HEALTH AND STRESS

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DEPRESSION, ANXIETY, STRESS AND THE HEART

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The links between stress and various emotional and physical diseases have been increasingly confirmed, and are now even acknowledged by previous skeptics. As noted in a previous Newsletter, a review commissioned by the prestigious and impartial Institute of Medicine and published in the *Journal of the American Medical Association* was designed to provide either convincing proof of such relationships or evidence to the contrary.

Also Included In This Issue

Institute members are elected because of their scientific contributions and receive no compensation. Their mission is to provide national advice on issues relating to medicine and health by providing independent guidance and analysis. Each report is devoted to a topic considered to be of great importance. After completion, it is then evaluated by a panel of external experts who remain anonymous until after the study has been published.

As the authors explained in their opening remarks,

> Despite widespread public belief that psychological stress leads to disease, the biomedical community remains skeptical of this conclusion. In this Commentary, we discuss the plausibility of the belief that stress contributes to a variety of disease processes and summarize the role of stress in 4 major diseases: clinical depression, cardiovascular disease (CVD), human immunodeficiency virus (HIV/AIDS), and cancer.

One wonders why these particular four diseases were selected. Was it because they were the most controversial or there was greater evidence to confirm or contradict the role of stress as an initiating or aggravating influence? The fact that depression and coronary heart disease received top billing suggests the latter, as these showed the most solid scientific support for a causal relationship. The Institute of Medicine report noted that,

> Stressful life events have been linked to major depressive disorder as well as to depressive symptoms. During the 3 to 6 months preceding the onset of depression, 50% to 80% of depressed persons experience a major life event, compared with only 20% to 30% of nondepressed persons evaluated during the same period. Approximately 20% to 25% of persons who experience major stressful events develop depression.
>
> Although most investigations have focused on life events as triggers of depression onset, increased stress also predicts the clinical course of major depression, including features such as longer duration, symptom exacerbation, and relapse. Evidence also suggests that events that occur concurrently with treatment reduce positive responses.

Several references from 1991 to 2005 were cited, but there was little discussion in any of these or the report about mechanisms of action that might explain the association between stress and depression or depression and heart disease. As emphasized in previous Newsletters, there is little doubt that stress can cause heart disease, and especially sudden death. This was recently confirmed in the INTERHEART study of 30,000 patients in over 50 countries, which evaluated the relative importance of nine risk factors associated with heart attacks. It found that psychosocial distress was a better predictor than hypertension, smoking, diabetes, abdominal obesity and other acknowledged risk factors. Psychosocial stress scores were based on ratings of stress at work or home, financial problems, stressful life events, depression, and perception of control over daily life circumstances. **Participants with high psychosocial stress levels were over 2.5 times more likely to suffer a heart attack than those at the lower end of the scale.** However, the figure is probably higher, since stress can also cause hypertension, smoking, diabetes and abdominal obesity. What is not clear is whether depression cause heart disease to a greater extent and/or by different mechanisms than anxiety, anger, hostility and other stressors.

How Could Depression Cause Or Worsen Coronary Heart Disease?

Most studies have concentrated on patients with a history of heart disease, demonstrating that those who are depressed have a poorer prognosis. The problem is that how that depression is defined and/or rated with respect to its severity can differ. Everyone feels down in the dumps occasionally, or for

prolonged periods following significant upsets, such as the death of a loved one or losing their job. When such individuals suffering from grief or sadness are evaluated, it can be difficult to distinguish these normal mood changes from clinical depression. According to the American Psychiatric Association, the diagnosis of a significant depressive disorder requires that a person experiences a loss of interest in the things they once enjoyed, has been depressed, sad, or down in the dumps for at least two weeks, and has had at least five of the following symptoms during this period:

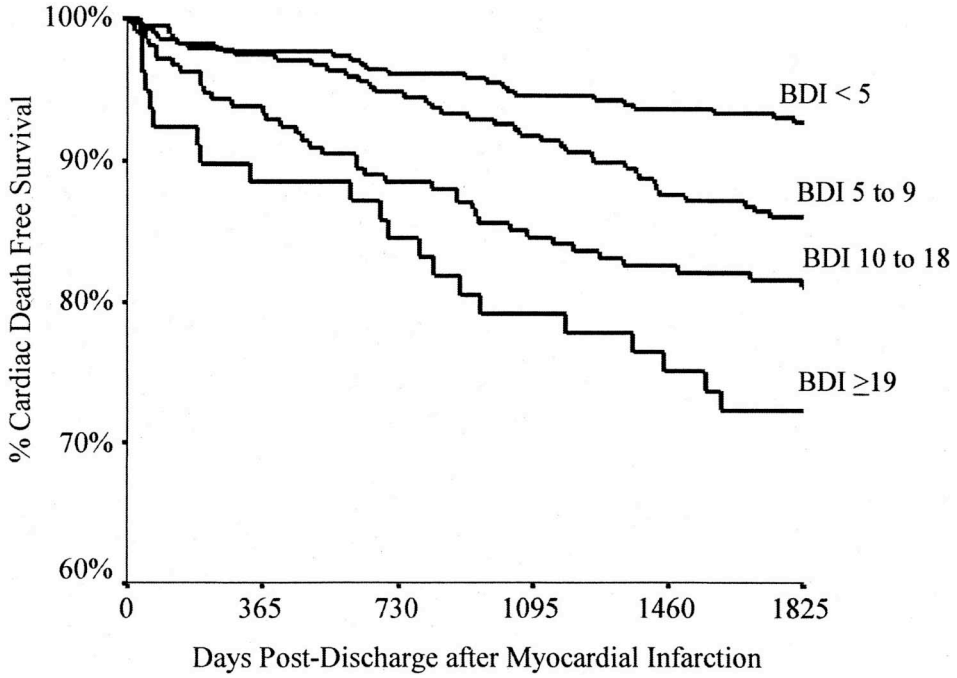
- thoughts of death or suicide
- problems concentrating, thinking, remembering or making decisions
- trouble sleeping or sleeping too much
- loss of energy or feeling tired all of the time
- feeling lethargic or restless and unable to sit still
- feeling worthless or guilty
- a significant increase or decrease in appetite or weight
- headaches
- digestive difficulties
- sexual problems
- feeling pessimistic or hopeless
- being anxious or worried

Bipolar disorder, or manic-depressive illness, is diagnosed when depressed patients experience a feeling of euphoria or being "high" for at least one week, along with inappropriate social behavior, increased talking, insomnia and other signs and symptoms of increased energy. While these dramatic mood switches can be rapid, they are more likely to be gradual and depression often predominates. When tested during this period, bipolar patients may have all of the symptoms of depression, but could require different treatment. In addition to problems related to accurate diagnosis, there can be difficulties in rating the severity of depression. This is important, since proof that depression contributes to heart disease would be more convincing if there were a clear correlation existed between the degree of depression and the incidence of coronary events. It is also necessary to exclude patients in which heart disease may have caused depression.

To explore this, a landmark 2002 article in *Circulation* by Lespérance, Frasure-Smith and co-workers examined the "Five-Year Risk of Cardiac Mortality in Relation to Initial Severity and One-Year Changes in Depression Symptoms After Myocardial Infarction." As the authors noted,

> Although previous research demonstrated an independent link between depression symptoms and cardiac mortality after myocardial infarction (MI), depression was assessed only once, and a dose-response relationship was not evaluated.

In this study, the 21-item Beck Depression Inventory (BDI) was administered to almost 900 heart attack patients during admission and one year later. Around 40% had BDI scores in the low normal range (<5), followed by 30% with high normal scores (5 to 9), 20% with mild depression (10 to 18), with 9% moderately to severely depressed (19 or higher).



As illustrated above, baseline BDI scores were significantly related to both 5-year cardiac and all-cause mortality. Furthermore, there was evidence of a dose-response relationship between the severity of depression symptoms and long-term prognosis. These results remained statistically significant after controlling for multiple measures of severity of cardiac disease and other possible confounding factors. One-year depression scores were also linked to cardiac mortality but the changes were not signigicant. Patients with higher baseline scores still had worse long-term prognosis, regardless of any improvement in symptoms, suggesting that the initial mechanisms linking depression to higher mortality rates were permanent.

If depression causes heart attacks - or vice versa, how are these effects mediated? Since the Institute of Medicine report, several attempts have been made to answer these and other intriguing questions about the "chicken or egg" interrelationships between depression and heart disease. One recent study published in the Nov. 26, 2008 issue of *The Journal of the American Medical Association* summarized the problem as follows:

> Despite the substantial body of evidence demonstrating a strong link between depression and cardiovascular disease, the explanation for this association remains unclear. Several candidate mechanisms have been

> suggested as potential mediators, including smoking, lack of exercise, medication nonadherence , worse underlying cardiac disease severity, lower heart rate variability, antidepressant toxicity, enhanced activity of the hypothalamic pituitary axis, greater catecholamine levels, dietary factors, low omega-3 fatty acid levels, increased serotonin and platelet activation, and inflammatory processes. However, the extent to which these proposed mechanisms explain the increased risk of cardiovascular events in depressed patients is unknown

In an effort to determine which of the above might be most important, these researchers at the Veterans Affair Medical Center in San Francisco, followed over 1000 outpatients with stable coronary heart disease for over four years. Patients were eligible to participate in this "Heart and Soul" study if they had a history of myocardial infarction, angiographic evidence of at least 50% stenosis in one or more coronary vessels, prior evidence of exercise-induced ischemia by treadmill or nuclear imaging testing, a history of coronary revascularization, or a documented diagnosis of coronary artery disease by an internist or cardiologist. All participants had a baseline psychiatric interview to ascertain whether there had been a recent major depressive disorder, completed a questionnaire to rate current depressive symptoms, an echocardiogram, exercise treadmill test, ambulatory electrocardiogram monitoring to assess heart rate variability, and a 24-hour urine collection to measure cortisol and norepinephrine excretion. In addition to routine chemistries, blood tests included measurements of LDL, HDL and total cholesterol, serotonin, C-reactive protein (CRP), and omega-3 fatty acids. Serotonin is a brain neurotransmitter believed to be deficient in depression, CRP is an indicator of inflammation, and omega-3 supplements have been found to significantly improve mood in some depressed patients and may also be effective in helping to prevent heart attacks. Potential behavioral and lifestyle influences such as smoking, drinking, and exercise habits, physical fitness, social support, general health, prescription and nonprescription medications and supplements were also evaluated.

This study confirmed the correlation between depression and heart disease. After careful analysis of all possible confounding influences, the authors concluded that depression causes behavioral changes like smoking and failure to take medication, **but it was primarily lack of physical activity and exercise that increased heart attack in depressed patients.** The possibility that less physical activity was due to more severe heart disease was ruled out. However, since all the participants had stable heart disease, and most were older men, it is not known if this also applies to women and younger individuals, or whether exercise has a similar cardioprotective effect in healthy people and patients with coronary complaints.

Some of these concerns were addressed in a study of middle-aged healthy men and women enrolled in the Scottish Health Survey, originally designed to provide information on the health of Scottish people living in private homes. Subjects completed a standardized questionnaire designed to measure symptoms of depression and anxiety, sleep disturbances and general level of happiness. Information was collected on height, weight, physical activity, alcohol intake and smoking, and researchers had access to hospital and medical records. Blood was tested for LDL, HDL and total cholesterol, as well as CRP. Over the seven-year follow up period, there were 63 deaths and 223 major cardiovascular events, defined as a heart attack, stroke, bypass surgery, or angioplasty. The results, published two months ago in the *Journal of the American College of Cardiology*, revealed that **depressed and anxious people had more than a 50 percent increased risk of cardiac problems and deaths compared to happier and less stressed controls.** The most significant finding was the link between stress and both the onset and relapse of depressive symptoms that altered lifestyle and behavior. This was particularly apparent following major life change events such as death of a spouse or divorce that frequently led to increased smoking and decreased exercise. Depression tended to be more frequent in participants with serious illnesses that similarly curtailed physical activity. Hypertension and increased CRP levels were associated with increased heart disease risk to a lesser degree, but both of these were also much more common in depressed participants.

These studies and others suggest that the mechanism by which depression causes heart disease is primarily by promoting poor health behaviors, and especially decreased physical activity. While there is little doubt that regular exercise benefits the heart and can also improve mood, there is no strong evidence that couch potatoes are more depressed than more physically active controls. Heart disease and depression are more common in the elderly than any other age group. One in five 80 year-old Americans has experienced symptomatic coronary disease, and depression affects 20 percent of senior citizens living in the community and 40 percent of those in care facilities. Older people also exercise less and physical activity is often limited due to physical limitations. However, a study of elderly people published two months ago in *The Archives of General Psychiatry*, reported that increased deep abdominal fat was much more important than lack of physical activity in explaining the link between heart disease and depression. Previous studies have shown a correlation between depression and larger amounts of deep abdominal fat, but not whether this was cause or effect.

An attempt to find out was made in this evaluation of over 3,000 actively functioning black and white community dwellers aged 70 to 79 living near Pittsburgh, Pennsylvania and Memphis, Tennessee, who were participating in

The Health, Aging, and Body Composition Study. Depression was rated at baseline, as was overall obesity using the Body Mass Index (the ratio of height to weight), and the percentage of body fat as determined by dual-energy x-ray absorptiometry. Abdominal obesity was assessed by waist circumference, sagittal diameter (the width of the body from front to back around the abdominal area), and visceral fat content, as measured by computerized tomography imaging. After adjustment for demographic, lifestyle, physical activity, disease, and other possible influences, patients who were depressed at the start of the study were much more likely to have an increase in both visceral fat and sagittal diameter measurements five years later. The association with greater waist circumference just fell short of reaching statistical significance. **Depression doubled the likelihood of a marked increase in visceral fat, and since there was no change in overall obesity, it is doubtful that this could be attributed to diet.**

Beer Bellies, Cortisol, Inflammation, HRV And Other Coronary Risk Factors

But how could abdominal obesity cause heart attacks and why should being depressed bring on a beer belly? Unlike fatty deposits in the buttocks and thighs, abdominal fat cells release cytokine chemicals that promote inflammation, insulin resistance, hypertension, Type 2 diabetes, and lipid disturbances that are associated with increased risk for heart disease. Studies in humans and animals have demonstrated that the deposition of deep abdominal or visceral fat is due to cortisol, which tends to be elevated in depression. Cortisol is often referred to as the "stress hormone" because it is secreted from the adrenal cortex during stress. This response originates in the hypothalamus with the production of corticotrophic-releasing hormone (CRH) that triggers the pituitary to make adrenocorticotrophic hormone (ACTH), which then stimulates the adrenal cortex to secrete cortisol. Under normal circumstances, when cortisol levels rise, ACTH production slows down or stops. Many depressed patients have a failure in this suppressive feedback mechanism and CRH continues to stimulate the pituitary to make ACTH, despite elevated cortisol concentrations. Depressed patients also often have increased amounts of CRH in their cerebrospinal fluid.

Cortisol levels usually peak at 8:00 a.m. and 4:00 p.m. and are lowest during the night. However, this normal circadian rhythm is disrupted in about half of depressed patients, so that cortisol is constantly elevated, or actually peaks in the middle of the night. This abnormality has been used to diagnose depression using the dexamethasone suppression test (DST). One mg. of Dexamethasone, a powerful synthetic cortisol-like steroid, is administered at 11 p.m. and cortisol is measured at 4:00 p.m and 11 p.m. the following day. This normally suppresses cortisol to less than 2 mcg/dL for 24 hrs. and blood levels greater than 5 mcg/dL in either specimen is indicative of endogenous depression. Dexamethasone suppression using

different dosages was originally developed to detect Cushing's disease, where elevated cortisol is due to a pituitary tumor and abdominal obesity is common. When the tumor is removed, cortisol levels and daily rhythms return to normal, and excess visceral fat disappears. Middle-aged men and baboons subjected to chronic stress similarly show high cortisol levels and increased abdominal fat deposits, both of which also return to normal when the source of stress is removed. The explanation for this is that abdominal fat cells are studded with receptor sites for cortisol that attract the hormone, which stimulates their proliferation and the production of chemicals that promote inflammation and coronary atherosclerosis.

One would therefore expect to see evidence of increased inflammation in depressed patients. To investigate this, researchers from the University of Montreal and McGill evaluated the impact of depression on markers of inflammation in 741 men two months following admission to the hospital for an acute coronary event. Depression ratings were based on Beck Depression Inventory scores and inflammatory markers included C-reactive protein (CRP), interleukin-6 and soluble intercellular adhesion molecule, all of which have been shown to be associated with increased risk for coronary disease. Over the next two years, 78 men experienced at least one major adverse cardiac event, such as a survived myocardial infarction or arrest, nonelective revascularization procedure or death. As noted previously, BDI scores of 10-18 reflect mild depression and in this study, scores of 14 or more correlated with an increase in cardiac complications, as did high CRP levels. Men with both elevated BDI scores and CRP did not experience more adverse events than those with only one, suggesting that these are overlapping, rather than separate and additive risk factors.

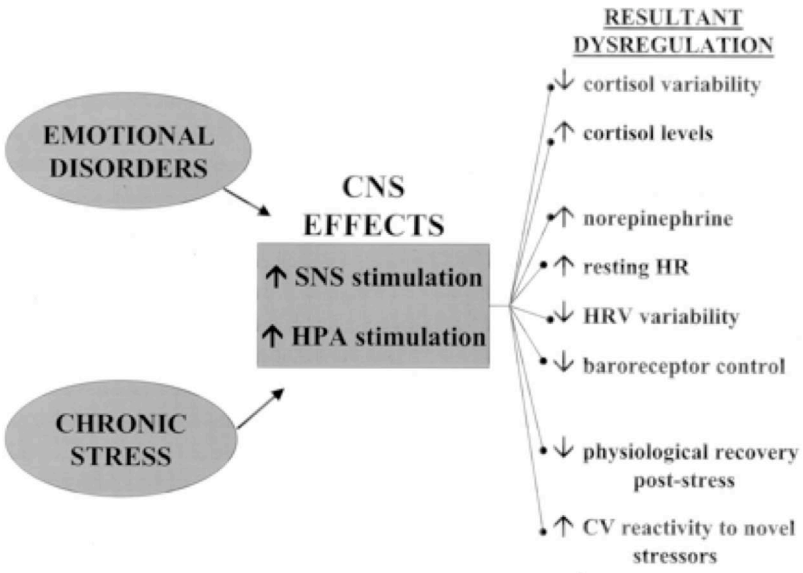
Heart rate variability (HRV), which is a measure of how well the body adapts to demand for change during respiration, may be the most accurate objective measure of stress. Low HRV due to sympathetic stimulation or suppression of parasympathetic activity is a powerful predictor of sudden death, the leading cause of death in developed countries. Sudden death is usually due to a lethal disturbance in heart rhythm, and while it has been reported in healthy young individuals who experience intense emotional excitement, it is much more likely to occur in patients with heart disease. Depression has been demonstrated to be an independent risk factor for sudden death, and sudden cardiac death accounts for most of the increased mortality from heart disease seen in depressed patients. These excess deaths appear to be due to low HRV based on the Enhancing Recovery in Coronary Heart Disease (ENRICHD) study, designed to determine whether psychosocial intervention would reduce mortality. Researchers compared 311 patients who became depressed following a heart attack with 367 non-depressed controls and followed them for an average of two-and-a-half

years. They found that **depressed patients were nearly three times as likely to die during the study period as comparable, non-depressed heart patients and that deaths tended to correlate with the degree of diminished heart rate variability.** Although cognitive-behavioral therapy improved symptoms in many patients, it had no effect on mortality rates.

The effect of depression on HRV has not been investigated as extensively in patients without heart disease. One study found that HRV was lower in pregnant women who became depressed and another reported similar findings in post-menopausal women without heart disease. To further explore this, healthy participants (average age 41) in the Netherlands Study of Depression and Anxiety (NESDA) were carefully interviewed and rated for past and present evidence of depression and monitored to evaluate several components of heart rate variability. They were divided into three groups: 1) controls with no history of depression or anxiety and low scores on a depressive symptom questionnaire; 2) those having a history of depressive disorder more than 6 months previously; 3) others with a confirmed diagnosis of depression within the past 6 months. Significantly low HRV was seen only in men and women with recent complaints or a history of past depression. Depression might also cause heart disease via increased sympathetic activity effects on platelets as well as the autonomic nervous system. Depressed patients often have increased platelet activation and aggregation that quicken coagulation and contribute to clot formation. Depression is also associated with elevated levels of blood norepinephrine that similarly disrupt autonomic balance and lower heart rate variability.

The question is, "Have any of the proposed mechanisms of action resulted in successful treatment approaches to prevent or reduce the heart disease that is associated with depression?" Unfortunately, the answer is a resounding NO! That's not surprising, since none of these abnormalities occur in all depressed patients, no matter how severely they are affected. As will be explained, the reason for this is that depression is not a discrete disease. Diseases can be defined by some objective finding that is always present, such as an elevated blood sugar in diabetes, or a positive sputum culture, biopsy, x-ray, skin test, etc. for tuberculosis. In many instances, such abnormalities provide a clue about the cause of the disease. Thus, all cases of tuberculosis are due to infection with the tubercle bacillus, just as all patients with diabetes have either a deficiency of insulin or an inability to utilize it. Depression is simply a description of subjective symptoms that a patient reports. There are likely multiple causes for these symptoms since they are not accompanied by any consistent objective finding that is shared by all. And the associated abnormalities are hardly specific for depression, since they can occur in different emotional disorders. They can also result from poverty, frustration and other types of chronic stress, suggesting they

may have a common pathway, as summarized below.



From Rozanski A, Kubzanski LD *Psychosom Med* 2005 67: S47-S53

As illustrated, people with depression and other emotional disorders as well as those subjected to chronic stress, have responses that are characterized by overstimulation of the hypothalamic–pituitary–adrenal (HPA) axis and sympathetic nervous system (SNS). The resultant dysregulation of these systems may lead to decreased cortisol variability, increased cortisol levels, disruption in normal cortisol secretory rhythms and regulatory mechanisms, high norepinephrine levels, low heart rate variability, elevated resting heart rate and other manifestations of autonomic dysfunction. The response to chronic stress is also characterized by a prolonged recovery period to physiological stimulation and exaggerated cardiovascular reactivity to novel stressors.

If Depression Is A Description, Not A Diagnosis, What's The Best Treatment?

There is a common tendency to assume that just because you have given something a name, that you have somehow defined it, or possibly even understand its cause. This is particularly true for diseases that are really only signs or symptoms, like hypertension and depression. Hypertension is merely the observation that a blood pressure measurement is higher than what has arbitrarily been established as the upper limit of normal. Hypertension can have many causes, which explains why we have a hundred or more drugs alone or in combination, with no guarantee as to which will work best in any given patient. In some instances, the same medication given to two hypertensive patients with the same blood pressure might be helpful to one, but harmful to the other. A similar situation existed centuries ago, when "fever" was a popular diagnosis in patients with an elevated temperature of unknown origin. However, treating a fever rather than its cause can be dangerous. A temperature of 104° will respond dramatically to

cortisone, regardless of whether it is due to an autoimmune disease or a severe infection. Nevertheless, although the identical course of cortisone therapy could remarkably improve a patient suffering from disseminated lupus, it might be lethal in another with tuberculosis. Successful treatment depends on eradicating causes, not relieving symptoms or signs.

There is no single cause for the complaints that we lump together as a disease labeled "depression", which again explains why we have so many very different treatments, including: various types of drugs (monoamine oxidase inhibitors, tricyclic and tetracyclic antidepressants, selective serotonin reuptake inhibitors, lithium, estrogen, melatonin, amphetamines); supplements (St. Johns wort, Ginkgo biloba, panax Ginseng, SAM-E, fish oils, omega-3, glutathione calcium, vitamin D, folic acid and other B vitamins); psychiatric interventions (psychoanalysis, cognitive restructuring, group therapy, stress reduction); sleep deprivation; exercise; ultraviolet light; acupuncture; surgery (stereotactic cingulotomy, deep brain or vagal stimulation with an implanted device); electroconvulsive therapy (ECT); and novel bioelectromagnetic approaches such as cranioelectrical stimulation and repetitive transcranial magnetic stimulation (rTMS). That is why, with a few exceptions, we don't know which will work or be best for any specific person. However, electroconvulsive (shock) therapy is effective in almost all severely depressed patients. Although it has been used for eighty years and is given to over one million patients annually, we still don't know why it works.

Depression can be seen in thyroid and other endocrine disturbances, in patients suffering from stroke, Parkinson's and other neurologic diseases, inflammatory disorders like lupus and rheumatoid arthritis, various vitamin deficiencies, increased homocysteine, and as a side effect of numerous medications. People with Seasonal Affective Disorder become depressed during the winter months because of diminished exposure to daylight. A family history of depression increases risk but how much is genetic as opposed to a behavior learned from contact with depressed relatives can be difficult to determine. Some researchers believe there is a specific depression gene but it seems more likely that multiple genes may be involved in different individuals and most patients with significant clinical depression do not have a family history. Hormonal influences obviously play a role since depression is two to three times more frequent in women than men, especially following delivery, where it is referred to as post partum depression, and can cause suicide and unbelievably violent acts. Depression is so common following menopause that there was formerly a disease called "involutional melancholia", the melancholy associated with "change of life". Melancholy comes from the Greek *mélas* (black) and *chole* (bile) because Galen believed that depression was due to an excess of black bile that

predisposed women to cancer of the reproductive organs. Studies now show that depression is a significant risk factor for cancer of the cervix and breast.

Depression, a leading cause of disability in the U.S., is projected to be the second leading cause of death by 2020, exceeded only by heart disease, which it also causes. Most patients are treated with drugs designed to boost serotonin despite the fact that they are hardly more effective than placebos in clinical trials, have serious side effects, and serotonin levels are normal in most patients. Several drugs are banned in the UK and other countries for anyone 18 or younger because of increased suicides. Some depressed patients who show a deficient energy pattern in the left prefrontal lobe with sophisticated imaging procedures respond to repetitive transcranial magnetic stimulation. This suggests that depression may be due to disturbed communication in the brain, but testing and treatment is quite expensive and long-term benefits or adverse side effects are unknown. So what should a depressed patient do? The best advice would appear to be to try anything that is perfectly safe, has scientific support, and has been demonstrated to help others. Certain supplements, cognitive and behavioral approaches, stress reduction programs and tapes, as well as lifestyle changes, such as regular exercise and increasing social support, do fulfill these criteria.

A good illustration is provided by two articles and an editorial in the current (Jan. 15, 2009) *British Medical Journal* on preventing and treating post partum depression. A Canadian study of mothers at high risk found that telephone based peer support from another who had personally experienced post partum depression was very effective in preventing this problem three months following delivery. A UK report evaluated the effect of regular visits to depressed mothers by healthcare workers who had received special training in post partum depression. Mothers who were depressed six weeks after delivery were 40% more likely to be markedly improved six months later compared to controls receiving usual care. Unfortunately, this type of counseling is not readily available. However, there is good evidence that stress reduction tapes and programs by individuals who have suffered and/or experienced similar problems may be equally effective by providing insight and strong social support. To find out more about this - stay tuned!

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