Several concepts and diseases are discussed in the chapters that follow. But first, it is useful to consider why, in the search for answers about unexplained illnesses and findings in Gulf War Veterans, it is reasonable to consider an infectious origin and why an infectious etiology does not seem likely. Arguments for and against an infectious etiology are presented and discussed.

REASONS TO CONSIDER AN INFECTIOUS ETIOLOGY

Epidemiologic Relationship

Epidemiology is the study of diseases in a population or group of people. Most of us are familiar with epidemics—for example, an influenza (flu) epidemic occurs when there is an increase in the number of cases above a baseline. An epidemic may be of short duration (e.g., food poisoning) or of long duration (e.g., cancer), but the common element is that a specific disease emerges with increased frequency over what would otherwise be expected. A second premise assumes that the increased incidence of disease follows a unique exposure or exposures.

Concern about Gulf War illnesses exists because many believe that the unexplained symptoms in Gulf War veterans might represent a constellation of findings in increased frequency among our Gulf War veterans. Like the flu or cancer, then, the unexplained illnesses represent an increase relative to the baseline (the epidemic) in a group of individuals with a common exposure (service in the Middle East during the Gulf War).

History of Infectious Diseases

Chapter One reviewed some concepts surrounding the natural evolution of diseases that have subsequently been shown to have an infectious cause. Medical
science today knows more about causes of illnesses than it ever has before. But clearly we do not know all the answers. Before a specific cause is found, diseases and syndromes are described clinically; that is, they are characterized by how patients describe their illness to their physicians, the findings that the physician observes during a physical examination, or the presence of abnormalities in the results of diagnostic studies (e.g., x-rays, blood and urine tests). With further study, including epidemiologic studies, possible causes are identified. Often, but not always, a common cause is identified for a constellation of clinical findings.

The natural history of most infectious diseases is such that some time passes before an infectious cause is identified. In fact, some infectious diseases, such as cholera, were recognized before the causative organism was identified. In the case of cholera, public health measures reduced the risk of gastrointestinal problems including diarrhea, dehydration, and death long before the causative bacteria, *Vibrio cholerae*, was isolated. More recently, the AIDS epidemic was recognized by a group of clinical and epidemiologic characteristics two years before the specific virus was identified. Similarly, only recently has *Helicobacter pylori* been identified as one cause of gastritis (inflammation of the stomach).

**Some Infectious Diseases Were Identified**

Infectious diseases, although not nearly as common as in past military deployments, were diagnosed during and after the Gulf War. The most notable is leishmaniasis because some of the Gulf War illness symptoms are consistent with the way some patients with *Leishmania* actually feel. It is also clear that we still have much to learn about this infection and the way it interacts with our bodies. Other infections, including hepatitis and tuberculosis, also can and do manifest as chronic diseases.

**REASONS TO DISMISS AN INFECTIOUS ETIOLOGY**

**Koch’s Postulates**

Robert Koch, a physician and microbiologist in the late 1800s and early 1900s, provided a set of criteria that established the experimental evidence required to support the relationship between a specific microorganism and a disease. The criteria have expanded over the years, but the basic principles still serve as the basis for establishing a relationship between an organism and a disease. Koch’s postulates state:

1. The microorganism must be observed in every case of the disease;
2. The microorganism must be isolated and grown in pure culture;
3. The pure culture must, when inoculated into a susceptible animal, reproduce the disease; and

4. The microorganism must be observed in, and recovered from, the experimentally diseased animal.

These guidelines provide a useful framework for the discussion that immediately follows. To date, Koch’s postulates have not been satisfied among those with Gulf War illnesses. However, Koch’s postulates are often not completely satisfied in illness. Completely satisfying Koch’s postulates provides strong evidence for a causal relationship; but inability to satisfy all postulates does not exclude a causal link between the organism and the disease.

A Missing Specific Finding

In one important way, unexplained Gulf War illnesses differ from some of the diseases just discussed. In the case of AIDS, researchers and epidemiologists described specific clinical findings that could be verified by laboratory tests, x-rays, and clinical examination. There were also lifestyle risk factors that were highly associated with the disease. Physicians readily identified gastritis in patients harboring \textit{H. pylori}, even though the infectious agent was not initially related to that observation. In contrast, despite attempts to demonstrate reproducible objective findings, no specific clinical findings or laboratory abnormalities have been observed in those identified with unexplained Gulf War illnesses. Usually, if there is a common thread to a specific disease, there will be common objective findings. Most infectious diseases are characterized by findings such as fever, abnormal laboratory tests, organ derangement, or specific outcomes such as recovery, paralysis, and death. For example, patients with hepatitis have jaundice (yellow skin) and abnormal liver tests; those with pneumonia have increased white blood cell counts and abnormal chest x-rays, and those with severe emphysema (a noninfectious example) have abnormal x-rays, lung tests, and physical findings. Because the reported findings in ailing Gulf War veterans with unexplained symptoms are few and not consistent from veteran to veteran, the lack of objective and consistent findings makes it difficult to conclude there is a single common pathological process or cause.

Some Evidence Does Not Fit

The Experience of Coalition Countries. U.S. forces worked closely with military forces from other countries. If the cause of illnesses in some Gulf War veterans is infectious, then it is spread to victims through some common exposure. If the exposure is unique to the Gulf region, then one would expect that those serving from other countries would experience illnesses at roughly the same
rate as U.S. troops. However, efforts to identify similar illnesses in coalition troops have not been confirmed to the same degree (i.e., at the same rate) as in U.S. Gulf War veterans. Some individuals from the United Kingdom report similar illnesses but in numbers considerably fewer than have been observed in U.S. veterans (DoD, 1996; Defense Science Board, 1994). However, because of different definitions of “disease” in different countries and different motivations among those who seek care for a given problem, it is difficult to draw firm conclusions regarding prevalence of similar findings in other countries.

**Family Studies.** As of December 1995, there were 332 spouses and 191 (119 of whom had a diagnosis other than “healthy”) children who were registered as part of the DoD CCEP. Because the CCEP is a clinical program with self-reporting rather than a population-based program, it is not possible to draw conclusions about the true prevalence of disease among military spouses and children. However, the number of children and spouses reporting illnesses in this registry does not exceed what might be expected in a population the size of the Persian Gulf deployment (697,000 troops). If considerable Gulf War illness was caused by an infectious agent that could be transmitted directly between Gulf War veterans in the Middle East, we might expect more direct person-to-person transmission among family members who would therefore have illnesses similar to those included among the Gulf War illnesses. It is possible, however, that even if person-to-person transmissible diseases did exist, their period of infectivity (contagious period) may have passed by the time they returned home.