HEALTH AND STRESS

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DEPRESSIVE DISORDERS: ARE THEY REALLY TRUE DISEASES?

KEYWORDS: Anhedonia, involutional melancholia, lunatics, exorcism, Bedlam, hypnosis, the "talking cure", *dementia praecox*, Thorazine, SSRI's, rTMS, heredity

Given the severe disability associated with the diagnosis of depression and the numerous medications and other modalities that are used to treat it, this might seem like a silly question. Yet, this has been an ongoing subject of debate between leading psychiatrists for over a decade despite the fact that depression has been firmly established in the Diagnostic and Statistical Manual of Mental Disorders (DSM) since it was first published over fifty years ago by The American Psychiatric Association.

Those who object to this argue that by definition, a disease is a disorder of body function characterized by at least two of the following: consistent anatomical alterations, identifiable signs and symptoms and an established cause. Thus, typhoid fever is a disease but Spring fever is not. It is a metaphor, just as the whale is a real animal but a metaphorical fish. This in no way is meant to minimize the human suffering from depression, which exists just as the whale exists, but it is not a true disease.

Diseases are usually diagnosed based on a cluster of signs, objective physical or physiological lesions, or abnormalities such as neurochemical imbalances that can be measured. The fact that you actively treat something with medication, surgery or something else does not automatically make it a disease. Depression treatment in the past has meant locking up people in prisons called asylums or hospitals, electroconvulsive shock and insulin coma therapy, lobotomy, and more recently, forcing them to take drugs, with no consistent results. That is not the same as treating diabetes with insulin.

Severely depressed individuals are at markedly increased risk of taking their own lives. However suicide is as old as mankind and it is not always due to depression. Numerous individuals throughout history have been exhilarated as they sacrificed themselves for some cause in the belief that they would be rewarded in the hereafter. Suicide is a moral and legal problem, just as is murdering other people or even animals, but it is not a medical disease.

ALSO INCLUDED IN THIS ISSUE

Depression is not found in a corpse at autopsy by either gross or microscopic examination because depression has no consistent physical or physiologic changes. Critics claim that it is crucial to distinguish between behavior and disease. Depression is simply a description of certain changes in mood or behavior. These changes can have various causes, which is why we have so many very different therapies.

How Can Depression Be Diagnosed?

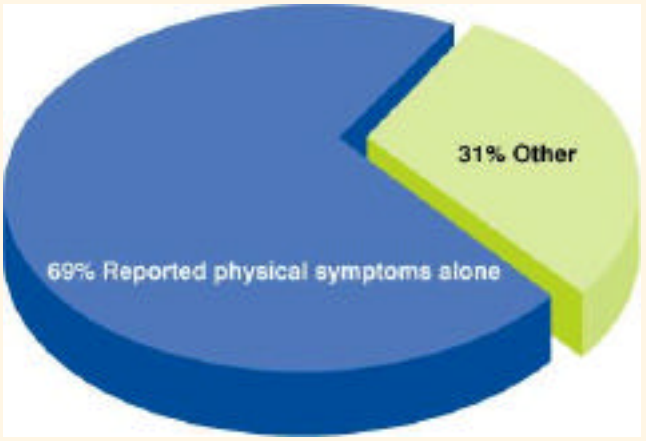
Depression can be manifested by chronic or intermittent depressed mood, sometimes commingled with anxiety, as well as mood swings that alternate between deep depression and severe hyperactive and manic behavior. According to the latest formal criteria listed in DSM-IV, the diagnosis of depression must include the following:

The presence of at least **FIVE of the following symptoms for at least 2 WEEKS**.

1. Sad, depressed mood, most of the day, nearly every day.
2. Anhedonia - loss of interest and pleasure in activities that are usually enjoyable.
3. Difficulties in sleeping (insomnia), or a desire to sleep a great deal of the time.
4. A shift in activity level, becoming either lethargic or agitated.
5. Poor appetite and weight loss, or increased appetite and weight gain.
6. Loss of energy, great fatigue, negative self-concept, self-reproach and self-blame, feelings of worthlessness and guilt.
7. Complaints or evidence of difficulty in concentrating, such as slowed thinking and indecisiveness.
8. Recurrent thoughts of death and suicide.

In addition, **at least ONE of these symptoms must include depressed mood or loss of interest and pleasure**. The severity of depression depends on the degree of disability. The above is a simplified version of the DSM-IV criteria that emphasizes emotional symptoms such as sadness, a loss of pleasure and interest in usual activities, feeling overwhelmed, anxious, inappropriately guilty and diminished ability to concentrate or make decisions.

What is often not appreciated is that there are also physical symptoms, including vague aches and pains, headache, a whole spectrum of sleep disturbances, fatigue, back pain or changes in appetite that result in either significant weight gain or weight loss. **It is often these physical symptoms that prompt visits to primary care physicians.**



The above diagram is taken from a *New England Journal of Medicine* study of 1146 patients diagnosed with major depression. It found that more than two out of three reported unexplained physical symptoms as their chief complaint. In many, if not most instances, these are apt to be attributed to some organic disorder rather than depression. This frequently results in extensive diagnostic workups that fail to find anything and lead to the conclusion that the patient is neurotic.

It is estimated that as many as 10% of all patients seen by family physicians and internists are significantly depressed. The vast majority are not diagnosed or treated properly because few patients mention this problem or doctors list some other diagnosis due to concerns that insurers will not reimburse for depression or because of its attached stigma.

Who Becomes Depressed Or Suicidal?

Depression is most likely to surface in the late teens or early twenties but is increasingly being seen in children and young adolescents. The incidence is relatively high in senior citizens where it is not treated because it is not recognized and/or misdiagnosed for reasons previously

cited. In one study, although 21% of elderly patients were depressed only 1% ever mentioned this problem to the doctor. Three out of four family physicians do not accurately diagnose depression because they ignore symptoms or confuse them with other problems in the elderly such as dementia, Parkinson's, arthritis, small strokes and thyroid disease. People who lack insurance that covers mental health costs are also likely to have adverse socioeconomic situations that greatly increase their risk for depression.

As many as 1 in 3 individuals will experience clinically significant depression at some point in their lives; the gender breakdown is 7 - 12% for males compared to 20 - 25% for females. Why are women two to three times more likely to develop depression than men?

The most likely explanation is some sudden fluctuation or derangement in female hormone levels. This is supported by the increased incidence of depression in women with premenstrual syndrome (PMS) complaints or following childbirth. Depression is so common following menopause that there was formerly a disorder called "involutional melancholia", or the melancholy associated with "the change of life". Affected individuals often improved with hormone replacement therapy. Women are also more likely to be diagnosed correctly because they are more willing to admit their true emotions and to seek treatment than men.

Others suggest that women suffer more stress than men. The Mitchum "Stress in the 90's" survey found that housewives were under more stress than CEO'S. Depression is on the increase in females. According to the WHO (World Health Organization), being a woman should be considered a risk factor for depression in all primary care patients. They predict that by 2020, depression will be the leading cause of long term disability in women.

The mean age of onset of depression is 25, the duration of symptoms is very variable, remissions are common, and the most serious concern is suicide. Over 300,000 people deliberately kill themselves every year. Suicide is the 9th leading cause of death and while more females attempt suicide than males, deaths from suicide are actually higher in men. Suicide is more likely to occur in those who have:

- A family history of suicide.
- A history of attempted suicide.
- A history or evidence of some significant psychological disorder.
- Problems related to alcohol or drug abuse.
- Low serotonin levels.
- Been subjected to a very shameful or humiliating experience.
- Been exposed to excessive publicity and media coverage about suicide.

There are numerous misconceptions and myths about suicide, including:

- People who talk about suicide won't do it.
- Suicide has no warning.
- Only people of a certain class are likely to commit suicide.
- Suicide is a lonely event.
- Suicidal people clearly want to die.
- Thinking about suicide is rare.
- All people who commit suicide are likely to be depressed. (The Japanese Kamikaze pilots and more recently the 9/11 tragedy and suicide bombings in Israel all involved individuals who were often elated because they believed they would be martyrs and heroes.)

The World Health Organization has warned that depression is reaching epidemic proportions. It has also predicted that by 2020 depression will be second only to coronary heart disease as the leading cause of death and disability in the world. One of the reasons for this is recent evidence confirming that the stress of depression is a significant risk factor for obesity, stroke, heart attack, hypertension, breast and other cancers. The common denominator that links all of these diverse disorders appears to be the well demonstrated role of stress in promoting the production of inflammatory cytokines that are known to contribute to each of these diseases.

Historical Highlights Of Depression

The Bible, Ancient Greece And Egypt

Saul, the first King of Israel, suffered from bouts of severe depression. The only relief came from the music that the young David played for him on the "Kinnor", the forerunner of the harp. After David succeeded Saul as King he also became depressed as a result of his adultery and in Psalm 38:6,8 wrote, "I am troubled, I am bowed down greatly; I go mourning all the day long." His relief came from confession and seeking God's forgiveness "...I acknowledged my sin to You, And my iniquity I have not hidden. I said, "I will confess my transgressions to the LORD," And You forgave the iniquity of my sin." (Psalm 31:22) Abraham, Jonah, Job, Elijah and Jeremiah also suffered from severe bouts of depression.

Hippocrates (400 B.C.), considered to be the Father of medicine, used hysteria to describe abnormal behavior, headache and vague abdominal complaints in unmarried Greek women. He attributed these symptoms to an unnatural state of sexual abstinence that caused the uterus (*hysterikos*) to wander throughout the body in an attempt to seek fulfillment. The cure was to coax the uterus back to its proper position in the pelvis by placing sweet smelling balms and herbs at the vagina and positioning noxious disagreeable potions at the nostrils, possibly one of the earliest attempts at aromatherapy. Hippocrates was also the first to describe postpartum depression.

Galen (150 A.D.) believed that an excess of black bile (Gr. *mélas chole*) caused depression (melancholy) in women and predisposed them to cancer of the reproductive organs. Numerous studies over the past 150 years have demonstrated that depression is a significant risk factor for cancer of the cervix and breast.

In ancient Egyptian medicine, depression was described as: "fever in the heart", "dryness of the heart", "falling of the heart", and "kneeling of the mind", since the heart and mind were viewed as synonymous. Hysterical disorders were described in the Kahun Papyrus and were treated by "incubation" or "temple sleep", during which several nights were passed in the court of a special sleep temple.

Divine healers and priests interpreted dreams received during this period and their psychotherapy efforts were enhanced by the temple atmosphere and the confidence in the supernatural powers of the deity. In ancient Egypt and Greece the mentally ill were cared for kindly and treated as victims of disease. Music and art were used to quiet the nerves and recreational and occupational activities were encouraged.

The Middle Ages To The 18th Century

Depression was thought to occur primarily in women and to be related to the monthly (lunar) cycle. Hence the term lunatic and the belief that the full moon was associated with violent behaviors and transformation into creatures like werewolves or vampires that attacked people. The Church viewed depression and mental illness as being due to demonical possession, particularly in witches. The mentally ill were not sick but possessed by devils that had to be driven out by visits to magical shrines and spiritual exorcism. More often, they were subjected to immersion in ice water, flogging, burning and other cruel punishments that bordered on torture. There were no hospitals and many were chained and confined to dungeons and treated like animals.

Rene Descartes (1596-1650), the famous French philosopher - scientist had a profound influence on furthering the split between body and mind and promoting the role of the church in treating mental illness. In his view, the body was an intricate machine. Illness resulted when disease or injury damaged any of its parts and the physician's function was to find and fix the problem. Mental disorders were entirely beyond man's comprehension and were under the jurisdiction of the church, so that they could be treated by priests.

Bethlehem Hospital was originally a priory established in 1247 in London for the order of the star of Bethlehem. Bethlem or Bedlam as it was called, was given by Henry VIII to the city of London in 1547 "as a hospital for lunatics" and became infamous for its brutal treatment of the insane. In the 1700's, people could pay a penny to view the freaks of the "show of Bethlehem" and laugh at their antics.

The Emancipation Of The Mentally Ill

The confusion, chaos and clamor at Bedlam were immortalized by William Hogarth in his famous 1735 etching "*The Rake's Progress*". We still use the word "bedlam" to describe such scenes and situations of pandemonium. This was largely brought to an end by the efforts of Phillipe Pinel (1745-1826), a Paris physician who was shocked by inhumane conditions in mental institutions. Pinel dispensed with the use of chains and in 1786 he introduced work treatment in the Bicetre Asylum for the Insane and later at the Salpêtrière Asylum in Paris, where he was placed in charge. He placed his patients under the care of specially selected physicians like Jean Esquirol, who described prior conditions as follows:

"These unfortunate people are treated worse than criminals, reduced to a condition worse than that of animals. I have seen them without clothing, covered with rags, and having only straw to protect them against the cold moisture and the hard stones they lie upon, deprived of air, given to mere gaolers and left to their surveillance. I have seen them in their narrow and filthy cells, without light and air, fastened with chains in these dens in which one would not keep wild beasts. This I have seen in France, and the insane are everywhere in Europe treated in the same way."

Pinel's 1801 "Medical philosophical treatise on mental alienation" describes his "physical exercises and manual occupations" method. It is the first reference to the medically prescribed use of activity for remediation of mental illness since the ancient Greeks. Around the same time, Dr. Benjamin Rush, a signer of the Declaration of Independence, similarly advocated work as a remedial measure for the treatment of patients in the Pennsylvania Hospital. Rush also introduced the straight jacket and restraint chair for resistant cases.

Jean-Martin Charcot (1825-1893), a neurologist and pathologist, was later placed in charge of the Salpêtrière asylum for women who were suffering from diseases of the nervous system. He attempted to "identify, describe and classify neurological diseases among those who were considered to be incurably ill" from epilepsy or emotional disturbances.

Charcot noted that some who were not epileptics also experienced similar convulsions for which there was no physical cause. Like Hippocrates, Charcot labeled these women as hysterics. By the mid 1800's hysteria came to be a very general term used to describe any excessive emotional behavior causing significant disturbances of the body that had no obvious organic origin. Some of these patients appeared to be blind, deaf or paralyzed despite the absence of any detectable physical defects. As Mesmer had previously demonstrated, Charcot found that such physical symptoms could often be dramatically relieved through the use of hypnosis.

Sigmund Freud (1856-1939), an Austrian neurologist, went to Paris in 1885 to study under Charcot and learn his treatment methods. He used hypnosis on his return to Vienna but soon abandoned it because of the erratic and temporary results and concerns about the magical and unscientific connotations associated with post hypnotic suggestion therapy. Josef Breuer (1842-1925), another of Charcot's pupils, noticed that patients under hypnosis frequently recalled past events they had apparently forgotten about. He found that by subsequently talking about those that seemed particularly significant resulted in an emotional outpouring that often eliminated whatever was causing their symptoms. He called this catharsis his "talking cure".

Freud believed that hysteria was due to an episode of psychic trauma that had not been adequately reacted to when it was initially experienced and remained in the "unconscious mind". Freud modified the "talking cure" by asking patients to simply report as faithfully as possible whatever occurred to them while in his presence. To minimize distractions and promote relaxation he had them recline on a couch outside of his field of vision. He found that such "free associations" usually turned to troublesome personal matters that allowed him to discover and explain what was causing their problem. He coined the term psychoanalysis in 1896 to describe his technique. Freud also suffered from bouts of severe depression, which led to his 20 or more cigars a day addiction to nicotine and use of cocaine.

Twentieth Century Breakthroughs

Emil Kraepelin (1856-1926), a German neurologist, is considered by many to be the Father of modem psychiatry. At the turn of the century, he grouped what were previously considered to be unrelated mental disorders under the term *dementia praecox*, to imply precocious or early onset of organic brain disease as distinct from senile or late onset dementia. He observed that many depressed patients followed a-clinical course quite similar to others who had initially presented with a manic mood and postulated that mania and depression were essentially components of a single disorder. He termed this "manic-depressive insanity" to distinguish it from the depression of *dementia praecox*. Kraepelin also studied the effects of drugs and nicotine, thus founding the field of psychopharmacology.

Eugen Bleuler (1857-1939), a Swiss psychiatrist and one of Freud's disciples, disputed Kraepelin's concept of *dementia praecox* as representing an early form of organic brain disease that was irreversible and incurable. His observation of such patients led him to conclude that the disorder represented a disharmonious state of mind in which contradictory tendencies existed together due to psychological disturbances. Bleuler introduced the term schizophrenia (Greek for "split mind") to describe these patients.

By the middle of the century, lithium had been found to prevent mania. Insulin coma, electroconvulsive (shock) therapy and psychosurgery (lobotomy) were being used to treat severe depression and other emotional disorders and the first Diagnostic And Statistical Manual of Mental Disorders (DSM-I) had been published. Thorazine (chorpromazine) became available in the U.S. in 1952. It produced a vegetative state similar to lobotomy that allowed you to do whatever you wanted to without having patients resist or complain in any way. Although Thorazine revolutionized the treatment of mental illness and permitted numerous institutionalized patients to be treated at home it had numerous adverse side effects. It was followed a few years later by Tofranil (imipramine), a tricyclic compound that was the first true antidepressant.

By 1980 several other types of antidepressant drugs had been developed. Today, we have numerous medications as well as nutritional supplements, including:

- Tricyclics (Elavil, Sinequan, Vivactil)
- Tetracyclics (Ludiomil)
- Monoamine oxidase inhibitors (Parnate)
- **Selective serotonin reuptake inhibitors (SSRI's) (Prozac, Zoloft, Paxil)**
- **Serotonin and norepinephrine inhibitors for depression and anxiety (Effexor, Lexapro)**
- Membrane stabilizers (Depakote)
- Lithium (manic depressive-bipolar disorder)
- Stimulants (caffeine, amphetamines)
- Hormones (estrogens, melatonin)
- Herbals and nutraceuticals, (St. John's wort, *Ginkgo biloba*, *Ginseng panax*, SAM-E)
- Fish oils (omega-3 fatty acids and particularly EPA or eicosapentaenoic acid)
- Vitamins (folic acid and other B vitamins)
- Calcium. supplements

Selective serotonin inhibitors (SSRI's) are highlighted since they have replaced most other antidepressant drugs. Freud first proposed that mental disorders would some day be found to be due to biochemical abnormalities in the brain. Psychoses were subsequently attributed to increased amounts of the brain neurotransmitter dopamine and Thorazine was believed to be effective because it blocked dopamine production. Since a deficiency of other neurotransmitters like serotonin and norepinephrine were thought to cause depression, Prozac, Zoloft and other SSRI's should help because they boosted serotonin levels.

Unfortunately, numerous studies have shown that these and other drugs like Effexor that also increase norepinephrine are not very much more effective in treating true clinical depression than placebos. In addition, they can have numerous side effects, including death from serotonin syndrome and have been found to increase the incidence of suicide in children and

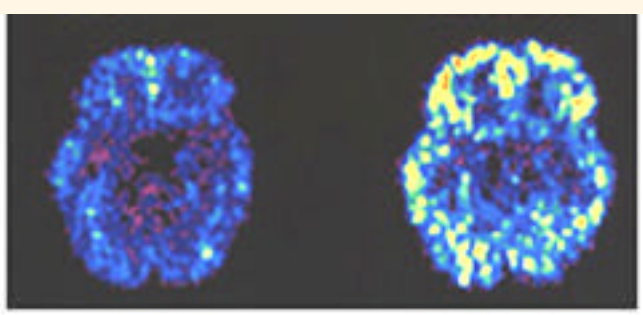
adolescents. While they are widely prescribed for "cosmetic" purposes since they rapidly produce feelings of confidence and self-esteem in neurotic individuals, there is no improvement in clinically depressed patients for at least 2 - 4 weeks. By six weeks, at least half of all patients stop taking antidepressants.

Bioelectromagnetic & Other Modalities

In addition to drugs, there are various behavioral and physical approaches, such as:

- Psychoanalysis
- Cognitive restructuring
- Stress reduction (group therapy)
- Exercise
- Sleep deprivation
- Ultraviolet light exposure (SAD syndrome)
- Acupuncture
- Surgery (stereotactic cingulotomy and brain stimulator implantation)
- Electroconvulsive (shock) therapy
- Vagal stimulation with an implanted device
- **rTMS (Repetitive transcranial magnetic stimulation)**

rTMS is highlighted because I believe it is the first treatment for depression that has a solid scientific basis. Depressed patients appear to have deficient function in the left prefrontal lobe that can often be demonstrated with sophisticated imaging studies. rTMS consists of the external application of specific electromagnetic fields targeted to this area. The treatment is non-invasive, has few side effects and results (that are seen within a week or two) correlate with objective improvement in metabolic abnormalities as shown below.



PET (Positive Emission Tomography) Effects of rTMS
The image on the left depicts diminished electrical energy activity in a depressed patient's brain prior to rTMS. After successful treatment (right) PET scan shows greatly increased activity of the prefrontal cortex (white areas at top of scan)

rTMS has been shown to be effective in patients who do not respond to antidepressant drugs. Similar results have been reported with periodic stimulation of the left vagus nerve using an implantable device.

Advances in medicine are made by observing some phenomenon and developing a hypothesis that explains it and allows you to make certain predictions. These predictions are then tested by experiments and observations to test the validity of the theory and make revisions as necessary to accommodate any contrary findings. This is repeated over and over until there is no discrepancy between the hypothesis and the experimental observations and results. An extension of this in recent years has been the use of clinical trials to determine if a drug is effective with a minimum of adverse side effects compared to a placebo.

The scenario for depression and mental illness cures has been quite different. Hypotheses and treatments that are thousands of years old are still adhered to as if they were true despite over a hundred years of research that have failed to prove their validity. Egas Moniz received a 1949 Nobel Prize for discovering the benefits of lobotomy, which is no longer done. Nor do we destroy the frontal lobes by jamming ice picks simultaneously up both eye sockets, which was Walter Freeman's modification. This former head of the American Medical Association's certification board for neurology and psychiatry used to line patients up for this procedure, which took less than ten minutes. Freeman considered the operation to be a success if the patient was "adjusting at the level of a domestic invalid or household pet."

The belief in demonic possession also persists. A few years ago, a Russian man, who believed a neighbor was a witch, was convicted for tying her to a stake and burning her to death. In July, two women in India thought to be witches had kerosene poured over them and were burned to death. The Vatican still endorses exorcism, since, as one official noted, "belief in Satan is a tenet of Catholic faith." Following in the footsteps of Jesus, Pope John Paul II performed an exorcism in 1982, "driving out the devil from a woman who was brought to him, writhing

on the ground." The revised 1999 ritual for exorcism differs little from the 1614 version save for advice to consult a physician if necessary.

How Much Does Stress Contribute To Depression And What Does The Future Hold?

The significant links between stress and depression discussed in prior Newsletters have been supported by subsequent observations. Cortisol is elevated in depressed patients as well as those with Post-Traumatic Stress disorder and is responsible for such common complaints as memory loss and poor concentration due to shrinkage of the hippocampus. Failure to lower cortisol levels by suppressing the pituitary with dexamethasone is often used as a diagnostic test for depression. Stress depletes levels of dopamine, serotonin and norepinephrine, all of which have been shown to be associated with risk and severity of clinical depression. There may be a hereditary predisposition to depression in some patients and a recent study showed that those with a short "stress-sensitive" version of the 5-HTT gene that manufactures serotonin are much more likely to become depressed following stressful events such as loss of a loved one. Whether this knowledge will lead to improved ways to prevent or treat depression remains to be seen but there is little reason to suspect that drugs will prove to be the solution. Specific and consistent abnormalities in serotonin and other neurotransmitters like melatonin have never been demonstrated in depressed patients. It seems unlikely that any medication could correct all of these and it is also possible that some brain chemical alterations are the result rather than the cause of the problem.

Shakespeare described numerous characters who suffered from depression, including the manic-depressive King Lear and Hamlet, "The Melancholy Dane". He also recognized the association between depression and premature mortality, e.g., Hamlet complains, "*My life sinks down to death, opress'd with melancholy*." We have learned little about what causes depression since Robert Burton's *Anatomy Of Melancholy* was first published in 1621. Burton described in detail the psychological and social causes such as poverty, fear and solitude that seemed to cause *melancholia*, the Elizabethan term for depression. Others believed that depression stemmed from innate disturbances as well as adverse environmental influences. In *Paradise Lost* (1667), John Milton wrote, "*The mind is it's own place, and in itself, Can make a heaven of hell, a hell of heaven*." But how the mind could influence the body was a mystery, for as Blaise Pascal noted a few years later in *Pensées* (1670), "*Man is to himself the most wonderful object in nature; for he cannot conceive what the body is, still less what the mind is, and least of all how a body should be united to a mind*."

We have little control over genetic factors or external events that contribute to depression, but as Voltaire advised one hundred years later, *Wounds of the soul are a disease in which the patient must minister to himself.* How to do this is not clear, although the observation that placebos are almost as effective as drug therapy suggests that we all have within us a vast innate potential for self healing. The body is its own best pharmacy and there is growing evidence of unappreciated subtle energy communication pathways in the body that may allow us to tap into this. Bioelectromagnetic approaches such as rTMS may have great potential for providing such a roadmap - so stay tuned.

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Paul J. Rosch, M.D., F.A.C.P.
Editor-in-Chief
www.stress.org
e-mail: stress124@optonline.net