Depression: Too Much Vigilance?

On the face of it, depression and Cushing's disease would appear to have nothing in common. The primary symptom of depression is overwhelming sadness, while victims of Cushing's disease are obese and suffer from high blood pressure, fragile bones and weak connective tissue. Yet until recently clinicians have had difficulty distinguishing the two disorders, and it has even been suggested that they might be different manifestations of the same neuroendocrine abnormality; many depressives tend, like all Cushing's victims, to have elevated levels of cortisol circulating in the bloodstream, and about half of those with Cushing's disease are also seriously depressed.

Now government scientists have developed a laboratory test that for the first time allows them to study the biological underpinning of each disorder, and they report that the defects are distinct. While both are linked to abnormalities in the body's stress response system, Cushing's disease appears to be a glandular disorder, while depression involves a brain defect that, in effect, keeps the body and mind in a constant state of readiness for a stressful situation.

When the brain perceives a stimulus as stressful, it signals the hypothalamus to secrete a neurohormone called CRF (for corticotropin-releasing factor), which travels through a privileged portal to the pituitary gland. There it triggers the release of opiates and another hormone called ACTH, which travels to the adrenal gland and in turn triggers release of cortisol and epinephrine (once called adrenaline); cortisol helps the body gear up for a stress response (fight or flight), while at the same time circling around to the pituitary to block the continued ACTH flow. Malfunction in this so-called HPA axis has long been implicated in both depression and Cushing's disease because of the apparently unregulated cortisol secretion seen in each.

What made the current studies possible was the isolation of CRF from the brains of sheep in 1981 (SN: 9/26/81, p. 200). Although it required decades of work and over half a million sheep brains to accomplish the task, scientists at the Salk Institute in La Jolla, Calif., finally succeeded in characterizing the small protein, leading to its subsequent synthesis. Using the synthetic CRF, psychiatrist Philip Gold of the National Institute of Mental Health and endocrinologist George P. Chrousos of the National Institute of Child Health and Human Development (both in Bethesda, Md.) have been probing the HPA axis; and as they reported at a recent NIMH seminar on stress, Cushing's patients and depressed patients respond differently.

When a Cushing's patient receives a CRF injection, the pituitary responds robustly, secreting ACTH, even though it should be held in check by the massive amounts of cortisol in the blood. This finding, they say, points to a pituitary defect in Cushing's disease. Depressed patients, in contrast, show a blunted pituitary response, indicating that the gland is responding normally to the negative feedback provided by the cortisol and that the HPA defect is in the hypothalamus. (Gold and Chrousos also used the CRF challenge test to distinguish among three forms of Addison's disease, a disorder of cortisol insufficiency that may originate in brain, pituitary or adrenal gland malfunction).

The hypothalamic defect in depression may be related to a persisting excess of CRF, Gold suggests. In a separate experiment, he administered CRF continuously to normal healthy subjects, and he found that they replicate the cortisol secretion pattern seen in depression. Unlike the normal controls, depressives given CRF also showed a significant increase in secretion of growth hormone, another normal response but one which is typically precipitated only by great stress (monkeys under chronic stress also showed the growth hormone response).

What this suggests, Gold and Chrousos conclude, is that high levels of CRF are persistently secreted in depressed brains. Evidence has been accumulating from several laboratories indicating that CRF exists in brain regions other than the hypothalamus and that it may be the single orchestrator of all the body's reactions — metabolic, circulatory and behavioral — to stressful situations; so in effect, Gold says, depressed people may be living in a state of chronic stress.

Based on this preliminary work, and on previous research with rats removed from their mother, Gold proposes a theoretical model linking early life stress and major psychiatric illness in adulthood. What may happen, Gold speculates, is that an early encounter with unpleasant stress may be relived throughout life, and the anxiety associated with that experience may make the hypothalamus chronically overactive to stress. —*W. Herbert*

Elaborating the stress response

Some 40 years ago the Austrian endocrinologist Hans Selye described the hormonal interplay that takes place during stress. Any environmental stimulus —good or bad, psychological or physical — produced the same general stress response, he said: The brain's hypothalamus signals the pituitary, which in turn signals the adrenal gland to secrete ACTH and beta-endorphin, the hormones involved in physical arousal (see adjacent story). The adrenal gland then provides a message to the pituitary to end the stress response. It was a neat and simple model.

A little too neat and simple, it turns out. Although Selye's model remains accurate as far as it goes, government research during the past few months has shown that several additional hormones are involved in triggering and controlling the stress reaction. According to National Institute of Mental Health biochemist and Nobel laureate Julius Axelrod, the new evidence suggests that the body does not respond generally and uniformly to stress. Instead, he says, the body may cope with different kinds of stressors in different ways, each way involving unique neurochemical pathways.

Axelrod and his colleagues have been studying the stress response in a cell line derived from mouse pituitary gland tumors; unlike normal pituitary gland cells, this unique line secretes only ACTH and beta-endorphin, making it a good model for studying which, if any, hormones can control the pituitary's stress chemicals.

They have found, for example, that synthetic catecholamines (a class of natural neurochemicals that includes epinephrine and norepinephrine) cause the pituitary to secrete ACTH, and that the secretion is blocked by the addition of cortisol — just as it occurs with CRF. They also found that a brain chemical called VIP (for vasoactive intestinal peptide, because it was originally found in the gut) and vasopressin have the same stimulating properties, and that somatostatin — a chemical that holds growth hormone in check — inhibits ACTH release, just as cortisol does.

The chemicals that stimulate ACTH release appear furthermore to do it through separate mechanisms in the pituitary gland, because when administered together their effects are additive. In addition, chronic triggering of ACTH release led to a steady decrease in the amount of ACTH released, suggesting that the system becomes sensitized and regulates itself downward when in chronic stress.

What all this indicates, according to Axelrod, is that an organism uses a sophisticated neuroendocrine network to maintain its internal chemical balance while coping with external challenges. — *W. Herbert*