

3. Use the available reporting systems in the civilian sector, VAERS and MEDWatch, as alerting mechanisms to identify potential interactions that should be studied. Adverse outcomes from interactions are often initially identified by astute clinicians. The committee recommends the adoption of appropriate directives requiring military medical facilities to use the MEDWatch reporting systems, similar to the directives for reporting to VAERS that already exist in the DoD immunization directives (Army Regulation 40-562).

4. Moderate to long latency effects are difficult to identify because military personnel spend relatively short terms in the military (even career personnel tend to leave after 20 years). Deployed reservists return to the civilian health care system immediately after deployment, so their health outcomes are difficult to identify. Those veterans who use the VA health care system after leaving the military are a select minority, so VA records will not identify many of those with disease. However, more efforts are needed to link VA records with military personnel records so that whatever follow-up the VA can provide is useable. The National Death Index is a record of all deaths in the United States, and this can provide death certificate information for all military personnel.

## Epidemiologic Investigation of Disease-Exposure Relationships

### Descriptive, Case-Series Studies

If a sentinel event triggers an investigation, the group of individuals identified as cases, those with the reportable condition, can be described as a case series. Exposure data for these individuals can be identified from the databases described above to monitor exposure, from hard-copy medical records, and by questioning the individual (unless he or she is deceased). If the event is otherwise rare and the exposure combination is very specific, the cause of the adverse health event may be inferred from such descriptive data; in most situations, however, it will be necessary to compare the cases with a group of controls to identify the risk factors. Nonetheless, recent methodological developments in the analysis of case series data allow the production of relatively good estimates of relative incidence without the use of controls—see Farrington et al. (1996) for an example of this methodology applied to adverse reactions to vaccines.

### Case-Control Studies

Case-control studies compare patients with a particular disease (cases) with individuals not having that disease (controls), looking for differences in the exposures of the two groups. They can be done relatively inexpensively to investigate any marked increase in a sentinel event identified through the reportable diseases program. The cases, individuals verified to have the reportable disease of interest, would have already been identified. Controls could be drawn at random from the target population from which the cases are identified, for example, all those who were active-duty personnel at the time of case identification. If potential exposures of interest have been identified, it may also be efficient to match cases with controls on such variables as gender, race, age, length of time in the military, and perhaps base location.

Case-control studies can also be done to evaluate outcomes not identified through the reportable diseases program. In such instances, case identification will need to be performed through a more cumbersome mechanism; for example, hospital discharges could be used to identify potential cases for a condition of interest. Because the discharge record lists diagnoses that were investigated (not necessarily confirmed), the discharge records merely give a pool of candidate cases. Cases to be studied should contain only confirmed cases (which are usually determined by a separate process that includes abstracting information from hard-copy medical records) from among the potential cases that were selected at random from the target population; matching on selected variables should be done when it is expected to improve efficiency. Case identification is particularly problematic when the disease to be studied does not have a well-defined diagnosis that can be tracked through International Classification of Disease coding.

Birth defects and reproductive outcomes could be studied using case-control design. Selected birth defects that are rarely fatal yet are distinct enough to be identified at birth are less problematic for study than all birth defects. Adverse reproductive outcomes are not uncommon in pregnancy and usually carry no unique characteristics that would link them to the exposures, with the possible exception of unusual congenital malformation syndromes. Aside from the situation of a unique malformation, however, most studies of reproductive outcomes will require comparison groups to determine if the association between the health outcome of interest and exposure to drugs, biologics, and chemicals is different from what would normally be detected within this population. In addition, the problem of identifying reproductive effects is magnified over the problem of identifying other health outcomes in that a couple's exposures, not an individual's exposure, may be related to the risk. The medical records of both members of the pair may not be in the military database, so that records would not be available within the same system. Many other confounding variables may influence the risk of reproductive problems, but all of these may not be known to the military.

The exposure data for a case-control study can be collected by computer linkage if exposures have been automated (see section entitled *Identifying and Recording Exposures* earlier in this chapter). In addition, the cases and controls can be found and asked to complete a personal, telephone, or self-administered questionnaire, if appropriate. The major disadvantage of self-reporting is that recall and reporting of exposures may well be different for cases and controls.

**Cohort Studies**

Cohort studies can be used to identify subsets of a population and to follow them over time, looking for differences in their outcomes. Cohort studies generally are used to compare exposed individuals with unexposed individuals, although they can also be used to compare one exposure to another. They can be performed either prospectively or retrospectively by recreating those past events with automated or manual medical records, questionnaires, or interviews. For example, there are plans under way to do clinical and epidemiologic studies of three cohorts of multiply-immunized civilians. All three cohorts consist of former or current U.S. Army Medical Research Institute for Infectious Diseases (USAMRIID) laboratory workers who have received multiple immunizations. These three separate cohorts consist of 99 men who were studied in 1954, 1962, and 1971; former "reunion" employees, who meet once every three years; and current USAMRIID employees. Although the proposed studies are not studies of military cohorts, they may provide useful data applicable to the military.

A cohort study provides the basis for determining the excess risk of adverse health outcomes associated with interactions of agents compared with the risk of adverse health outcomes in those not exposed to the same agents. Considerations in the design and conduct of a cohort study of the association between interactions of agents and adverse health events include the following: the ability to select a well-defined cohort (study population), the ability to obtain accurate exposure histories and data on potential confounding factors, and the ability to ascertain all relevant disease events of interest.

This type of study can be used to assess the effects of agents that are known to interact but whose use cannot be avoided in field operations, those that have potential interactions, and those whose potential for interaction is as yet unknown. For example, this is one of the strategies being used to evaluate the health effects of the Persian Gulf War; hospitalization data have been compared for deployed and nondeployed personnel. Unfortunately, military personnel tend to leave the military, so their health can no longer be monitored within the military health care system. Therefore, most medium- to long-term sequelae will not be identified in military records. VA records can be used if they are available, but those who use the VA system will not be representative of the exposed and unexposed groups. With SSN availability, researchers could link to other (non-VA) public and private administrative databases concerning health care. For example, the National Death Index provides unbiased data on long-term sequelae, but it can only be used to study all-causes mortality and mortality associated with conditions having high fatality rates, such as some cancers. These overall death rates and specific causes of death can be compared among different exposure groups (assuming that sufficient exposure data are collected so that groups can be identified; see *Monitoring Exposures* section above). Linkage to

the Army/Navy Serum Repository can provide biomarker data for subjects during their time in the military. Finally, randomized experiments and intervention studies, when feasible and ethical, can provide very useful data on the effects of the interactions of various agents.

## CONCLUSION

The military will be faced with increasing and continuously evolving problems involving the interactions of drugs, biologics, and chemicals. Each combination of agents with the potential for adverse interactions is likely to pose specific research challenges and unique problems to the detection, evaluation, and management of interactions. The advice of experts in the fields of toxicology, epidemiology, and pharmacology will be needed on a continuing basis to assist military scientists and program managers in developing experimental approaches, selecting model systems, designing epidemiologic studies and surveillance programs, and providing information during policy discussions concerning the costs and benefits of potential decisions. An expert advisory panel established under a chartered advisory structure, such as the Armed Forces Epidemiology Board, and comprising experts in the several needed disciplines could provide the appropriate advice and guidance to the military research community, those who perform preventive medicine activities, and health care providers.

In addition, close coordination among the programs within the DoD—including, but not limited to drug and biological product development, preventive medicine, clinical medicine, chemical warfare defense activities, and oversight committees—will be necessary to address the recommendations of this committee. The committee acknowledges that it will not be possible to complete all of the database development and recommended research immediately and simultaneously. Cost-benefit considerations and feasibility issues will need to be addressed to prioritize and develop a feasible agenda of future research activities. Coordination among the programs will be particularly important to the successful completion of this task.

# 6

# Findings and Recommendations

In this chapter, the committee summarizes its major findings and recommendations. Throughout the report, however, especially in Chapter 5, the committee makes additional suggestions that, although not carrying the weight of final recommendations, it thinks would be useful.

## FINDINGS

1. Military personnel, especially when they are deployed, are exposed to a large number of drugs, biologics, and chemicals to which their civilian counterparts in the United States are not exposed. None of the information gathered on additional planned prophylactic-preventive agents had a substantial impact on the committee's deliberations.
2. The published scientific literature on the interactions of militarily relevant drugs, biologics, and chemicals does not provide an adequate basis for assessing the degree of safety; the committee, however, did not find any basis for extraordinary concern.
3. Discussions held with liaisons from the medical divisions of the Canadian and British militaries indicated the international need for increased information and research regarding interactions.
4. The diversity and number of agents precludes not only the testing of all possible combinations for interactions but also the development of systems that could be used to identify and predict with confidence all possible interactions that could result in increased toxicity.

5. Operational requirements may necessitate the use of combinations of agents of known or potential toxicity. The committee understands that it is Department of Defense (DoD) policy to ensure that the benefits outweigh the risks when these combinations of agents are used.
6. Many programs are under way within the military in the areas of drug and vaccine design and development, research on the effects of those agents that are administered to military personnel or to which military personnel are known to be exposed, and the development of surveillance systems and related databases that could be used in epidemiologic studies. However, many of the surveillance systems are incomplete, and databases that contain related, relevant information have not been linked to date. Most important, a coordinated effort among the services to link the relevant programs is lacking.

## RECOMMENDATIONS

1. A focused strategy for evaluating and managing the effects of interactions needs to be developed. This strategy should also be suitable for new agents. The proposed approach involves the characterization of interactions into three broad categories:

a. *Known:* those interactions for which there is documented evidence of risk in humans;
b. *Potential:* those interactions that are known from animal studies or that can be anticipated or predicted on the basis of the individual properties of the agents in putative combinations; and
c. *Unknown:* the interactions of combinations of agents that cannot be anticipated on the basis of current knowledge (this is the largest class).

2. For agents with known interactions, if exposure cannot be avoided, surveillance measures should be implemented and focused studies should be undertaken to identify ways to minimize risk levels.
3. Potential interactions might be predicted by use of a matrix based on target organ toxicity, pharmacokinetics, and pharmacodynamics. High-priority potential interactions should be investigated in a tiered process involving in vitro, animal, human volunteer, and epidemiologic studies.
4. For agents with unknown interactions, three strategies are recommended.

a. The first strategy is to develop, enhance, and implement surveillance systems to monitor both exposure combinations and health outcomes. Surveillance systems for exposures should include data regarding drugs, biologics, and other deployment-site-specific chemicals. Surveillance systems for health outcomes should be expanded to capture additional sentinel events (using notifiable conditions) and could be used to support focused

prospective studies, provided they are of sufficient sample size, to compare specific health measures before and after deployment.

b. The second strategy is to conduct a battery of in vitro and in vivo experimental studies to investigate a core set of exposures anticipated for most deployed troops.

c. When outcomes of interest are identified, they should be investigated with carefully designed epidemiologic studies of disease-exposure relationships. The committee recommends further that efforts be better coordinated within and among all those military units and branches involved with the development of these systems.

5. Programs within the Army and DoD that involve product development, preventive medicine (including the development of surveillance systems and integrated databases), clinical medicine, and the medical defense against biological and chemical warfare weapons should be closely coordinated. An advisory committee should be established to help identify and use existing and future research tools for the purposes of anticipating, studying, and minimizing harmful interactions.

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# Appendix

## PRESENTERS AT THE SEPTEMBER 5, 1995, COMMITTEE MEETING

Anna Johnson-Winegar, Ph.D.
Director
Medical Chemical and Biological Defense Directorate
U.S. Army Medical Research and Materiel Command
LTC Claude Woodard, D.V.M.
Medical Chemical and Biological Defense Directorate
U.S. Army Medical Research Institute of Infectious Diseases
LTC Edward M. Eitzen, M.D., and LTC Phillip Pittman, M.D.
U.S. Army Medical Research Institute of Infectious Diseases
LTC James King, Ph.D.
Chief, Research Operations Division
U.S. Army Medical Research Institute of Chemical Defense
LTC Robert F. DeFraites, M.D.
Walter Reed Army Institute of Research

## PRESENTERS AT THE MARCH 5–6, 1996, COMMITTEE MEETING

COL George Lewis
Commander
U.S. Army Medical Materiel Development Activity, Fort Detrick
Ron Clawson, Ph.D.
U.S. Army Medical Materiel Development Activity, Fort Detrick

Judy Pace, Ph.D.
U.S. Army Medical Materiel Development Activity, Fort Detrick
Rick Kenyon, Ph.D.
U.S. Army Medical Materiel Development Activity, Fort Detrick
MAJ John Grabenstein
Clinical Investigation Regulatory Office
Army Medical Department Center and School
LtCol John T. Graham
Defence Medical Services Directorate, British Ministry of Defence
United Kingdom
COL John Brundage, M.D., MPH
Director, Epidemiology and Disease Surveillance
USA Center for Health Promotion and Preventive Medicine
Susan Ellenberg, Ph.D.
Director, Division of Biostatistics and Epidemiology
Food and Drug Administration
Robert Chen, Ph.D.
Chief, Vaccine Safety and Development
Centers for Disease Control and Prevention

# Glossary

| | |
|---|---|
| **additive effect:** | When the combined effect of a combination of agents is equal to the sum of the effects of each of the agents given alone. |
| **antagonistic effect:** | When the combined effect of a combination of agents is less than that predicted on the basis of simple addition of the effects of the doses or responses of those agents. |
| **ARD:** | acute respiratory disease. |
| **BIRLS:** | Beneficiary Identification and Records Locator Subsystem, an automated database containing information (including vital status) on all veteran beneficiaries of the U.S. Department of Veterans Affairs. |
| **CDC:** | Centers for Disease Control and Prevention. |
| **CWI:** | cold weather injury |
| **DEET:** | *N,N*-diethyl-*m*-toluamide |
| **DoD:** | U.S. Department of Defense. |
| **EPA:** | U.S. Environmental Protection Agency. |
| **FDA:** | Food and Drug Administration. |
| **GIS:** | geographical identification system. |
| **HIV:** | human immunodeficiency virus. |

**ICD:** International Classification of Diseases, now in its ninth revision, is a scheme for coding medical conditions.

**IND:** investigational new drug.

**interaction:** When the presence of one agent affects an exposed individual's reactivity to other agents.

**IPDS:** Individual Patient Data System, an automated system of the U.S. Army containing records for each inpatient discharge.

**Morbidity and Mortality Weekly Report:** a publication of the Centers for Disease Control and Prevention containing, among other things, national data on reportable diseases.

**Medical treatment facility:** a place where health care is delivered.

**MedWatch:** FDA medical products reporting system.

**MOS:** military occupational specialty.

**PB:** pyridostigmine bromide.

**PBPD:** physiologically based pharmacodynamic.

**RDSS:** Reportable Disease Surveillance System.

**SSN:** Social Security number.

**synergistic effect:** When the combined effects of a combination of agents are greater than would be anticipated from the simple addition of the effects of the doses or responses of those agents.

**USAHDS:** U.S. Army HIV Data System, which acquires and maintains the data for the Army's HIV testing program.

**USAMRIID:** U.S. Army Medical Research Institute for Infectious Diseases.

**USAMRMC:** U.S. Army Medical Research and Materiel Command.

**USPDP:** Uniformed Services Prescription Database Project, an Army database containing nationwide information on prescribed drugs.

**VA:** U.S. Department of Veterans Affairs.

**VAERS:** Vaccine Adverse Event Reporting System, operated by the Centers for Disease Control and Prevention and the Food and Drug Administration.