

The Newsletter of THE AMERICAN INSTITUTE OF STRESS

Number 4

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Stress, Depression, and the Future of Psychiatry

Over the past few decades, the practice of psychiatry has progressively moved from the shrink's sofa, to the chemist's cauldron. Manipulating the mind is now more apt to be accomplished by molecular maneuvers based on objective observations, rather than the chitchat that constitutes many conventional consultations. Some have long considered this to be little more than a palaver predicated on the psychotherapist's personal perspective. The question really boils down to whether psychiatry should now represent the study of disorders of the brain, rather than its former focus on abnormalities of the mind. Will tomorrow's psychiatrist be a neuroscientist, or a behavioral therapist? Are these two approaches mutually exclusive, or can they be integrated in such a fashion that the whole is greater than its parts?

This dilemma is illustrated by considering recent developments in our understanding of the relationships between stress and depressive disorders, and the development of novel therapeutic advances. What skills will

be required for the diagnosis and treatment of the depressed patient? Can the neuroscientist's chemical armamentarium completely replace the empathy and expertise of the experienced psychotherapist, or are both required? As a recent *Lancet* editorial pointed out "People and their problems will not change merely because the science advances; symptom recognition, empathy, and the ability to deal with difficulties at all levels from the molecular to the metapsychological will remain essential throughout psychiatry". However, the quality and quantity of pertinent scientific discoveries relevant to depression have increased so rapidly in recent years, that there can be little doubt as to where psychiatry is heading.

As indicated in a prior Newsletter, part of the problem is that depression is a description, rather than a discrete diagnosis. It may be a manifestation of many different psychiatric and physical disorders. Finding which drug works best depends on the ability to categorize the correct cause of the problem. Kraepelin first observed that many depressed patients followed a course similar to those who initially exhibited a manic mood. He postulated that mania and depression were components of the same disorder, which he labeled manic-depressive insanity, a term later replaced by bipolar disease. This added little clarification, and classifications are still inept.

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The Newsletter of
**THE AMERICAN INSTITUTE OF
 STRESS**

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Stress and Depression

Support for a relationship between stress and depression stems from several sources. About half the patients suffering from a major depressive disorder can be shown to have inappropriately increased cortisol levels and faulty feedback inhibition of ACTH. This hypothalamic-pituitary-adrenal (HPA) axis represents one of the most important and fundamental responses to stress. What is particularly intriguing, is that these abnormalities disappear after successful treatment with antidepressant drugs, which act primarily on noradrenergic and serotonergic mechanisms in the brain.

Antidepressant drugs and cortisol exert reciprocal effects on β -adrenergic receptors in the brain. In addition, stress tends to increase neuronal firing rates in the locus ceruleus, the brain's major source of norepinephrine, whereas antidepressants have the opposite effect. This suggests that antidepressants may prevent or lower stress induced increases in noradrenergic activity. A similar antagonistic relationship between stress and antidepressant drugs and serotonin activities has also been proposed. Does stress disrupt mechanisms of neurotransmitter homeostasis in the brain? Although lithium is

one of the more widely used drugs in bipolar disease, its mechanism of action is unknown. It is most effective in preventing manic episodes, which tend to occur during days when there is maximal exposure to sunlight. It is possible that its efficacy is due to its ability to decrease sensitivity to light, which in turn affects melatonin secretion. Conversely, depression occurs more often during dark seasons, as in Seasonal Affective Disorder, appropriately called SAD Syndrome. Such patients improve remarkably with added exposure to ultraviolet light, which reduces melatonin production.

Electroconvulsive therapy has been one of the oldest treatments for severe depression. Although it is now enjoying a resurgence, its mechanism of action is also not known. Anticonvulsant drugs which alter electrical activity in the brain are increasingly being utilized to treat bipolar disease. The most effective, Depakote, was recently reported to be as effective as lithium, and in addition to having fewer side effects, may provide benefits in patients not responsive to lithium. Cranioelectrical stimulation has been shown to be beneficial for the treatment of depression and jet lag, and significantly affects melatonin and other brain neurotransmitter activities. Noradrenaline, serotonin, and melatonin all play an important role in the response to stress. We have emphasized in every Congress, the important stress reduction effects that can be exerted by subtle energies such as feeble photic and electromagnetic stimuli and will expand on this in 1995.

Finally, in some cases, stressful environmental factors appear to cause depression, and behavioral stress is used to produce animal models of depression, such as learned helplessness. Behavioral therapy produced objective changes in brain function in one study, where patients were either given the antidepressant Prozac, or met twice weekly with a therapist. In both groups, successful outcomes were accompanied by normalization of previously abnormal PET scans, particularly in frontal cortex areas involved in worrying. All of these observations suggest a strong relationship between the pathophysiology of depression and various mechanisms involved in the response to stress.

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21st Century Psychiatry

There can be little doubt as to the direction in which psychiatry is heading. *The Molecular Basis of Psychiatry* by Herman and Nestler, which is reviewed in this Newsletter, clearly points the way. Mental disorders obviously need to be put on a solid scientific basis, and DSM revisions are not the answer, since they do not provide accurate classifications that can identify the most effective therapeutic interventions. Depression has been treated with serotonin reuptake and monoamine oxidase inhibitors, tricyclic and tetracyclic antidepressants, anticonvulsants, lithium, light, cranioelectrical stimulation, music and other subtle energies, electroconvulsive shock treatments, psychotherapy, jogging, etc., etc. However, we do not yet have any algorithm that allows us to predict which approach will work best in any given patient.

In the last century, lunatic asylums were filled with hallucinating patients thought to be bewitched, until it was discovered that many had neurosyphilis, which could not only be treated, but prevented. Similarly, we need to get away from the Cartesian view still held by many lay people that mental illness is inscrutable, or represents some supernatural spell or religious "possession".

At our last Congress, Professor Joel Elkes emphasized in his Hans Selye lecture, "On Psychobiology and Communication: Psychiatry and the Future of Medicine", that psychiatry is about communication. This includes intercellular communication by way of special signal molecules that send messages between the brain and the body; communication between neural and immunological networks; communication between the brain and organ systems, and between the brain and our psychosocial environment. The different languages used in these transactions may be different, but they undoubtedly share certain common features. The goal of 21st century psychiatry must be to translate this into a lexicon with a common vocabulary that integrates and reconciles the seemingly disparate disciplines, in which mind and molecules have become entangled.

Paul J. Rosch, M.D., F.A.C.P.
Editor

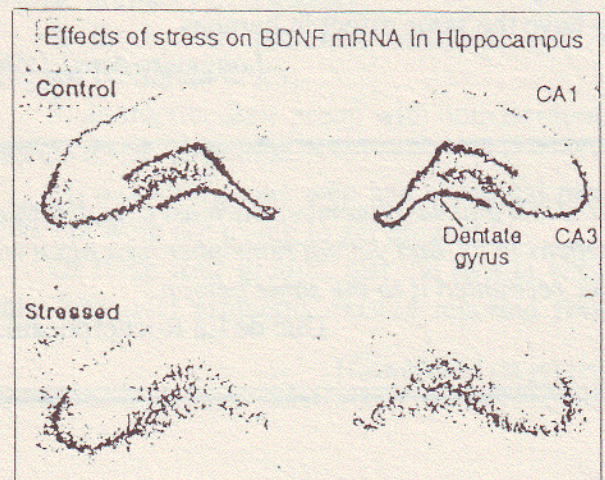
"Doctors make the treatment of insanity not a leading part of their professional requirements. Those who have the opportunity are often engaged in another line, and for want of time, do not pay the due attention to this object. Others fear any innovation, and, from want of courage to exercise their own powers of reflection, follow the doctrines of their predecessors or of titled contemporaries."

Lancet, 1825

Here's Your Brain on Stress

Prolonged exposure to stress causes atrophy in the hippocampus, a region of the brain involved in learning and memory. Decreased hippocampal activity and progressive shrinkage occurs as we grow older, which explains the recent memory loss and other cognitive deficits that are characteristic of advanced age. This process is accelerated in Alzheimer's disease, and as noted previously, MRI's demonstrating this may help confirm an early diagnosis of this disorder. Neuroscientists have shown that this deficit is due to damage to dendrites in the hippocampus. Dendrites are tiny projections emanating from nerve cells that are responsible for receiving communications from adjacent neurons. They normally synthesize nourishing chemicals or "trophic factors" that defend against damage, but stress related hormones interfere with their ability to manufacture these shielding substances. One of these protective proteins, brain-derived neurotrophic factor (BDNF), is seen as dark specks in the diagram below, where it is clearly being ejected from hippocampal neurons during stress. This research may help in developing drugs to improve memory loss in Alzheimer's Disease and old age.

Science-November 19, 1993



Stress, Memory and Aging

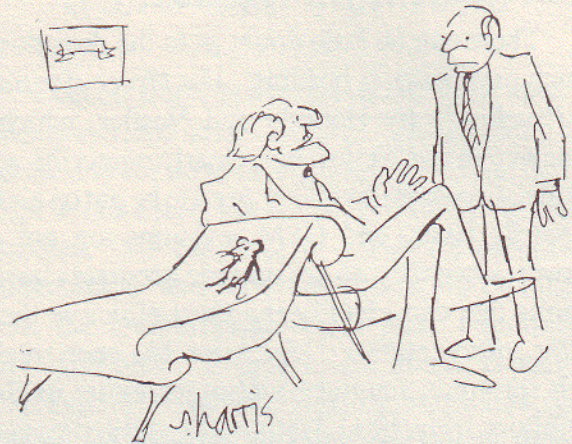
In acute situations, stress hormones like adrenaline improve memory and decision making. As noted previously, prolonged exposure to stress in animals can impair memory because of cortisol damage to neurons in the hippocampus. The ability of chronic stress to exert similar effects in humans has recently been confirmed in a Canadian study of adults aged 55 to 87. Half of these had chronically high levels of stress-related hormones, even when there was no evidence of unusual stress in their lives. When given standard memory tests, these individuals showed deficits similar to patients with evidence of atrophy of the hippocampus, although not as severe as those seen in Alzheimer's disease. Most of the memory deficits were described as "subtle", and were primarily manifested by a diminished ability to learn new facts.

The observation that the majority of these individuals with high cortisol were not perceived to be under increased stress, suggests that other factors may be involved. These might include biochemical disturbances such as those linked to adult-onset diabetes and depression, where cortisol is often inappropriately elevated. In depressed patients who also have increased cortisol levels, successful treatment with antidepressants also restores cortisol to normal. Further exploration of this relationship might lead to the development of novel new drugs for memory loss and depression because of their ability to lower cortisol, as indicated in the following article. Antidepressant drugs have been shown to improve cognitive performance and memory in experimental animals, and could possibly have the same effect in humans.

Longevity-April 1994

"How is it that we remember the least triviality that happens to us, and yet not remember how often we have recounted it to the same person?"

Duc de La Rochefoucauld



"I believe I have a new approach to psychotherapy, but like everything else, it first has to be tested on mice."

Fungicides for Depression?

Ketoconazole is a broad spectrum anti-fungal drug used to treat various infections, including candidiasis, oral thrush, and histoplasmosis. In higher doses, it has also been found to blunt the rise in cortisol seen following the administration of ACTH. Since elevated cortisol has been linked with depression, researchers gave large doses to ten patients with major depression who also had high cortisol levels. At the end of a month, the seven patients who were able to complete the study had a 25% reduction in cortisol, with corresponding improvement in their symptoms of depression, particularly suicidal feelings, insomnia, feelings of guilt and worthlessness, and loss of learning and memory.

Cushing's syndrome is a disorder in which cortisol levels are constantly elevated, usually due to a pituitary tumor or a lesion in the adrenal cortex. Common signs and symptoms include hypertension, depression, and hirsutism in females. When the condition is successfully cured, these complaints also disappear. In patients with Cushing's syndrome, ketoconazole has been shown to be effective in lowering blood pressure even when powerful antihypertensive drugs have failed.

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The hirsutism seen in women with Cushing's syndrome is due to increased adrenal cortical production of testosterone like hormones, which cause increased growth of body hair. Because of this, ketoconazole has also been used to treat hirsutism in women due to genetic or other causes, with considerable success. Ketoconazole has now been shown to be effective in patients with depression who were resistant to regular antidepressant medications. Related anti-fungal compounds which also lower cortisol have shown similar benefits in depression, and these observations may lead to the development of newer drugs that may be even more effective.

Depression is a major health problem that costs in excess of 47 billion dollars annually, which is more than is spent on coronary heart disease. The shameful fact is that at least 70 per cent of patients go untreated, and most remain undetected even when seen by a physician. The important implication of this research is that certain types of major depression are quite likely due to hypothalamic-pituitary-adrenal axis disturbances, since when these are corrected with surgery or medication, depressive symptoms disappear. This axis is responsible for the major neuroendocrine response to stress, again confirming the strong links between stress and depression referred to in this issue's editorial.

Am. Journal of Psychiatry, 150:810-12, 1993

Medical Tribune-6/24/93

Mending Bad Memory

Most people have problems with their memory as they grow older, particularly for recent events. They forget names, phone numbers, or even what they ate or saw on TV two days previously. Similar complaints are seen in young individuals when they take Valium or other benzodiazepine tranquilizers which are often prescribed for stress related complaints. Overdoses of these drugs are treated in Emergency Rooms with flumazenil, a benzodiazepine receptor antagonist. In animal experiments, it has now been reported that chronic administration of this drug can improve memory in elderly rats. Small doses were put in their drinking water for ten

months, and eight weeks after discontinuing this, memory was tested by putting them through a standard maze experiment. Their ability to negotiate this was compared with older and younger rats that had not received the medication. The elderly rats in the flumazenil group made 43 per cent fewer errors than a control group their own age, and they performed at about the same level as much younger rats.

It is theorized that the drug restores biochemical communication abilities in the brain which decline in old age, and are even more seriously impaired in Alzheimer's disease. Trials in humans have now begun in patients suffering from this and other chronic brain disorders, and it is believed that flumazenil "could ultimately be used to prevent diseases of the aging brain."

Longevity-October 1993

Stress and Infertility

There's little doubt that infertility can cause a great deal of stress. Numerous studies have shown that women who can't conceive are much more anxious and depressed than their fertile counterparts. There is also considerable anecdotal evidence that stress can cause infertility. In many instances, a couple will adopt a child after many frustrating and stressful years of unsuccessful attempts to have one of their own, after which, one or more pregnancies quickly follow.

A recent study suggests that stress can indeed cause infertility. Thirty eight such patients were divided into four groups:

- 1) those with hormonal problems who did not ovulate normally or regularly;
- 2) those with anatomic problems such as clogged Fallopian tubes;
- 3) an intermediate group with both hormonal and anatomic problems;
- 4) a control group who had hormonal problems but were not trying to get pregnant.

Of these four groups, just the two in which only hormonal problems existed reported fewer

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sources of emotional support, such as family or close friends they could confide in, and this is particularly significant.

Strong social support is a powerful stress buffer, and the stress associated with lack of support could adversely affect hormones responsible for fertility, according to one of the authors of the report. The size of the study was admittedly small, and it would be premature to draw definitive conclusions without replicating these results in a larger population. However, in the interim, what else can an infertile woman do? As the Director of the behavioral medicine program for infertility at New England Deaconess Hospital in Boston where the study was conducted noted "It certainly can't hurt to try keeping stress in check. If nothing else, relaxation therapies will make the infertility process less trying." There are also numerous stress management books and stress reduction tapes that may be helpful. This is particularly important in certain ethnic groups where women who cannot become pregnant are looked down on, or when no abnormalities can be found in either partner, and each may tend to blame the other. However, the best stress reduction strategy may be to get involved in a support group for infertile couples. Further information can be obtained from Resolve, a Boston infertility group that provides referrals to infertility specialists, and may be able to recommend a local program. (SASE to Resolve, Dept. LM, 1310 Broadway, Somerville, MA 02144).

Longevity-September 1993



"For the last time, Harriet . . . I had a vasectomy. Stop telling

Stress and Your Teeth

Lots of people grind their teeth when they are under stress, and some develop a habit of doing this excessively for no apparent reason, or even in their sleep, a condition known as bruxism. In many instances, this can lead to serious problems of malocclusion, and pain and limitation of motion about the temporomandibular joint, resulting in TMJ syndrome. People under stress, especially those Type A's with time urgency, may tend to have poor dental hygiene because they hurry through brushing their teeth in the morning, and rarely take time out to floss, or visit the dentist for prophylactic checkups and periodic professional cleaning.

Stressed out patients also don't do as well once they are in the dentist's office. In one University of Iowa study, 33 healthy but very anxious patients who were about to have their wisdom teeth extracted, were compared with an equal number of matched controls who appeared to be relatively relaxed. The high stress group had twice as many post surgical complications. As noted in prior Newsletters, increased stress can be associated with a higher incidence of periodontal disease, and this has also been confirmed in animal studies at Ohio State University. Powerful and properly functioning teeth are obviously very important for rodents. Researchers found that in rats with periodontal disease, those animals living under stressful conditions had much greater and more severe problems than low-stress controls. There are a number of possible explanations for this, but the most likely reason is that stress-induced suppression of the immune system may increase susceptibility to infection. An Iowa Professor of Preventive Dentistry suggests a soothing 15 minute talk before treatment, since this can "favorably alter the bacterial balance in the mouth".

American Health-July/August 1993

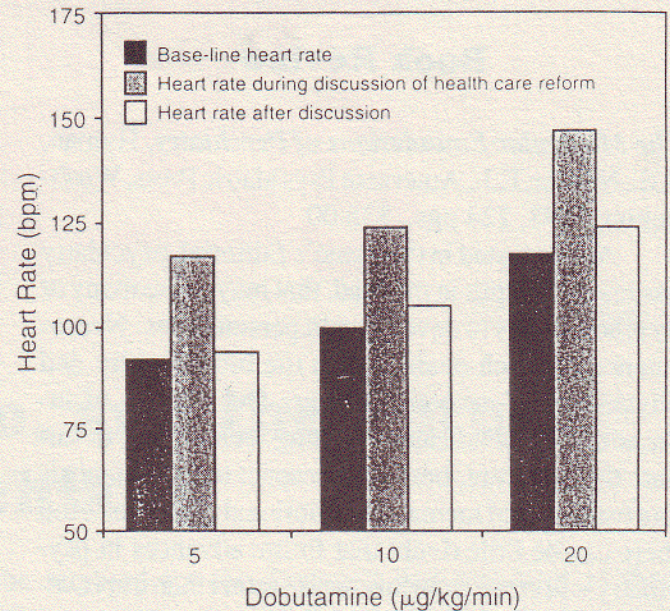
Some tortures are physical, and some can be mental, but the one that is both - is clearly, dental.

Ogden Nash

A New *STRESSFUL* Stress Test

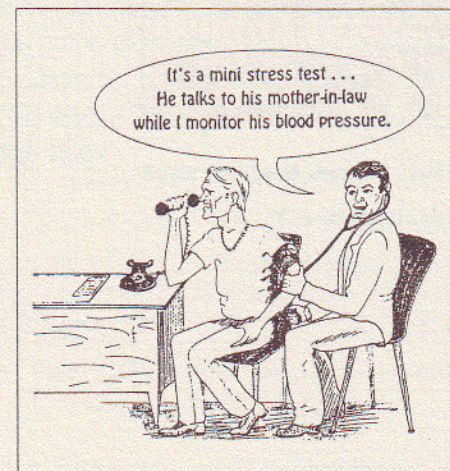
Treadmill stress tests are commonly used to evaluate cardiac function, particularly after heart attacks, or to determine the need for other diagnostic measures in patients that may require angioplasty or bypass surgery. The standard protocol requires progressive physical exertion while heart rate, blood pressure and electrocardiographic changes are being monitored. As heart rate increases, more oxygen needs to be supplied by blood flowing through the coronary arteries. If there is some obstruction that prevents adequate delivery, anginal chest pain and/or ECG changes result, and the test is terminated. In patients who cannot perform a treadmill test, stress testing can be performed by administering increasing doses of dobutamine, an adrenaline-like compound that increases heart rate and cardiac metabolism. Emotional stress can also influence treadmill tests results. Under normal conditions, the speed of the treadmill and its inclination are progressively increased in a standardized fashion until the target heart rate is reached. Some patients who develop angina or ECG changes at a certain heart rate, can significantly exceed this level without symptoms, if they are allowed to regulate the speed and slant of the treadmill, so that the procedure is less stressful because of greater control.

In one recent report, a 71 year old patient undergoing dobutamine stress testing had a resting pulse of 81, which increased to 92 after the first dose. While initially calm and soft spoken, he engaged one of the physicians in a discussion of the proposed Clinton health plan, which he was strongly opposed to. During this conversation, his heart rate shot up to 117 beats per minute, but quickly returned to baseline when he stopped. Following the second dose, his pulse rose to 100, and upon resuming the conversation, increased to 124. The third dose achieved a heart rate of 117, and promptly soared to 147 while talking about Hillary Clinton and the Clinton Administration's new proposed health care reforms. Since this was the target rate, the study and the conversation were terminated, and the pulse promptly decreased to 124.



As demonstrated in the above diagram, the additional stress induced by talking about this emotionally charged subject, caused an average increase of over 25 heart beats per minute for each of the doses of dobutamine administered. As a consequence, the target heart rate was achieved with a lower dosage of the drug than would otherwise have been possible. This has important implications, since, as the researchers concluded: "When a stress test with dobutamine is conducted, the addition of emotional stress may lower the risk of untoward effects of high-dose dobutamine. With judicious application of the discussion, we were able to complete the test in a cost-efficient manner". These findings are not surprising, since one would expect that stress induced adrenaline would potentiate the cardiovascular effects of dobutamine. Other topics might have proven even more effective.

New England Journal of Medicine, 3/24/94



Book Reviews • Meetings and Items of Interest

Book Review

The Molecular Foundations of Psychiatry, Hyman, S.E., Nestler, E.J., American Psychiatric Press, Washington, 1993, 224 pgs., \$35.00

As suggested in this issue's Editorial, psychiatry has reached a split in the road, that may cause many of its practitioners to develop split personalities. Neuroscience research dealing with the biochemistry and physiology of neurotransmitters and the use of increasingly sophisticated imaging technology, dominate the literature, both with respect to the diagnosis and treatment of mental and emotional disorders. And there can be little doubt that future advances in psychiatry will come from this sector, rather than improvements in traditional psychotherapy approaches. A clear sign of the times, is that one of the authors is Director, Division of Molecular Psychiatry, and Associate Professor of Psychiatry and Pharmacology, and the other is Assistant Professor of Psychiatry and Neuroscience, titles that were probably nonexistent a decade ago. Psychiatrists must quickly learn how to use these new tools, and this requires learning the fundamentals on which they are based. This volume goes a long way in satisfying this need. However, even some of the chapter titles ("Mechanisms of Neural Plasticity", "Overview of Psychiatric Genetics") may be intimidating to many practitioners, as well as discussions like the "Molecular Basis of Gene-Environment Interactions".

This meaty little volume covers this complex subject in a comprehensive fashion, down to explanations of DNA and RNA activity, and how neurotransmitters function. These are further enhanced by

the high quality of accompanying diagrams. This book will be an invaluable aid in deciphering the profusion of future articles that will focus on mind and molecules. Highly recommended.

Meetings and Items of Interest

April 24 Women's Healthcare: Clinical Perspectives in Natural Medicine, The Stamford Marriott Hotel, Stamford, CT, (203) 623-2520

April 26 Recent Advances in Acupuncture Research, The Center for Frontier Sciences Spring, 1994, Colloquia, Temple University, Philadelphia, PA, call (215) 204-8487

April 28-May 1 Children: Our Ultimate Investment, The Celebration of the Birth Centenary of Aldous Huxley, Wilshire Ebell Theatre, Los Angeles, CA, (213) 461-8976

May 5-8 National Medical Seminars, Drugs of Abuse, AIDS, Sex & Aging, Obesity, Antibiotics, Athletes & Drugs, Osteoporosis, STDs, Club Med Locales, call (916) 784-6200

May 12-14 National Conference on Psychosocial and Behavioral Factors in Women's Health: Creating an Agenda for the 21st Century, Washington, DC, contact Gwendolyn Puryear Keita (202) 336-6044

May 13-14 Psychosocial and Behavioral Factors in Women's Health: Creating an Agenda for the 21st Century, Combined book and journal exhibit, Hyatt Regency Hotel, Washington, D.C., call Catherine Giordano at the APA (202) 336-5574

May 18-20 American Society of Clinical Hypnosis, Albuquerque Hilton Hotel, Albuquerque, NM, call (708) 297-3317

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