# THE DEPRESSION-STRESS LINK

By CHRISTOPHER VAUGHAN

A country threatened with invasion mobilizes: Movement on roads is controlled, and consumers find everyday goods in short supply as industry switches to military production and food becomes scarcer with rationing. This course of action is highly advisable for a nation under siege, but what would happen if the threat went away and someone at the top forgot to demobilize?

National Institute of Mental Health (NIMH) psychiatrist Philip Gold suggests a comparable situation exists in the body during depression. When confronted with a threat, we all experience a complex biochemical and behavioral mobilization — an increased respiration rate, the release of stored energy, an increased sense of arousal — that helps us respond to that threat. This stress reaction — called the "fight or flight" response — is beneficial in the short run, but over time its effects might be devastating.

Gold proposes depression results when mechanisms that normally would regulate the stress response fail to do so. In a two-part article in the Aug. 11 and Aug. 18 issues of the NEW ENGLAND JOURNAL OF MEDICINE (NEJM), Gold and two colleagues present a stress-related model for depression that seeks to reconcile many scientists' longstanding psychological and physiological research about the origin and course of the illness.

Gold says he chose to focus on one kind of major depression, called melancholic depression, because other forms have a variety of symptoms that make it unclear whether they have one or more causes. Melancholic depression, which is diagnosed in 40 to 60 percent of those hospitalized for unipolar and manic depression, has a very consistent set of symptoms, making it a good subject for study, Gold says. It is typically characterized by low self-esteem, hopelessness and intense anxiety about the future, along with decreased eating, sleeping and sexual desire.

Psychiatrists have long accepted that stress can play a role in bringing on episodes of major depression, especially in young adults, but Gold is intrigued by the parallels between the biological stress response and what happens in the body during depression itself.

He notes that both melancholic depression and stress involve a decrease in feeding and sexual behavior, a suppression of the immune system, a decrease in the body's regenerative processes and an increased breakdown of molecules that store energy in the body. And although depressed patients often seem to think and react slowly, they are actually in a highly aroused state, focusing obsessively on their own sense of inadequacy, Gold says. This state of mind parallels the heightened sense of awareness and focus that plays a positive role in a short-term response to stress, he adds, but in depression that intense awareness and focus is turned inward, with psychologically crippling results.

Is it possible the same biochemical factors are at work? The chemical signals initiating the different aspects of the stress response are triggered by two factors in the brain, says Gold: corticotropin-releasing hormone (CRH) and a bundle of neurons called the locus ceruleus. Actions of both are strongly implicated also in melancholic depression, he says.

An often-noted biochemical abnormality in depressed patients — one whose diagnostic value remains in dispute — is a higher-than-normal level of cortisol, a stress-related hormone. Research by Gold and George Chrousos of the National Institute of Child Health and Human Development — a coauthor of the NEJM paper with Gold and Frederick Goodwin, director of the Alcohol, Drug Abuse and Mental Health Administration — suggests this hypercortisolism is indirectly caused by an overproduction of CRH and therefore by an activation of the stress circuits in the brain and body. Ordinarily, high levels of cortisol would deactivate the CRH stress system, but they seem unable to do so in depression, says Gold (SN: 5/24/86, p.324).

In stress, the locus ceruleus fires more rapidly and delivers the arousal-producing neurotransmitter norepinephrine to many diverse regions in the brain. The locus' role in depression is suggested by the calming effect some antidepressant drugs have on it. During treatment with antidepressants and after recovery, depression patients experience a lowering of norepinephrine levels in the central nervous system. Since the locus ceruleus is the biggest distributor of norepinephrine in the brain, this supports a major role for the locus ceruleus in depression, Gold says.

The picture of melancholic depression espoused by Gold and his colleagues is that the locus ceruleus and CRH systems, once activated, reinforce each other and activate the stress-response system. However, cortisol and other glucocorticoid hormones produced in the stress response, for reasons yet unknown, don't regulate the CRH and locus ceruleus systems properly. This leads to a free-running state of constant stress.

The model fits well with established psychological theories of depression, Gold says. One such theory holds that a person's exposure to a hypercritical or exploitive environment as a child leads to painful, unprocessed feelings that emerge reflexively when the person is exposed to stress later in life. Recent research by Gold and NIMH scientists Susan Weiss and Robert Post has revealed that chronic exposure to CRH in animals can sensitize areas of the brain involved in the emotions associated with stress, such as anxiety. After repeated exposure to CRH, these parts of the brain may become so sensitive that they will become activated by almost any novel situation, and sometimes by nothing at all. "This closely parallels the natural history of chronic depression," Gold says.

In animals, chronic exposure to high levels of cortisol can destroy brain cells that monitor cortisol levels and play a role in regulating the stress response, Gold says. A hyperactive reaction to stress or lack of stress-response regulation could also be due to genetic defects, he adds, noting that such a finding would agree with studies showing a genetic component involved in depressive disorders (SN: 3/28/87, p.199).

Other researchers find Gold's model intriguing. "The usefulness of the theory is that it provides a framework that should open things up for research," says Daniel X. Freedman of the University of California, Los Angeles, chief editor of the ARCHIVES OF GENERAL PSYCHIATRY. Gold has taken many longstanding concepts about depression "and anchored those concepts far better [than other researchers] in terms of established brain mechanisms," he adds.

Ironically, the overriding reason for depression may be that the stress response is "archaic" for modern humans, Gold says. "Much of the stress response — a higher heart rate, cessation of feeding, loss of sexual interest and so on — may be adaptive for a physical threat, but they aren't much use during emotional stress," he says. In other words, a system designed for short-term mobilization may be inadequate for handling the stresses of modern life, which tend to span longer periods and are often incompletely resolved, he suggests. "Emotional stresses tend to smolder, whereas physical stressors are often acute and short-lived," Gold says. □