

Medically Unexplained Symptoms

The hazards described in Chapter 2, such as infectious disease, psychological stress, chemical and biological warfare agents, and injuries, remain among the serious threats to deployed military forces. The military has exerted tremendous effort in countering these hazards through preventive medicine. Continued effort and an emphasis on preventive measures against these hazards are required, but the study team does not believe that it can provide additional expert advice about them.

In contrast, the experiences of the Gulf War and the illnesses reported in its wake point to an area where additional effort is needed: medically unexplained symptoms. Such symptoms are not new, but the many health problems reported after the Gulf War have brought new recognition of their tremendous effects on both military and civilian populations. It has become clear that there remain many unresolved issues related to the causes of symptoms and how they might be prevented and treated.

After wars dating back at least to the Civil War, soldiers have reported clusters of symptoms that have not been satisfactorily explained medically (Hyams et al., 1996). These symptoms have included fatigue, shortness of breath, headache, sleep disturbance, memory problems, and impaired concentration (Hyams et al., 1996). However, no single demonstrable disease is apparent. Multiple studies in Gulf War veterans have not found a unique illness to account for the multiple symptoms experienced (Fukuda et al., 1998; Iowa Persian Gulf Study Group, 1997; Gray et al., 1996). Unexplained illnesses reported by veterans of the Gulf War have led large numbers of veterans and their family members to be concerned about their health and have led to the expenditure of millions of dollars in research into causal factors.

At the same time, research in the civilian health care system has elucidated similar unexplained symptoms in the general population (Hyams, 1998; Barsky

and Borus, 1999). The study team believes that increased attention to prevention and treatment of the medically unexplained symptoms among military populations during and after deployment is warranted because of their prevalence and attendant potential disability.

The section that follows draws heavily upon the paper, *Unexplained Physical Symptoms in Primary Care and the Community: What Might We Learn for Prevention in the Military?*, which was written for this study under commission by Charles C. Engel, Jr., and Wayne J. Katon. A condensed version of the paper is found in Appendix A.

This report uses the term *medically unexplained symptoms* to refer to symptoms that are not clinically explained by a medical etiology and that lead to use of the health care system. Many common diagnoses are not based on etiologically defined factors but are based on clusters of medically unexplained symptoms for which a more satisfactory designation cannot be found (Jablonski, 1991; Hyams, 1998). The terms *symptom-based diagnosis* or *symptom-based condition* can be used to describe such health problems diagnosed almost exclusively by using patients' verbal descriptions or observed behaviors, when no clinically demonstrable alterations in normal physiology or biological structure can be found. Symptom-based diagnoses tend to provide a label for clinicians and patients without providing any clear explanation of the reason for the symptoms. Indeed, some symptom-based diagnoses most likely involve underlying and measurable alterations in physiology that are as yet poorly characterized or understood (Engel and Katon, 1999). There is some evidence that the prognosis, treatment, and factors that determine disability are similar across different symptom-based diagnoses (Buchwald and Garrity, 1994; Gomborone et al., 1996; Plesh et al., 1996; Clauw et al., 1997; Hyams, 1998; Engel and Katon, 1999).

EPIDEMIOLOGY

Surveys of the general population indicate that 85 to 95 percent of community respondents experience at least one physical symptom every 2 to 4 weeks, although few of these symptoms are reported to physicians (White et al., 1961). Analysis of the population-based Epidemiologic Catchment Area Study found that more than 4 percent of people had a lifetime history of multiple, chronic, unexplained complaints with at least one episode in the past year (Escobar et al., 1987; Swartz et al., 1991). Similarly, in the general population the prevalence of a history of at least six bothersome medically unexplained symptoms during one's lifetime in women and at least four medically unexplained symptoms in men is about 4 percent (Escobar et al., 1987, 1989). These criteria were associated with significant functional impairment and high levels of use of the health care system.

Unexplained symptoms are common in the population of people who seek health care. According to the 1989 National Ambulatory Medical Care Survey,

such symptoms account for 57 percent of the roughly 400 million ambulatory care visits per year in the United States (Schappert, 1992). A third or more of these symptoms remain unexplained after a routine medical evaluation. Research by Kroenke and colleagues similarly indicated that a large component of primary care involves the management of medically unexplained symptoms (Kroenke and Mangelsdorff, 1989; Kroenke et al., 1990).

Studies of patients with medically unexplained symptoms indicate high rates of major depression and panic disorder (Katon et al., 1985, 1991a; Goldenberg, 1987; Black et al., 1990; Simon et al., 1990; Hudson et al., 1992; Clauw and Chrousos, 1997). Several mechanisms might account for this correlation. Physical illness may cause psychosocial distress through a direct biological link such as through neurotransmitters involved in both pain and mental disorders. Physical symptoms may cause emotional distress by overwhelming an individual's ability to cope. Distress may increase unhealthy behaviors that increase the risk of such symptoms. The disordered sleep and changes in autonomic nervous system functioning associated with stress may cause these symptoms. Finally, both mental disorders and medically unexplained symptoms may be found together in some people simply by chance.

Studies indicate that increasing numbers of physical symptoms are accompanied by an increasing likelihood of experiencing anxiety and depressive disorders (Katon and Russo, 1992; Kroenke et al., 1994; Russo et al., 1994; Kisely et al., 1997). For example, in a study using self-reports from a sample of more than 1,000 health maintenance organization enrollees, increasing numbers of pain complaints were strongly associated with elevated levels of anxiety, depression, and physical symptoms that did not cause pain (Dworkin et al., 1990). In a separate study, the percentages of people with anxiety and depressive disorders increased with increasing numbers of physical symptoms (both medically explained and unexplained from the perspective of the interviewer) (Kroenke et al., 1994). Indeed, depression and anxiety are consistently associated with medically unexplained symptoms across many studies that have used several different methods and that have had cross-sectional (Simon and VonKorff, 1991), case-control (Katon et al., 1988, 1991a; Sullivan et al., 1988; Walker et al., 1988, 1990b), and longitudinal designs (Leino and Magni, 1993; Von Korff et al., 1993) designs. Katon and colleagues have found that the relationship of physical symptoms to common anxiety and depressive disorders is linear. As the number of anxiety and depressive symptoms or lifetime episodes of these disorders increases, so does the prevalence and number of medically unexplained symptoms (Katon et al., 1991b).

These data suggest that medically unexplained symptoms may sometimes be a marker of psychosocial distress (Engel and Katon, 1999). In occupational medicine settings, like the military, with a younger and medically healthier population than the general population, this effect is probably amplified. With a lower base rate of most diseases, there is a higher likelihood that unexplained symptoms are due at least in part to more common and less easily recognized psychiatric disorders like anxiety and depressive disorders (Engel and Katon, 1999).

Medically unexplained symptoms are important not only because of their prevalence but also because of the loss of functioning, impaired quality of life, and high levels of health care utilization that accompany them. Consistent evidence suggests that those with medically unexplained symptoms report poor functioning and diminished quality of life (Escobar et al., 1987; Katon et al., 1991b; Schweitzer et al. 1995; Anderson and Ferrans 1997; Gureje et al. 1997, 1998; Piccinelli and Simon 1997). Health care utilization is also increased among those with medically unexplained symptoms. In one study, patients with somatization disorder had a six-fold per capita increase in hospital service expenditures, a 14-fold increase in physician costs, and a nine-fold increase in personal health costs compared with national averages (Coryell and Norten, 1981; Smith et al., 1986a). Escobar et al. (1987) found that multiple medically unexplained symptoms (four or more for men and six or more for women) were significantly related to use of general medical services. Medically unexplained symptoms also frequently lead to dissatisfaction with health care because most patients believe that finding a medical explanation for the symptoms is the physician's job.

Understanding the natural history of medically unexplained symptoms is important to considering routes of prevention and treatment. Engel and Katon (1999) described predisposing factors, precipitating factors, and perpetuating factors that play a role in the natural history of medically unexplained symptoms. Rather than being empirical in nature, these categories are part of a heuristic model used to provide a framework for understanding individual variation in medically unexplained symptoms. Predisposing factors are characteristics of individuals that make them more vulnerable to distress, physiological arousal, and bothersome physical symptoms. Precipitating factors are events or factors that send vulnerable asymptomatic individuals into a physically symptomatic episode or that increase levels of disability or distress among those who are already symptomatic. Perpetuating factors are those that maintain symptoms, distress, and disability and that extend their period of duration (Engel and Katon, 1999).

PREDISPOSING FACTORS

There is a large body of literature about predisposing factors for medically unexplained symptoms. These factors fall into categories of hereditary differences, physiological differences, adversity in early life, chronic medical illness, and chronic or recurrent psychiatric illness. Although many of these factors are difficult or impossible to modify (for example, genetic predisposition or childhood experiences), there may be approaches to mitigating the influences of these factors on the subsequent risk of symptom onset, symptom persistence, impaired coping, psychosocial distress, and diminished functional capacity (Engel and Katon, 1999). Each of the predisposing factors is discussed at greater length by Engel and Katon (1999).

Physiological Differences and Susceptibilities

Physiological differences in the susceptibilities of individuals to medically unexplained symptoms are not yet well understood, but it is likely that they are the result of both genetic predisposition and developmental influences and experiences. The following section describes some hypothesized physiological bases of some of the previously unexplained symptoms. Other hypotheses are presented by Engel and Katon (1999).

One of the critical physiological control systems of the body is the hypothalamic-pituitary-adrenal (HPA) axis, which mediates the neuroendocrine stress response. This system is an important common pathway through which responses to the range of physical, psychological, or immune and inflammatory stimuli are mediated. When the HPA axis is activated by a stimulus, the hypothalamus secretes corticotropin-releasing hormone, which in turn stimulates the pituitary gland to secrete adrenocorticotropic hormone and the adrenal glands to produce glucocorticoids. Glucocorticoids feed back at every step to contain and ultimately shut off this response. The HPA axis is also regulated by an internal biological clock entrained to the light-dark cycle. Sleep and activity are related to troughs and peaks in HPA function, respectively, but these are unrelated to external life stress. Sleep deprivation and depression are associated with elevated and flattened diurnal IIPA function, and "burn out" from job or other intense experiences is associated with a flattened and lower IIPA function.

Activation of the IIPA axis and the sympathetic nervous system during acute stress is linked to behaviors and physiological responses, including increased heart rate, sweating, focused attention, and decreased vegetative functions, such as feeding and reproductive behavior (Sternberg, 1998b). With exposures to stressors of moderate intensity for a relatively short duration, activation of the HPA axis and sympathetic nervous system activation enhance performance with increased attention, more efficient muscular activity and energy metabolism, and readiness for response to threat or attack (Sternberg, 1998b), including enhanced immune function (Dhabhar and McEwen, 1999). With exposures of longer durations or with exposure to higher-intensity stressors, some of these responses may fail or may be suppressed (Dhabhar and McEwen, 1997; Sternberg, 1998b).

The HPA axis regulates the immune system systemically, generally playing an immunosuppressive role through the actions of glucocorticoids. Evidence from animal models suggests that genetic differences in the reactivity of the HPA axis system result in differences in susceptibility or resistance to inflammatory and infectious diseases (Sternberg et al., 1989a,b; Sternberg, 1998b). Differences between the Lewis and Fischer rat strains indicate that blunted or underactive HPA axis responses predispose the rats to enhanced susceptibility to inflammatory disease, whereas overactivity of the HPA axis predisposes the rats to enhanced susceptibility to infectious disease (Sternberg, 1998b). However, similar levels of IIPA activity do not mean that the immune responses are also similar. Genetic traits determine the optimal level of IIPA function required to

maintain the proper balance of immune function, and these genetic traits have not yet been identified in animals or in humans (Mason, 1991; Sternberg, 1998b).

These findings have interesting implications for humans. Inherent or developed differences in the responsiveness of the HPA axis could underlie some of the differences in symptoms or illnesses that individuals experience, including thus far medically unexplained symptoms. Although studies of the relationship between differences in the responsiveness of the HPA axis and human disease are not as far advanced as they are for animals, associations have been observed between a blunted or relatively low HPA axis response and rheumatoid arthritis (Neeck et al., 1990; Cash et al., 1992), atopic dermatitis and asthma (Buske-Kirschbaum et al., 1997), chronic fatigue syndrome (Demitrack et al., 1991), fibromyalgia (Crofford et al., 1994), atypical depression (Joseph-Vanderpool et al., 1991), posttraumatic stress disorder (PTSD) (Resnick et al., 1995; Yehuda et al., 1995), and burnout (Sternberg, 1998a,b).

The degree to which individual differences in the responsiveness of the HPA axis are genetic or environmental is not yet known. However, powerful developmental effects are recognized. In rats, early stress and neonatal handling are believed to set the level of responsiveness of the HPA axis and autonomic nervous system. The HPA axis overreacts in animals subjected to early unpredictable stress and underreacts in animals exposed to neonatal handling (Meaney et al., 1994). A factor that determines the activity of the stress hormone axis and the overall allostatic load is early life experience. This has been shown in animal models (Meaney et al., 1988; Higley et al., 1991; Dellu et al., 1994).

In humans, a growing body of data suggests a relationship between developmental or other experiences and physiological changes in the HPA axis. Recent studies raise the possibility that organic changes in the brain may be linked both to early life events, adult trauma, and disorders such as depression and PTSD and to the regulation of the stress hormone axis (Bremner et al., 1995, 1997; Gurvits et al., 1996). How does all of this relate to medically unexplained symptoms? At this point one can only speculate whether the connections exist. By definition there is no clear mechanistic understanding of the medically unexplained symptoms described in this report. However, the studies with animals and humans described above suggest the possibility of systemic effects mediated by neuroendocrine stress response dysregulation. Answers to such questions for humans will require time and additional study, including prospective studies of potential markers for HPA axis hypo- and hyperreactivity.

Early Life Adversity

There is some evidence that traumatic experiences in childhood might be related to health in adulthood. Cross-sectional and case-control studies have shown consistent associations between childhood maltreatment and irritable

bowel syndrome (Walker et al., 1990a,b; Irwin et al., 1996) fibromyalgia (Walker et al., 1997; Alexander et al., 1998), back pain in women (Linton, 1997), and chronic pelvic pain in women (Walker et al., 1988; Walker and Stenchever, 1993). A 2-year prospective cohort study examining the natural history of medically unexplained symptoms found that persistent unexplained symptoms were significantly associated with patient reports of poor parental care in childhood, chronic parental medical illness, and chronic medical illness (Craig et al., 1993).

Chronic Medical Illness

Social learning theory holds that people learn behaviors and patterns of communication from those around them beginning very early in life. Some aspects of illness-related behavior may be influenced by behaviors modeled by chronically ill family members. Children of patients with low back pain chose more pain-related responses to situations than children of healthy parents or diabetic parents (Richard, 1988). These children's teachers also rated them as manifesting more illness-related behaviors than the children of healthy control parents. In a prospective study in the United Kingdom, parental health complaints, physical illness during childhood, and teachers' assessments of the behavior and personality of subjects at age 15 predicted medically unexplained physical symptoms in adulthood (Hotopf et al., 1997). The complex contributions to illness-related behavior of parenting roles as well as intrinsic genetic factors passed from parent to child remain to be sorted out.

PRECIPITATING FACTORS

Precipitating factors are those related to the acute onset of medically unexplained symptoms. They include biological stressors, psychosocial stressors, acute psychiatric disorders, and epidemic unexplained illness. A biological stressor might be a concurrent medical illness. Conversion disorder can cause the amplification of a symptom primarily caused by a coexisting medical disorder (Sharma and Chaturvedi, 1995; Silver, 1996). For example, some individuals with diagnosable seizure disorders also experience pseudoseizures of apparent behavioral rather than neurological origin (Lelliott and Fenwick, 1991; Blumer et al., 1995).

Psychosocial events can frequently lead to the start of medically unexplained symptoms in susceptible individuals. Several studies indicate a higher percentage of traumatic life events in patients who seek health care or who are about to undergo surgery and who were found to have nonspecific or unexplained pain compared with the percentage of traumatic life events among those with identifiable disease (Creed, 1981; Craig and Brown, 1984; Craufurd et al., 1990). For example, Creed (1981) interviewed patients with undiagnosed ab-

dominal pain for stressful life events just before they underwent appendectomy, so that during the interview he did not know the eventual pathological diagnosis for the removed appendix. Of individuals with a normal appendix, 60 percent reported that a severely threatening life event had occurred in the previous 38 weeks, whereas 25 percent of those later diagnosed with appendicitis and 20 percent of a healthy control group reported that such an event had occurred.

The acute onset of psychiatric disorders, particularly depressive and anxiety disorders, can also lead to the onset of medically unexplained symptoms. Existing evidence suggests that recognition and successful treatment of panic disorder also reduces physical symptoms and physical health concerns (Kellner et al., 1986; Noyes et al., 1986). Early interventions for patients with panic disorder and major depressive disorder may prevent exposure to perpetuating factors that increase the likelihood of acute medically unexplained physical symptoms becoming chronic with associated disability (Engel and Katon, 1999).

Epidemiclike outbreaks of medically unexplained illness occasionally occur, often in industrial or workplace settings. The controversial sick building syndrome involves the development of symptoms among many individuals living or working in the same building. Although microbial contamination may play a part in some of these outbreaks, they may also be associated with psychosocial factors including job-related stress (Menzies and Bourbeau, 1997; Kroenke, 1998a; Menzies, 1998). Outbreaks of chronic fatigue syndrome are known to occur (Chester and Levine, 1997), and epidemic unexplained illness has been reported to occur in military settings (Struwing and Gray, 1990). Such illnesses often occur after some environmental trigger, after a significant emergency response to a threat, and with the belief of those with symptoms that the environmental event was the cause of their illness or anxiety (Small et al., 1994; Boss, 1997).

PERPETUATING FACTORS

Perpetuating factors, sometimes referred to as illness maintenance systems, are those that may sustain or prolong medically unexplained symptoms once they have occurred (Katon et al., 1982a,b). Personal beliefs about the causes of one's symptoms can sustain or prolong medically unexplained symptoms. For example, the belief that physical activity produces debilitating fatigue may begin a cycle of decreasing activity that further promotes fatigue (Irish Times, 1999). However, a program of regular physical activity is an essential element of successful treatment in most multidisciplinary approaches to chronic pain and fatigue (Engel and Katon, 1999). Misinformation from others, such as health care providers, may also be a perpetuating factor. Continued diagnostic testing, regardless of the physician's reasons for it, sometimes perpetuates patients' beliefs that a disease may yet explain their symptoms and lead to a cure (Kouyanou et al., 1997).

Support groups may also perpetuate medically unexplained symptoms. Although they can reduce the sense of isolation many sufferers experience, they can also encourage a struggle for the medical legitimacy of the illness and reinforce beliefs that a quick fix is possible (Abbey and Garfinkel, 1991). Other sources of social support can also reinforce illness-related behavior. Well-meaning friends or loved ones can enhance disability by urging unnecessary relaxation and relief from undesirable responsibilities (Block et al., 1980; Jamison and Virts, 1990; Engel and Katon, 1999).

Although frequently helpful, diagnostic labeling can sometimes have negative effects by unnecessarily causing patients to define themselves as ill (Meador, 1965). Haynes and colleagues (1978) found that steelworkers participating in hypertension screening and diagnosed with hypertension, an asymptomatic illness, missed 80 percent more days of work after screening than before screening, whereas there was a 9 percent increase among workers who were screened but who did not receive a diagnosis of hypertension. For symptom-based conditions, it has been suggested that the iatrogenic effects of labeling may outweigh the potential for clinical and societal benefits (Hadler, 1997). Furthermore, embedding the putative cause of a new condition into its name or diagnostic criteria may preclude the acceptance of findings that indicate other explanations for the symptoms (Feinstein, 1998).

Workplace factors have been associated with illness-related behavior, in that dissatisfaction with job tasks and elevated scores on the Minnesota Multiphasic Personality Inventory, a psychological test, were the best predictors of subsequent back pain in a prospective study of more than 3,000 aircraft workers (Bigos et al., 1991).

Although disability compensation fulfills a critical role in helping people with occupational injuries or impairments, it can also perpetuate illness by requiring continuing symptoms and disability for the worker to be eligible for benefits. The worker cannot attempt an assertive recovery without risking the loss of a legal settlement or needed benefits (Engel and Katon, 1999). As noted by Hadler, "It is hard, if not impossible, to get well if you have to prove that you are sick" (Sullivan and Loeser, 1992, p. 1834). The period of "proving" the illness can also be protracted, sometimes lasting even years in the military system (Engel and Katon, 1999). Nevertheless, caution is indicated in applying such thinking to any individual.

PROGNOSTIC INDICATORS

Although the predisposing, precipitating, and perpetuating factors described above as influencing the natural history of medically unexplained symptoms are based on theory to provide a heuristic model, prognostic indicators are developed empirically. Prognostic indicators are characteristics of individuals or populations that clinicians, epidemiologists, and policy makers can use to estimate the future burden of illness and the magnitude of future treatment and re-

source needs (Engel and Katon, 1999). Empirically tested prognostic indicators for medically unexplained symptoms include indicators of prior level of use of the health care system, psychiatric manifestations, physical symptoms, and levels of functioning (Engel and Katon, 1999).

The prognostic spectrum of medically unexplained symptoms includes acute, recurrent, and chronic subtypes. Acute medically unexplained symptoms occur in the absence of a previous pattern or history of medically unexplained symptoms and last a few months at most, and the associated disability is often temporally associated with an acutely stressful life event. Recurrent medically unexplained symptoms are characterized by alternating symptomatic, asymptomatic, and mildly symptomatic periods. Chronic medically unexplained symptoms are a pattern of persistent unexplained symptoms associated with chronic disability, high levels of use of the health care system, and persistent problems with coping. Chronic coping problems are often associated with large numbers of physical symptoms (Russo et al., 1994, 1997). Individuals with chronic medically unexplained symptoms also often describe the occurrence of adversity during childhood (Walker et al., 1992).

Recognition of the importance of medically unexplained symptoms after wars going back at least as far as the Civil War and their importance in civilian populations makes clear the need to consider strategies to prevent and ameliorate them after future deployments. Throughout the chapters that follow, an emphasis is placed on the early recognition of medically unexplained symptoms and steps that might be taken to try to address them early, as well as the research effort that is needed to better understand their natural history and treatment.