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SEVENTH INTERNATIONAL MONTREUX CONGRESS ON STRESS

February 19 -24, 1995

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Plenary Sessions on Stress and Depression, The Evolution of Global and Coronary Prone Type A Behavior, Clinical Applications of Psychoneuroimmunology, International Labor Organization Survey of Job Stress Around the World, Advances in Occupational Health Promotion and Stress Management, Stress Reduction Effects of Subtle Electromagnetic Energies, Stress and Sleep, Stress, Neurotransmitter Disturbances, Antioxidants, and Aging, Eastern Stress Reduction Strategies. Presentation of Hans Selye Award to Ray H. Rosenman, M.D. Round Table Discussion with previous Hans Selye Award Recipients on "Stress and Quality of Life" (Stewart Wolf, Bjorn Folkow, Jim Henry, Yujiro Ikemi, Lennart Levi, Joel Elkes). Registration Limited.

THE CHOLESTEROL CONUNDRUM

First it was cholesterol and triglycerides, then levels of HDL ("good") or LDL ("bad") cholesterol, that were thought to be important predictors for heart attacks. The association of these lipid abnormalities implies a causal relationship that may not be warranted. Both may simply reflect some common hereditary basis. Cholesterol is a large, inert molecule, and it's hard to see how it could invade arterial walls. Individuals with extremely elevated levels due to genetic disorders such as familial hyperlipoproteinemia, and animals on very high cholesterol diets, do develop increased fatty deposits on arterial walls, and have more heart attacks due to vascular occlusion. However, these lesions are quite different than the atherosclerotic plaque found in most cases of coronary heart disease and advanced arteriosclerosis. This microscopic picture suggests more of an inflammatory response in the vessel wall, with prominent macrophage activity, and foam cells engorged with lipids, rather than simple deposits of cholesterol due to serum saturation.

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The Importance of LDL

Recent emphasis has been on LDL, (low density lipoproteins), and particularly VLDL (very low density lipoproteins such as Apolipoprotein A), since these smaller molecules can more easily penetrate vessel walls. Current federal guidelines advise physicians to base their treatment on measurement of total cholesterol and LDL levels.

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

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But even LDL is fairly inactive, and it is oxidized LDL that appears to be the real culprit. Oxidation of LDL occurs following bombardment by unstable molecules known as free radicals. These are formed as a result of normal oxidative metabolic activities. Because they lack an oxygen atom, they are unstable, and race around the body, latching on to whatever can supply this need, injuring cell membranes and wreaking havoc. Free radical activity is increased by smoking and by stress. It is normally held in check by natural antioxidants, but our ability to manufacture these declines as we grow older. Free radical damage not only contributes to atherosclerosis, but cancer, cataracts, gray hair, wrinkled skin, and other lesions. This may explain why Vitamin C, E, beta-carotene, and other antioxidants, appear to retard the development of atherosclerosis, and other stigmata of the aging process caused by oxidized LDL. Estrogen, which is structurally similar to Vitamin E, also inhibits the oxidation of LDL cholesterol. This may be the reason why fertile females have significantly lower rates of heart attacks, and post menopausal estrogen replacement therapy provides similar protection.

Or Is It HDL?

However, a recent report reveals that people with low cholesterol may still be at risk if they have reduced amounts of HDL, or good cholesterol. By simply

measuring the ratio of total cholesterol to HDL in 8,000 subjects from previous studies, researchers at the University of Pennsylvania improved their prediction rate for subsequent heart disease by 15%, compared to the standard approach. In addition, certain forms of HDL appear to provide unusual protection. Some residents of Limone, Italy have sky-high levels of cholesterol and triglycerides, but no coronary artery disease, because of a genetic HDL mutation called Apolipoprotein A-1 Milano. It was named after the University of Milan researcher who first discovered the longevity and absence of heart attacks and strokes in those carrying the gene, despite diets high in red meat, sausage and butter. As he noted, "They are almost all smokers. They eat like hell, and have the worst diet". Rabbits injected with recombinant Apo Milano attached to a fat molecule developed 70 percent less atherosclerotic plaque buildup, compared to those receiving only the fat molecule. Similar studies are underway in other animals and monkeys, as a prelude to human trials. A U.S.-Swedish team is currently investigating its potential to reduce the disturbing incidence of coronary artery reclogging following balloon angioplasty. As its leader commented, "Eventually, it is not inconceivable that the gene could be transferred to the liver or other organs of very high-risk people, who could then end up manufacturing it on their own".

To Treat or Not To Treat?

While there is little doubt that very high levels of cholesterol should be treated aggressively, there is not as much support for this in those with modest elevations and no evidence of heart disease. Critics argue that cholesterol lowering drug trials reveal that despite achieving the desired decrease in lipid levels, there has been no diminution in the rate of progression of atherosclerosis, or reduction in overall mortality. Age also appears to be another important factor. In a recent study, Yale researchers found that high cholesterol, however it is measured, does not appear to pose any risk for older individuals. They spent 4 years tracking down about 1,000 senior citizens who had various cholesterol measurements made in 1988. Those with the highest levels and worst profiles had no different death rates from heart disease or other causes, compared to others with the most favorable values. However, under federal guidelines, about 1 out of 6 should be receiving cholesterol lowering drugs, many of which have disturbing side effects. As one authority commented, "until someone

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shows that high cholesterol is dangerous in old folks, they may want to skip an occasional dose of lovastatin and down a fried egg".

Does Lowering Cholesterol Always Reduce Heart Attacks?

Lovastatin, or Mevacor, is the largest selling cholesterol lowering drug, and one of the most effective in this regard. However, it does not appear to reduce the development of atherosclerosis in experimental animals, nor lower the incidence of restenosis following coronary bypass surgery, possibly because it is not an antioxidant. Although cholesterol lowering drugs can be shown to reduce cardiovascular mortality, concern has been expressed because of lack of lowering of overall death rates, and possibly some increase in those due to cancer, suicide, homicide, and violent accidents. However, at the November American Heart Association meeting, a Scandinavian study found that simvastatin (Zocor), a new, potent cholesterol lowering drug, reduces coronary events and mortality, without an increase in these other problems. Approximately 4500 men and women between the ages of 35 and 70 with a history of heart disease and moderate to high cholesterol were followed independently at 94 clinical centers in Denmark, Finland, Iceland, Sweden and Norway. Half received Zocor, and controls were given a placebo. Five years later, the Zocor group had a 42% lower death rate from heart disease, and a 30% reduction in overall mortality. For every 100 people on the drug, nine would normally have succumbed to heart disease over the study, but there were only four deaths. Instead of 21 non fatal heart attacks, there were seven, and only six required bypass surgery or angioplasty, rather than an anticipated nineteen. There were few side effects, the drop out rate was six percent in both groups, and no increase in deaths from other causes was observed. The cost of the drug varied between \$650 to \$1000 a year depending on the dose.

Finnish researchers have also reported that pravastatin (Pravachol) reduced artery clogging heart attacks. Combined with other studies in a total of almost 1000 patients, heart attack rates fell by 62% along with a reduction in overall mortality. These, and two other drugs, fluvastatin and lovastatin, interfere with an enzyme used by the liver to manufacture cholesterol, and are particularly designed to lower LDL cholesterol. Whether all are equally effective and safe remains to be

determined. An even more important question is whether these drugs would be useful in the more than 50% of heart attack victims with normal cholesterol, and pravastatin is being investigated in some 4000 such patients. Similarly, it is not clear whether these benefits would be extended to individuals with no history of cardiovascular disease. Drug therapy is necessary because nutritional interventions to reduce cholesterol are notoriously ineffective. What is not generally appreciated, is that emotional stress has a much more powerful influence on serum cholesterol, heart attacks, and sudden death, than dietary fat intake.

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

Editor

Stress, Mornings, Mondays, and Heart Attacks

"Grimm death took me without any warning:

I was well at night and dead at nine in the morning."

is the inscription on an old English tombstone. It has long been observed that heart attacks tend to occur in the first few hours after awakening, and the same holds true for stroke and sudden death. Several possible explanations have been offered based on recent research findings. Waking up is associated with the release of stress related hormones that increase platelet stickiness and clotting, as well as a rise in heart rate and blood pressure. In addition, there may be a greater likelihood of silent ischemia, a condition where blood flow to the heart is significantly reduced, but patients do not experience anginal chest pain or other symptoms. This was confirmed in a study involving some 1300 patients at 30 U.S. medical centers who wore portable heart monitors for two days, as they went about their normal daily activities. Electrocardiograms confirmed that the longest and most frequent episodes of silent ischemia occurred between 8 a.m. and 10 a.m. It is important to emphasize that the subjects were entirely unaware of this.

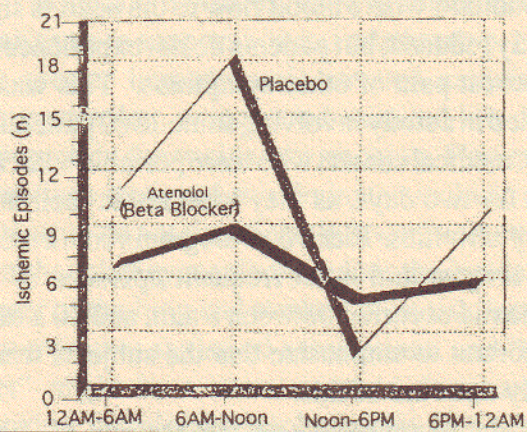
An examination of the records of 100,000 heart attack patients also reveals an increased risk of heart attacks on Mondays, and days preceding and following birthdays, possibly because of increased emotional stress and excitement. Stress can cause spasm and narrowing of coronary vessels, as well as

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platelet clumping, which further impedes and slows blood flow to heart muscle. Both of these changes could increase the likelihood of permanent damage, and fatal disturbances in heart rhythm. However, it's not likely that people will stop celebrations on birthdays, or avoid going to work on Mondays.

One practical solution would be the administration of beta blockers. These have clearly been shown to reduce the incidence of heart attacks, because they block both platelet clumping and coronary vasospasm due to stress. The Atenolol Silent Ischemia Study (ASIST) focused on over 300 patients with documented coronary artery disease, but no symptoms of chest pain. Half of these received one dose of atenolol, a long acting beta blocker, and matched controls received a placebo. Continuous ambulatory electrocardiographic monitoring revealed that prior to receiving the medication, evidence of insufficient coronary blood flow was greatest between 8 a.m. and 9 a.m. If the day were divided into quarters, almost half of such changes occurred between 6 a.m. and noon, with a second, smaller peak in the early evening. After four weeks, there was no change in these spikes in the placebo group. However, they were markedly suppressed in those receiving the beta blocker, as shown below. Similar protection was noted at 6 and 12 month follow-up.



Average number of ischemic episodes during a 48-hour ambulatory electrocardiographic monitoring after four weeks of atenolol therapy or placebo.

These observations have important implications. Patients with coronary heart disease who suffer from angina, usually have some warning if

the blood supply to the heart is not adequate for its requirements. This often occurs with exercise, when heart muscle needs more oxygen, or during emotional stress, when there may be spasm of the coronary arteries which diminishes blood flow. The onset of anginal chest pain signals the need to stop any exertion, and/or take nitroglycerin to increase coronary blood flow. Patients with silent ischemia have no such early warning system, and thus may continue dangerous activities or not take medications that could be lifesaving. Beta blockers and long acting vasodilators could clearly provide prophylactic benefits for such patients. However, since ischemic episodes that trigger heart attacks and sudden death occur most often in the morning, it is important to time the dosage of such drugs so that maximal blood levels are achieved from 6 a.m. to noon. Long acting beta blockers, which are given once daily accomplish this, but other drugs may need to be taken more often to provide protection.

Science News-4/10/93, Cardio-June 1994

Can Country Music Kill?

Country music is certainly not in the same genre as the type of jazz referred to as "the blues". However, its themes, such as loneliness, lamenting a lost love, and otherwise being down on your luck, are often similar, and may have a more potent punch. Country music also seems to attract a different type of audience, particularly young single males, who are possibly more susceptible to its despondent, depressing and melancholy musical messages.

One Alabama sociologist believes that this can cause problems, since some receptive individuals may be driven to such a state of despair, that they become suicidal. He explains that in the subculture of country music aficionados, "You tend to have single men lined up at the country music bar, drinking their beer, as the music wails about being alone". In addition, the lyrics often encourage drinking as a way of forgetting or solving stressful problems, and alcoholism increases suicidal risk. To test this, he plotted suicide rates for 49 major metropolitan areas, and compared them with the

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radio time each devoted to country music. To his astonishment, the study confirmed that the greater the exposure to country music, the higher the rate of suicide.

He is not suggesting that Johnny Cash should be replaced by Perry Como just yet. But he does believe that if others confirm his findings, impressionable individuals at risk should be made aware of this potential problem. "Once people know how factors influence them, they often cease to be influenced". However, it's hard to visualize how this could be accomplished, unless disk jockeys start to insert more upbeat selections, since such a warning is not likely to cause these macho music fans to seek other forms of entertainment.

New Age Journal-Nov./Dec. 1993

Heart Attacks, Depression and Death

Depression is associated with increased mortality rates, particularly for suicide. However, it may also be a risk factor for heart attacks. Conversely, having a heart attack often causes depression. If depression becomes severe or protracted, it would not be surprising to find an associated increased incidence of further cardiac damage or death. To examine this, 222 patients underwent diagnostic psychiatric interviews 1-2 weeks following hospitalization for an acute heart attack. The study confirmed that significant depression during hospitalization proved to be a powerful predictor for subsequent cardiac mortality.

One out of five satisfied the diagnostic criteria for major depression, and six months following discharge, their death rate was 17%, or more than five times greater than the 3% incidence for non depressed patients. All deaths in both depressed and other patients were due to cardiac causes. Put another way, half of those who died showed evidence of major depression while in the hospital, compared to a depression rate of only 14% in survivors. Depression persisted as a major prognostic indicator for cardiac death even after all other modifying variables, including severity of cardiac

disease, had been taken into consideration. Indeed, most cardiologists would be astonished to learn that in this study, depression proved to be a risk factor of the same or greater magnitude, as a history of a prior heart attack, or poor left ventricular function.

Unfortunately, many physicians ignore or don't treat depression following a heart attack because they assume it is a normal transient reaction that will improve over time. In addition, some antidepressant medications are contraindicated, or must be used with caution in the presence of abnormal cardiac rhythms or other disturbances. However, major depression is not normal, and is usually not self limited. The researchers urged that more aggressive efforts should be made to diagnose significant depression in heart attack patients early on, so that immediate treatment can be initiated with drugs and/or psychotherapy. Other studies suggest that prompt intervention, such as providing strong social support not only reduces mortality, but can also remarkably improve the quality of life.

*Internal Medicine News & Cardiology News-
July 15, 1993*

Teenage Crime and Post-Traumatic Stress Disorder

Post-Traumatic Stress Disorder is usually identified with army veterans and others who re-experience war time catastrophic events. In recent years, it has been increasingly identified in civilians who have been victims of rape and violent crimes, or have witnessed murders, serious accidents and other traumatic scenes. Children in urban areas are particularly prone to observe and be victims of injuries and fatalities due to gunfire and other weapons. Homicide is the leading cause of death for 15 to 19 year old blacks, and ranks third for whites, after automobile accidents and suicides. As noted previously in the Newsletter, post-traumatic stress disorder is steadily surfacing in younger age groups, and a new survey suggests that it may be a major contributor to teenage crime.

In this report, more than two out of three teens studied in California Youth Authority wards dem-

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onstrated convincing evidence of PTSD, and another 13 percent had some of these symptoms. In addition to exposure to violence, painful family episodes appeared to be a common source. Affected individuals tended to be depressed and confused, often reliving painful experiences. In many instances, this resulted in outbreaks of erratic and violent behavior. Although medication and psychotherapy can provide effective therapy, most facilities able to provide this have limited resources. Consequently, their efforts are directed towards treating severely disturbed individuals, rather than attempting to prevent problems. Some authorities suggest the latter is equally important, and might be more cost effective in the long run.

Brain/Mind-October 1994

Low Back Pain and Heart Disease?

As noted previously, there are several hundred "risk factors" for heart attacks and cardiovascular deaths. These range from various lipid abnormalities and Type A behavior, to arcus senilis, premature graying of the hair, not drinking alcohol, and social isolation. There is often the inference that these contribute to coronary heart disease, and therefore, their elimination should reduce its incidence. In certain instances, there is some reasonable rationale to support a causal relationship, such as the greater hemodynamic stresses associated with hypertension, or increased oxidized low density lipoprotein due to cigarette smoking. However, interventions designed to eliminate smoking and hypertension do not significantly lower heart attack rates, although they markedly reduce the incidence of cancer of the lung and stroke. Most risk factors merely represent statistical associations, and "risk marker" might be a more accurate designation. Although a prominent earlobe crease and vertex baldness are seen more frequently in patients with coronary heart disease, correcting these will not prevent heart attacks, and their link is likely due to some common genetic or other factor.

The most recent addition to the risk factor list appears to be low back pain, according to Finnish

researchers. They studied almost 9,000 farmers between the ages of 30 and 49 for over 13 years, evaluating their physical and mental status, weight, smoking, socioeconomic standing, and other factors associated with coronary artery disease. Even after taking all these into consideration, those farmers who had complained of low back pain at the beginning of the study, were four times more likely to die from heart disease at the end of the follow-up period.

Back pain resulting from arterial narrowing due to atherosclerosis has previously been reported. It was suggested that just as anginal chest pain results from a reduction in blood flow to the heart, some types of back pain might also be due to a similar mechanism that prevents the delivery of sufficient oxygen to back muscles, particularly when this becomes increased because of physical exertion. A back pain-heart disease association is not seen in women or in men over 49, possibly because these muscles are not used as much in this population, and oxygen requirements are not as great. It may also be that the development of increased atherosclerosis in blood vessels supplying back muscles is associated with an accelerated pattern elsewhere, as in the heart. Increased emotional stress could also be another factor, since this is clearly linked with, and can contribute to both low back pain and coronary heart disease.

USA Today-November 14, 1994

Reducing the Stress of Business Travel

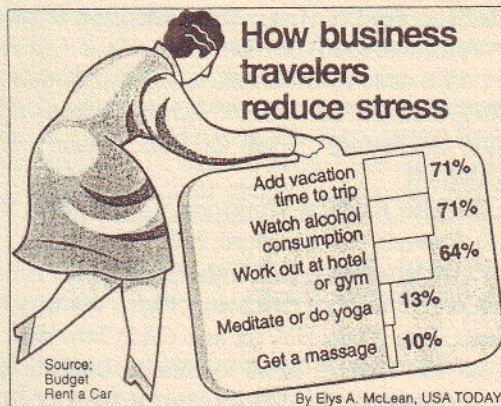
Job Stress is clearly the major source of stress for U.S. adults. For some, having to be on the road a lot is an important component. In addition to being away from home and loved ones, there are the unavoidable hassles of delayed flights, mixed connections, jet lag, and a variety of inconveniences over which one has little control. A recent survey of over 500 business clients by Budget Rent a Car, revealed that more than two out of three found business travel stressful, and felt that little could be done about it. Often, it's not the trip itself, but worrying about what might happen, that generates stress.

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One consultant suggests taking a hot shower as soon as you hit your hotel room, or a 20 minute walk to help you relax. Try to use in-flight time productively, by catching up on personal correspondence, reading a book, or listening to a tape that you haven't had time to get to. For more information, send a 52 cent stamped, self-addressed envelope to Budget Health and Fitness Travel Tips Brochure, P.O. Box 233375, Milwaukee, WI 53223. If you're lucky, you may also receive a free "stress ball". You can also order a tape on *101 Tips to Stay Healthy and Stress-free on the Road* for \$9.95, by calling 1-800-632-0700. Some other suggestions are shown below.

USA Today-11/9/94



Preventing Cancer and Heart Attacks

One of the characteristics of cancer cells is their rapid and uncontrolled growth. In certain instances, the accelerated deposition of atherosclerotic plaque also seems to override normal regulatory mechanisms. This is a particular problem following balloon angioplasty, when affected coronary arteries frequently become occluded again at an alarmingly rapid rate. Excessive cellular growth is normally inhibited by a protein known as p53. However, if this becomes damaged or disabled, cells continue proliferating in an unbridled fashion. Defects or mutations in p53 have been implicated in a wide variety of malignancies. A recent study now reports that in one out of three patients whose arteries quickly clog up again following angioplasty, failure of p53 activity may be responsible. It is

believed that trauma to the arterial wall during catheterization or angioplasty activates cytomegalovirus, a herpes-like agent present in most of the population over 35. Like other herpes viruses, it is usually dormant, but becomes enlivened by trauma, emotional stress, and depression of immune system function. Antibody studies suggest that chlamydia and other microorganisms may also be involved.

Patients with severe coronary artery disease have increased concentrations of T4 lymphocytes in atherosclerotic plaque. These specialized white cells help the immune system ward off infections as well as malignancies. Studies are now in progress to determine whether antimicrobial drugs may help prevent the rapid reaccumulation of inflammatory atherosclerotic deposits seen so frequently following cardiovascular surgery. In addition, U.S. and U.K. companies are engaged in a joint venture to develop chemicals capable of correcting mutated p53 protein abnormalities. This might offer a major breakthrough in preventing the growth of tumor cells, as well as the accelerated atherosclerosis due to damage to this protective protein.

Cancer, atherosclerosis and other manifestations of the aging process have also been linked to free radical activity, which increases with stress, poor nutrition, smoking and age. Free radicals are normally neutralized by natural substances produced in the body known as antioxidants, but our ability to manufacture these declines as we grow older. However, Vitamins C, E, and beta carotene also have powerful antioxidant properties, and have been shown to retard the development of cancer and atherosclerosis in both animal and human studies. Dehydroepiandrosterone (DHEA), which bolsters the immune system, also offers great promise. This naturally occurring adrenal steroid is a building block for testosterone and estrogen, but secretion declines with age, and falls during stress. Very low levels appear to be associated with a significantly increased incidence of cancer and heart attacks in humans, suggesting that correcting this might provide benefits. DHEA has already been shown to retard the development of both atherosclerosis and malignancy in experimental animals.

Henderson File-12/19/94, Longevity-November 1994, New York Times-July 15, 1994, Science-June 8, 1994, Science News-11/28/92

Book Reviews • Meetings and Items of Interest

Book Review

Biological Bases of Brain Function and Disease, Frazer, A., Molinoff, P., and Winokur, A., Raven Press, New York, 1994, 479 pages, hard cover \$69.00, paperback \$39.00

This volume represents a sequel to the textbook, *Biological Bases of Psychiatric Disorders*, published two decades ago. Since then, there has been an explosion of interest in psychopharmacology that has led to the development of increasingly effective psychotropic drugs, many of which have become useful research tools. Particular advances have been made in identifying central nervous system neurotransmitters and receptors that modulate mood and behavior, and these are reviewed in a comprehensive and authoritative fashion. The organization of the text reflects its original purpose as a syllabus for college students. The first section, Principles of Neurobiology, covers neuroanatomy, and the basic physiology of nerve conduction and receptor activity. The second section deals with synaptic transmitters and modulators, with chapters devoted to biogenic amines, amino acids, and peptides. Section three is devoted to complex brain functions such as biological rhythms, learning and memory. Chapters discussing the significance of REM and non REM sleep, and the relationships between stress and depression, are particularly valuable. Section four examines animal models for exploring brain-behavior relationships, studies in humans utilizing neurophysiologic and imaging techniques, and genetic influences. The final chapter discusses how these advances have increased our understanding of the etiology of a variety of clinical disorders, and may point the way to exciting new therapies. Some examples include schizophrenia, anxiety states, substance abuse,

obesity, epilepsy, Parkinsonism and Alzheimer's disease. Each chapter begins with a listing of key concepts succinctly summarizing the points to be made, as well as a two or three page overview of the contents. Useful diagrams, illustrations, and tables are of high quality, references are complete and up-to-date. The list of commonly used abbreviations is particularly helpful in navigating the alphabet soup of acronyms in this rapidly expanding field.

Meetings and Items of Interest

March 3-8 The Association for Applied Psychophysiology and Biofeedback, 25th Annual Meeting, Hyatt Regency, Atlanta, GA, for info (303) 422-8436

March 5 & 6 Weekend Workshop at The Healing Tao Center, Jolly Madison Towers Hotel, Dolly Madison Room, New York, NY, for info (516) 367-2701

March 7-11 Balancing Individual and Social Responsibility in Health Promotion, 6th Annual "Art and Science of Health Promotion Conference", Hyatt Orlando, Orlando, FL, call (810) 650-9600

March 23 Life Balance Workshop for Working Women (#59556), Ramada Inn, Elmsford, NY, call (303) 447-2300

March 23 Understanding Psychotherapy, Cornell University Medical College, Dept. of Psychiatry, Payne Whitney Psychiatric Clinic, New York, NY, for info (212) 746-3669

March 23 The Role of Mind in Health, Disease, and the Practice of Homeopathy, The Center for Frontier Sciences Spring, 1994, Colloquia, Temple University, Philadelphia, PA, call (215) 204-8487

March 25 Acupuncture in the Treatment of Substance Abuse and Chronic Mental Illness, Cornell University Medical College, Dept. of Psychiatry, North Shore Hospital, Manhasset, NY, call (516) 562-3051

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