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EFFECTS OF THE *TRANSCENDENTAL MEDITATION* PROGRAM ON ADAPTIVE MECHANISMS: CHANGES IN HORMONE LEVELS AND RESPONSES TO STRESS AFTER 4 MONTHS OF PRACTICE*

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SUMMARY

Stress has been implicated in both somatic and mental disorders. The mechanisms by which stress leads to poor health are largely unknown. However, studies in animals suggest that chronic stress causes high basal cortisol and low cortisol response to acute stressors and that such changes may contribute to disease. Previous studies of the Transcendental Meditation® (TM) technique as a possible means of countering effects of stress have reported altered levels of several hormones both during the practice and longitudinally after regular pratice of this technique. In this prospective, random assignment study, changes in baseline levels and acute responses to laboratory stressors were examined for four hormones—cortisol, growth hormone, thyroid-stimulating hormone and testosterone—before and after 4 months of either the TM technique or a stress education control condition. At pre- and post-test, blood was withdrawn continuously through an indwelling catheter, and plasma or serum samples were frozen for later analysis by radioimmunoassay. The results showed significantly different changes for the two groups, or trends toward significance, for each hormone over the 4 months. In the TM group, but not in the controls, basal cortisol level and average cortisol across the stress session decreased from pre- to post-test. Cortisol responsiveness to stressors, however, increased in the TM group compared to controls. The baselines and/or stress responsiveness for TSH and GH changed in opposite directions for the groups, as did the testosterone baseline. Overall, the cortisol and testosterone results appear to support previous data suggesting that repeated practice of the TM technique reverses effects of chronic stress significant for health. The observed group difference in the change of GH regulation may derive from the cortisol differences, while the TSH results are not related easily to earlier findings on the effects of chronic stress. © 1997 Elsevier Science Ltd

Keywords—Meditation; Cortisol; Stress; Health; Aging; Prevention.

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INTRODUCTION

Many clinical researchers agree that stress is an important factor in disease and ageing (Elliot and Eisendorfer, 1982). However, questions persist as to the mechanisms involved and what, if anything, can be done to reduce or reverse the deleterious effects of stress. Although there is evidence for mutual connections between the endocrine and immune systems, which may explain stress-related differences in susceptibility to communicable diseases (Ader et al., 1991), the possible mechanisms are less clear for cardiovascular and other prevalent diseases which may result from psychosocial stress (Henry and Grim, 1990). The line of research that appears most promising with regard to the relationship between stress and these chronic diseases is that concerned with long-lasting changes in adaptive or homeostatic mechanisms (see for review Sapolsky et al., 1986; McEwen and Stellar, 1993; Walton and Pugh, 1995). Such changes may be induced by 'chronic stress', a term used here to denote frequent or continuous stressful experiences.

Effects of chronic stress on hormone levels and regulation have been documented in numerous animal and human studies. Among the clearest and most thoroughly studied examples is the case of glucocorticoid regulation through the hypothalamic–pituitary–adrenocortical (HPA) axis in animals. For instance, in the wild baboon, the chronic stress associated with subordinate social status in males appears to elevate baseline cortisol, to reduce the cortisol response to acute stressors, and to impair mechanisms of negative feedback responsible for returning cortisol to its baseline after an acute rise (Sapolsky, 1990). These effects may be due to alterations in hippocampal neurons caused by frequent stress-induced elevations of this glucocorticoid (Sapolsky et al., 1991), as shown for the principal glucocorticoid in the rat (Sapolsky et al., 1986). These and other studies suggest that similar mechanisms may operate in humans as well (Brooke et al., 1994; Seeman and Robbins, 1994; Sapolsky, 1996). Since the above cortisol profile is associated with poorer health than its opposite, these and additional results may support a stress-induced loss of hippocampal regulation of the HPA axis as an important factor in human disease and ageing (Sapolsky et al., 1986, 1991; Young et al., 1990; McEwen and Stellar, 1993; Seeman and Robbins, 1994; Walton and Pugh, 1995; Sapolsky, 1996).

Although glucocorticoids and their regulation have been the most intensely studied, regulation of other hormones also is affected by chronic stress. In contrast to the tendency of chronic stress to elevate baseline cortisol, it appears to decrease testosterone, both in animals and in humans (Sapolsky, 1982; Allen et al., 1985; Leedy and Wilson, 1985). Furthermore, an increase of testosterone in response to acute stress is found in successful (low stress) male baboons, while subordinate (chronically stressed) males show a decrease (Sapolsky, 1982). As with cortisol, such effects of stress on testosterone may involve alterations in central regulatory mechanisms, although these may well be secondary to elevated cortisol (Chandran et al., 1994).

Thyroid-stimulating hormone (TSH) is another hormone that may be affected by chronic stress. It has been reported to increase in humans during acute challenges such as strenuous exercise (Rolandi et al., 1985) and a stressful interview (Mougey et al., 1991). On the other hand, prolonged stress, as well as hypercortisolism, may raise baseline TSH and blunt the TSH response to acute stress (von Zerssen et al., 1986; Armario et al., 1987; Sawin et al., 1979). The response of growth hormone (GH) also may be affected differently by acute and chronic stress. In humans, GH has been shown to rise acutely in response to virtually all stress-evoking stimuli (Reichlin, 1988). However, sustained or chronic stress may inhibit

GH release in humans (von Zerssen et al., 1986; Martin and Reichlin, 1987; Malarkey et al., 1991; Mougey et al., 1991; Sapolsky, 1992).

With respect to psychosomatic disease, stress reduction techniques continue to receive attention, especially from the population at large, as preventive or treatment alternatives (Eisenberg et al., 1993). An ability of these techniques to alter levels or regulation of hormones in a manner opposite to that of chronic stress might provide a mechanism for their purported usefulness in maintaining health. It is possible that changes in baseline levels and/or response characteristics of cortisol, TSH, GH, testosterone and other hormones form part of a coordinated pattern of effects of chronic stress which may contribute to disease and ageing. It is preferable to examine several such hormones in evaluating the mechanisms through which stress reduction might produce physiological benefits.

Among the systematic techniques used for stress reduction, the Transcendental Meditation® (TM) technique of Maharishi Mahesh Yogi has been studied widely (Jevning et al., 1992), and recent controlled trials support its effectiveness in reducing cardiovascular disease (Schneider et al., 1995; Alexander et al., 1996; Zamarra et al., 1996), as well as ageing and mortality rates (Alexander et al., 1989, 1996). Possibly involved in some of these benefits, previous research has shown declines of cortisol, TSH, and GH acutely during practice of the TM technique (Bevan et al., 1976; Jevning et al., 1978, 1987, 1992). Based on the apparent longitudinal effects of regular practice of the TM technique on these hormones, it has been suggested that the technique strengthens adaptive mechanisms, with effects on hormonal regulation opposite to those resulting from chronic stress (Bevan et al., 1976; Werner et al., 1986; Alexander et al., 1994; Walton and Pugh, 1995; Walton et al., 1995). The present prospective, randomized controlled study attempts to elucidate this possibility further by investigating baseline changes and changes in neuroendocrine responses to acute laboratory stressors before and after 4 months of twice-daily practice of the TM technique compared to a cognitive approach to stress reduction. Portions of this work have been presented in preliminary form (MacLean et al., 1992a, 1994).

EXPERIMENTAL

Subjects and Research Design

Healthy male Caucasian volunteers, ages 18–32 years, were screened through the use of health questionnaires and a medical exam. Only subjects with normal blood pressure and heart rate, not on prescription medication, and free of any disease, were accepted into the study. Following the first laboratory stress session (pre-test), subjects were assigned randomly, by an outside investigator who communicated with subjects only by mail, to participate in 4 months of either the TM program or a stress education control (SEC). After the 4 months, there was a second laboratory stress session (post-test). Investigators conducting measurements were blind to the assignment until after post-test.

Treatments

The TM technique is a simple, standardized, mental procedure practiced 15–20 min twice daily while sitting comfortably with the eyes closed. The technique, developed 40 years ago by Maharishi Mahesh Yogi, is based on the ancient Vedic tradition of India and is intended not only as a means of eliminating stressful experiences and removing the long-term effects of such experiences but also as a means of unfolding the human potential well beyond the

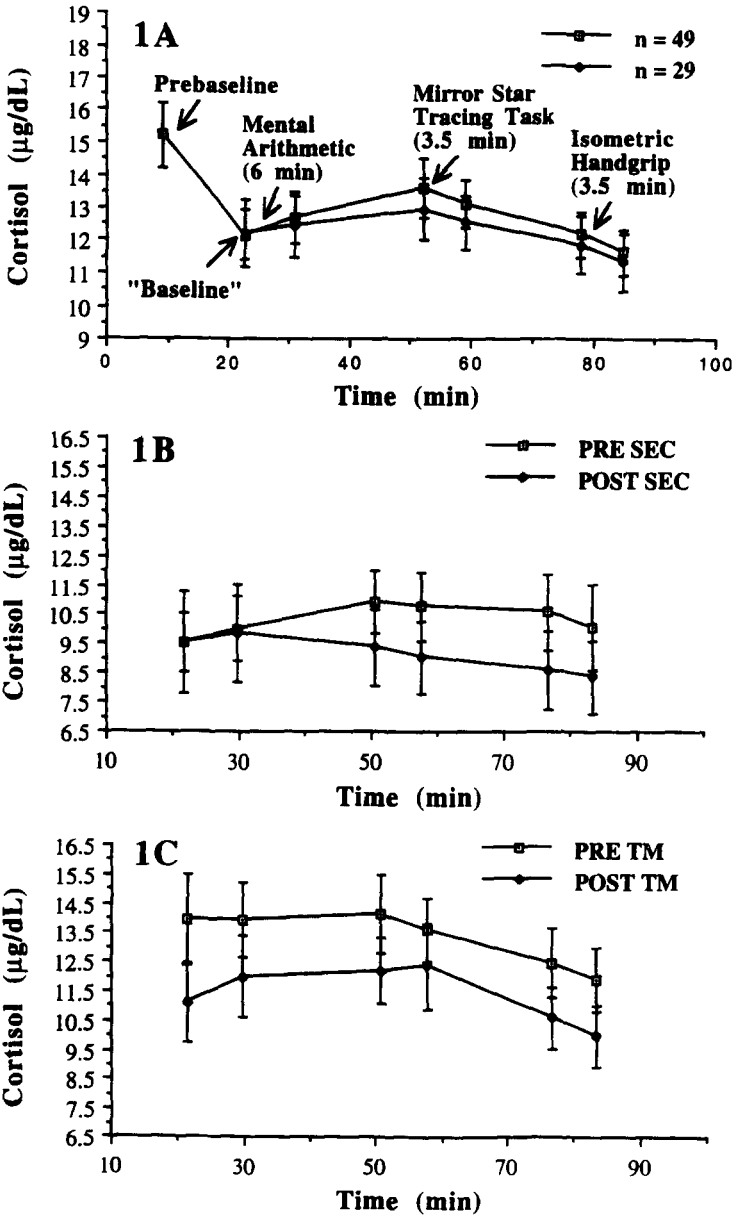

Fig. 1. Changes in cortisol across the stress session. (A) For all subjects at pre-test ($n = 49$), cortisol changed significantly relative to the 'baseline' (MANOVA, omitting the pre-baseline; $F(5, 44) = 4.39$, $p = .003$). The change also was significant for the smaller number of subjects with cortisol data for both pre- and post-test ($n = 29$, see Results section). (B) and (C) Pre- and post-test changes in cortisol secretion during the stress session for the SEC ($n = 13$) and TM ($n = 16$) groups, respectively.

usually accepted norm (Maharishi Mahesh Yogi, 1967/90; Bloomfield et al., 1975; Alexander et al., 1990). There are no required changes in lifestyle, philosophy, diet or physical activity. Evidence indicates the technique facilitates quieting of the mind and body to a state distinctly different from sleep or eyes-closed rest (see for review Jevning et al., 1992; Alexander et al., 1990), and numerous studies have found this technique to outperform other approaches to stress reduction in relieving psychological stress, anxiety and physiological signs of stress or fatigue (see for review Eppley et al., 1989; Alexander et al., 1989, 1991). The TM program was taught by a qualified instructor according to standard procedures used worldwide (Roth, 1994; Alexander et al., 1994).

The stress education class, which served as an active control treatment, was taught by an instructor from the University of Iowa Counseling Center. Topics included 'Recognizing Stress in One's Life' and 'How to Effectively Deal with and Reduce the Impact of Stress' as well as lessons in time management (Girdano et al., 1990). The course format was similar to that for the TM technique, controlling for schedule, total amount of time spent and attention from the instructor, with daily entry of experiences into a diary as a control for the daily attention to practice of the TM program. Physiological effects of stress education have not been reported and were not expected, based on published studies of similar procedures. However, the instructor believed this approach to be valuable and appeared to convey the same level of enthusiasm to the subjects as did the TM program instructor.

Blood Sampling

Subjects had not eaten for 12 h prior to their laboratory session. They arrived between 0830 and 0930h at the University Hospital Clinical Research Center, where a 19 gauge catheter (Dakmed, specially treated with heparin to prevent clotting during blood withdrawal) was inserted into the antecubital vein of their non-dominant arm and connected to a blood-withdrawal pump (Dakmed Model ML-6-5S3R). Blood withdrawal was maintained at a set flow rate of 1.7 ml/min for about 110 min. Serum and plasma samples were prepared by standard procedures, and samples were stored at -70° C until assay.

Protocol for Laboratory Stressors

Blood sampling began after a resting period. Since this study was part of a larger study in which blood pressure reactivity was a key variable, the choice of a starting point was based on the time necessary for blood pressure to stabilize ('venipuncture recovery'). During this period of time, six blood pressure readings were taken 5 min apart. If the blood pressure had leveled off by the last two measurements, this time (usually about 35 min after catheterization) was designated 'time zero' and the 'baseline' plasma sample was taken. Plasma for cortisol was sampled several times for 3 min each time, whereas serum for growth hormone, thyroid-stimulating hormone and testosterone were sampled in two 4 min periods, one at the beginning and one nearer the end (5–10 min after the handgrip stressor) of the 1 h stress session.

Subjects were given taped instructions prior to each of the three laboratory stress tasks or 'stressors.' The tasks were carried out under time pressure. After each stressor (Fig. 1) there was a 20 min resting or recovery period. The stressors were: 6 min of self-paced, serial subtraction, 3.5 min of the mirror image, star-tracing task, and 3.5 min of isometric handgrip at 25% of maximal strength. These tasks were chosen for their previously demonstrated suitability in discriminating between groups determined to be at high and low risk for heart disease (Stoney and Matthews, 1988).

Biochemical Assays

Samples of plasma and serum were assayed for hormones by radioimmunoassay using commercially standardized kits (Diagnostic Products Corporation). The interassay and intra-assay coefficients of variation, respectively, for the hormone assays were as follows: cortisol, 8.2 and 5.4%; TSH, 13.4 and 8.0%; GH, 9.5 and 5.6% and testosterone, 9.8 and 6.6%.

Variables and Analyses

A mathematically derived, area-under-the-curve variable was developed to determine the degree of 'rise and fall' of plasma cortisol during the laboratory stress session. This variable was designed to represent the area on the graph encompassed by the changes in cortisol secretion between the baseline sample and the last sample, bound by the straight line connecting these two points (the reference line). Thus, if cortisol increased during the stress session relative to the reference line, then the value of the net area variable was positive, and if it decreased, the value was negative. Unless noted otherwise, data are given as means ± SEM.

RESULTS

Fig. 1(A) shows the changes in cortisol secretion over the pre-test stress session. Cortisol secretion across the session, omitting the pre-baseline point (see below), changed significantly for the group of all subjects ($n = 49$) by MANOVA [$F(5, 44) = 4.39$, $p = .003$]. As Fig. 1(A) indicates, the change during the session for this group appears as an increase of 8.3%, going from a baseline value of 12.0 ± 1.1 μg/dl to a peak value of 13.0 ± 0.9 μg/dl. However, due to the circadian decline of cortisol at this time of day, the true effect of stressors was likely to be greater. In fact, because it was not possible to include a no-stress control condition, it may be instructive to note that a 30% peak increase was obtained when the increase was calculated by comparison with no-stress control data from a highly similar experiment (McCann et al., 1993).

In the smaller group of subjects for which there were complete post- as well as pre-test cortisol data ($n = 29$), secretion also changed significantly across the session by MANOVA [$F(5, 24) = 2.62$, $p = .05$], increasing 6.4% from a baseline value of 11.9 ± 1.0 μg/dl to a maximum of 12.7 ± 0.9 μg/dl. Thus, there appeared to be a cortisol response to the stress session, with the likely true increase being 25–30%. However, the time allowed for cortisol to return to pre-stress level between individual stressors appears to have been insufficient for a return to baseline. Therefore, it was not possible to evaluate separately the cortisol responses to the sequentially administered stressors. Rather, it was necessary to consider the cortisol response in terms of the stress session as a whole.

Frequently, venipuncture itself causes an increase in cortisol. Thus, because the measurement of hormones was part of a larger set of objectives which dictated the design of this study, there was concern, at the beginning of data analysis, that the time allowed for venipuncture recovery (approximately 40 min) might not have been sufficient for cortisol to return to baseline. To investigate this point, a post-experiment analysis of cortisol in a plasma sample from an earlier time point (approximately 30 min after catheterization) was conducted. This time point was referred to as the 'pre-baseline' [see Fig. 1(A)]. To insure that the absolute value of the pre-baseline point was comparable with other time points, other samples from the same experiment were re-assayed together with the pre-baseline

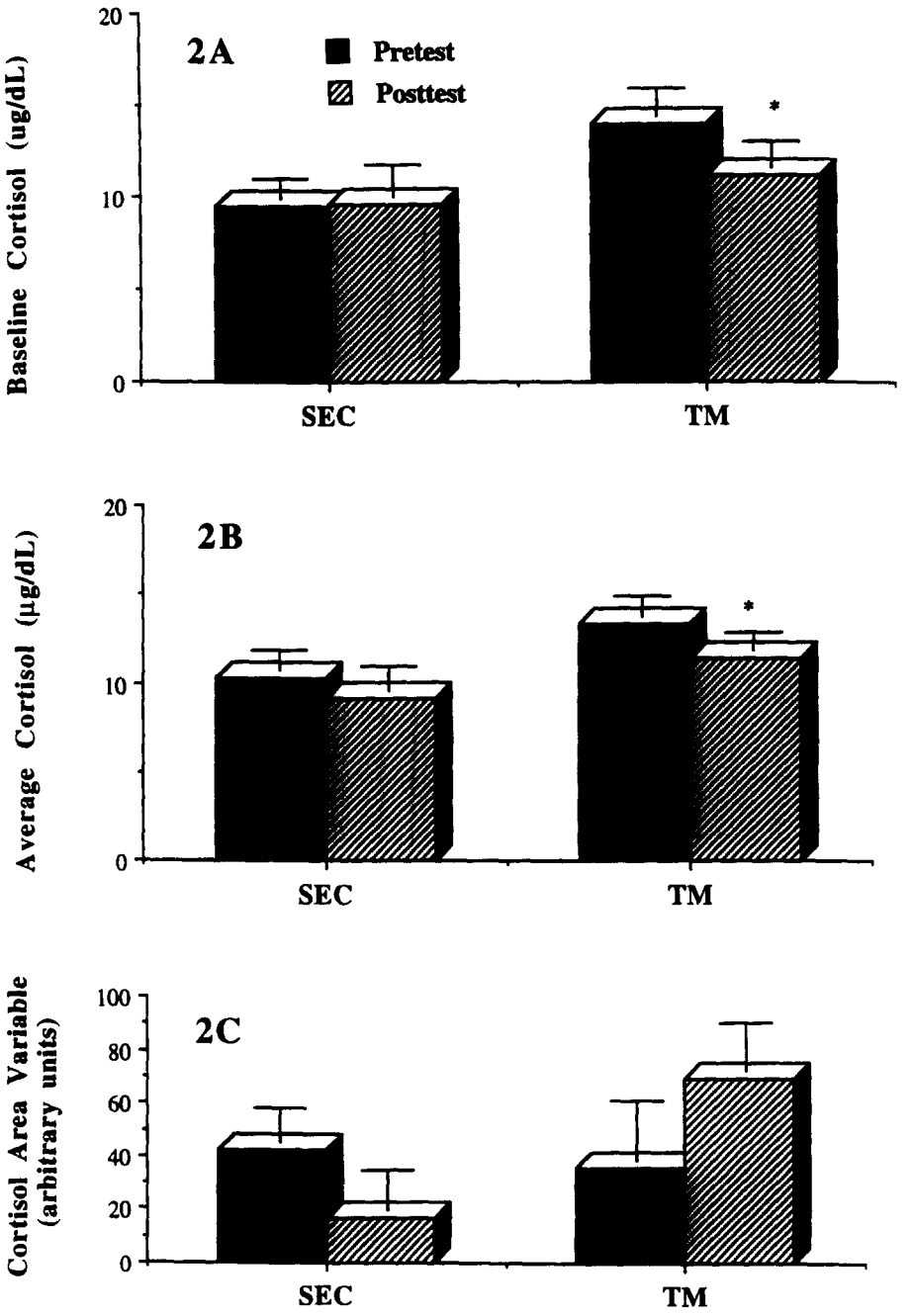

Fig. 2. Changes in cortisol baseline, average and response to stress from pre- to post-test. (A) Cortisol decreased significantly at baseline and (B) for average across the session in the TM group, but not in the SEC group (see Results section for statistics). (C) The two groups changed significantly differently in an area-under-the-curve variable representing the degree of cortisol response to stressors across the session [$F(1, 26) = 5.8$, $p = .02$, ANCOVA]; $^*p < .05$, paired t-test.

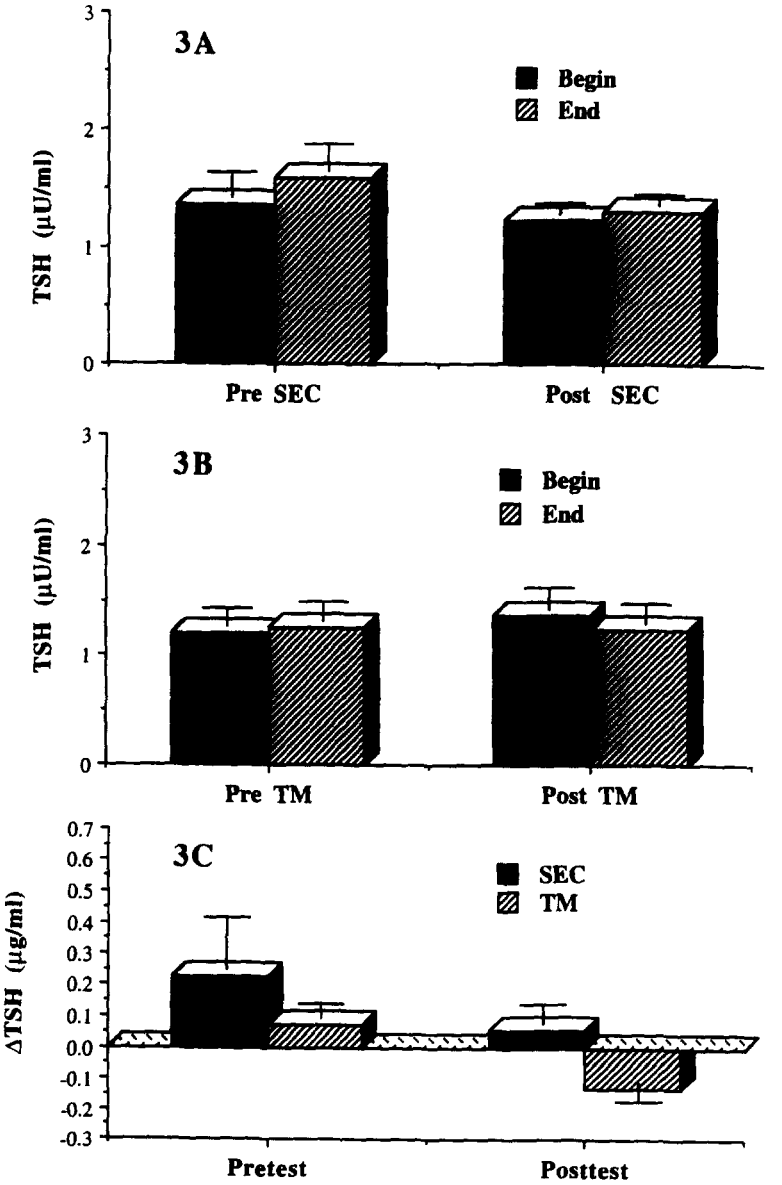

Fig. 3. Pre-test and post-test changes in TSH across the stress session. (A) and (B) Pre-test changes across the session were in the same direction for the SEC and TM groups, but at post-test they were opposite. The changes across the session (ΔTSH, defined as end of session minus baseline) at the post-test (C) were significantly different by ANCOVA covarying for pre-test [$F(1, 26) = 6.07$, $p = .02$].

samples, and a correction factor was calculated. It is clear from the data shown in Fig. 1(A) that cortisol decreased sharply between the pre-baseline and baseline samples. This presumably was due to continuing recovery from venipuncture and to a decline because of the usual circadian rhythm of cortisol. At the point designated baseline, cortisol was lower than the pre-baseline. Since the mean cortisol level appeared to rise beginning with the first point after baseline, the point labeled 'baseline' appears a reasonable approximation of the true baseline for cortisol. Fig. 1(B) and (C) show pre- to post-test changes for the SEC and TM groups, respectively.

Fig. 2(A) shows that, from pre- to post-test, baseline cortisol decreased significantly for the TM group using a paired t-test [$t(15) = 2.21$, $p = .04$], going from 13.9 ± 1.5 μg/dl at pre-test to 11.1 ± 1.3 μg/dl at post-test. In addition, a decrease in the average cortisol for the six observations during the session [Fig. 2(B)], i.e. going from 13.3 ± 1.1 μg/dl at pre-test to 11.4 ± 1.0 μg/dl at post-test, was significant for the TM group based on a paired t-test [$t(15) = 2.25$, $p = .04$]. For the SEC group, neither the change in baseline cortisol, which increased slightly from 9.49 ± 1.0 μg/dl at pre-test to 9.52 ± 1.8 μg/dl at post-test [$t(12) = 0.02$, $p = .98$], nor the change in average cortisol, which went from 10.3 ± 1.1 μg/dl at pre-test to 9.1 ± 1.4 μg/dl at post-test [$t(12) = 0.79$, $p = .45$], was statistically significant by paired t-test [Fig. 2(A) and (B)]. The ANCOVA comparison is not reported here because the assumption of equivalence between the groups at pre-test was not met for these two measures of cortisol. This apparently was due to self-selected attrition, because the mean baseline value for all randomly assigned subjects at pre-test showed no significant difference between groups; i.e. for TM ($n = 25$) it was 12.5 ± 1.1 μg/dl and for SEC ($n = 24$), it was 11.2 ± .89 μg/dl [$t(47) = 1.0$; $p = .32$]. However, in those subjects remaining after attrition (16 and 13 subjects in the TM and SEC groups, respectively), a significant difference was found; i.e. for TM it became 13.9 ± 1.5 μg/dl and for SEC it became 9.5 ± 1.0 μg/dl [$t(27) = 2.30$; $p = .03$]. A similar situation existed for the cortisol average across the session. However, in this case, the difference between the two groups after attrition only tended towards significance [$t(27) = 1.90$; $p = .07$].

Since this pre-test difference in the groups remaining after attrition potentially affects interpretation of the outcomes, the importance of this cortisol imbalance was evaluated further in two ways. If the pre- to post-test reduction of baseline cortisol and cortisol average across the session in the TM group reflected regression to the mean, high correlations would be expected between pre-test values and the pre- to post-test change scores. The modest correlations actually obtained were $r = 0.44$ for baseline and $r = 0.46$ for the average, accounting for 19 and 21% of the variance, respectively. The second approach was to exclude a sufficient number of TM subjects with high pre-test cortisol values to make the means equal to the pre-attrition values. No outliers were found using conventional tests. However, excluding the three subjects with highest baseline and average values (i.e. 34.5, 16.6 and 15.6 μg/dl for baseline, and 25.4, 15.9 and 20.8 μg/dl for the average) gave pre-test means = 12.0 ± .66 and 11.6 ± .64 μg/dl, respectively, very close to the means obtained for all pre-test subjects before attrition. Starting with this lower mean, the pre- to post-test decreases in baseline cortisol [$t(12) = 1.95$; $p = .075$] and average [$t(12) = 1.76$; $p = .10$] remained strong trends. (As decreases were predicted based on previous studies, one could argue also for the use of one-tailed tests, giving significance at the .05 level for both baseline and average.) Neither this result nor the correlations provide substantial support for self-selected attrition as the cause of cortisol decreases in the TM group.

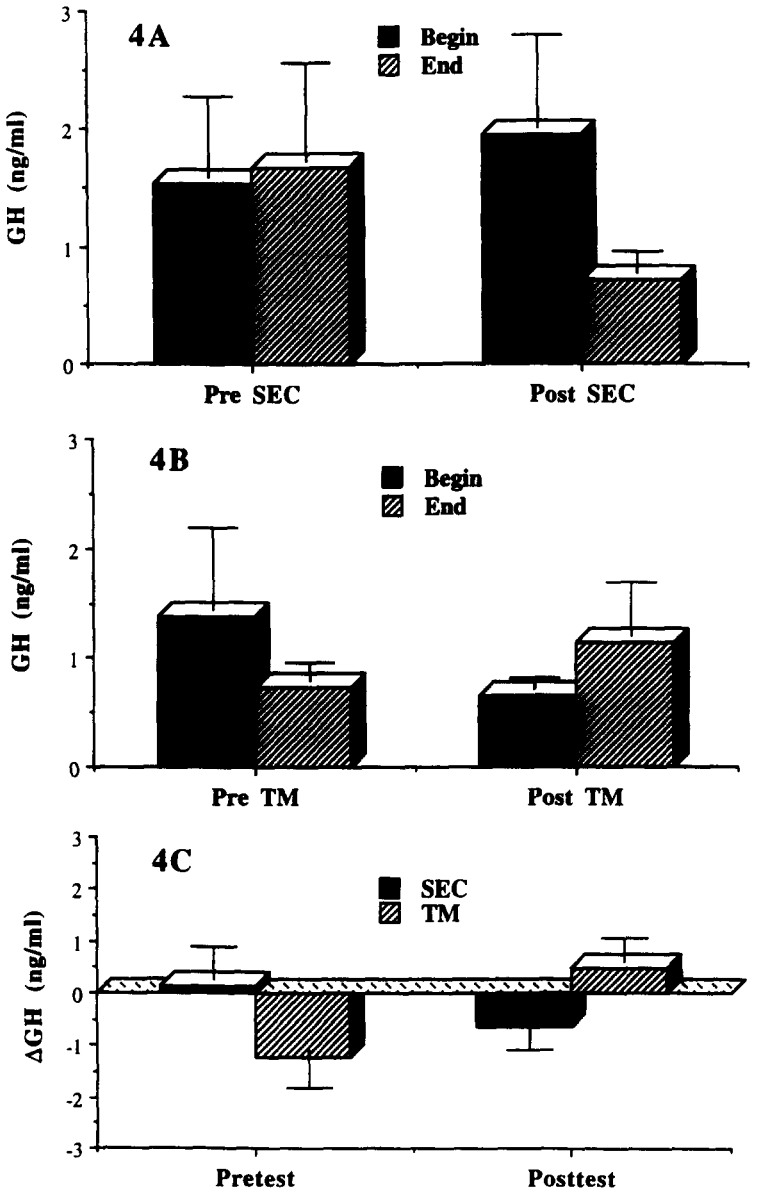

Fig. 4. Pre-test and post-test changes in GH across the stress session. The GH values (A) for the SEC group and (B) for the TM group changed in opposite directions across the stress session in going from pre- to post-test. The change scores for the two groups (ΔGH, end of session minus baseline) (C) for the two groups at post-test were significantly different by ANCOVA, covarying for pre-test [$F(1, 27) = 4.05$, $p = .05$].

Repeated measures ANOVA proved insensitive as a test of whether cortisol response to stress was affected differently by the interventions. Thus, a more sensitive measure often used in such comparisons—change in area-under-the-curve from pre- and post-test—was tried. This approach revealed a significant difference between the groups by ANCOVA co-varying for pre-test [$F(1, 26) = 5.8$, $p = .02$]. The cortisol area variable increased for the TM group, going from 35.3 ± 22.5 to 69.1 ± 18.2 (in arbitrary units), while it decreased for the SEC group, going from 42.1 ± 13.1 to 16.5 ± 14.9 [Fig. 2(C)]. Thus, apparent effects of treatment on cortisol secretion were observed for three key variables: baseline, average across the stress session, and response to the stress session. However, only the third and most comprehensive of these measures, the area-under-the-curve variable, showed a statistically significant difference between the two groups.

No significant differences between the groups were found for TSH at pre-test. Neither were there significant changes in TSH secretion across the stress session at pre- or post-test [Fig. 3(A) and (B)]. At pre-test, for all subjects with complete TSH data ($n = 29$), there was an insignificant increase of 11% during the stress session. Pre-test changes for the TM and SEC groups were in the same direction. However, at post-test [Fig. 3(B)], changes across the session appeared opposite for the two groups. The TSH increased an average of 6.5% for the SEC group ($n = 13$), going from 1.23 ± 0.08 to 1.31 ± 0.08 μg/ml. On the other hand, for the TM group ($n = 16$) it decreased 9.5%, going from 1.36 ± 0.20 to 1.23 ± 0.08 μg/ml, apparently due primarily to a pre- to post-test rise of baseline. Thus, a small but distinct difference between the two groups was found on the basis of TSH change scores from the beginning to the end of the stress session [Fig. 3(C)]. Post-test change scores analyzed by ANCOVA (co-varying for pre-test change scores) indicated significantly different responses of TSH to laboratory stressors [$F(1, 26) = 6.07$, $p = .02$].

At pre-test, there were no differences between the TM and SEC groups in baseline GH or GH response across the stress session. However, on average, an overall decrease of GH across the stress session was found for subjects with complete GH data ($n = 30$). The decrease was 19.3%, going from 1.45 ± 0.50 ng/ml at baseline to 1.17 ± 0.40 ng/ml at the end. Like the cortisol and TSH responses to stress, changes in GH across the stress session appeared to be affected in opposite ways in the two groups over the 4 months of treatment. Whereas, for the SEC group ($n = 16$), it increased slightly across the session at the pre-test (9.1%, going from 1.54 ± 0.68 to 1.68 ± 0.83 ng/ml), it decreased markedly during the post-test session [63.5%, going from 1.95 ± 0.77 to 0.71 ± 0.17 ng/ml; Fig. 4(A)]. On the other hand, for the TM group ($n = 14$), the change in response to stressors was in the opposite direction, decreasing at pre-test by 47.1%, from 1.38 ± 0.74 to 0.73 ± 0.16 ng/ml, but increasing at post-test by 75.4%, from 0.65 ± 0.09 to 1.14 ± 0.47 ng/ml [Fig. 4(B)]. Thus, when post-test change scores from baseline to end of the session [Fig. 4(C)] were analyzed by ANCOVA (co-varying for pre-test change scores), the two groups showed significantly different responses of GH to laboratory stressors [$F(1, 27) = 4.04$, $p = .05$]. This overall significant difference reflects in part a substantial (but insignificant) difference in GH response to stressors at pre-test.

For testosterone, baseline for the SEC group decreased from pre- to post-test by 12.4% (going from 6.36 ± 0.51 to 5.57 ± 0.55 ng/ml), whereas for the TM group it increased by 1.8% (going from 5.64 ± 0.30 to 5.74 ± 0.41 ng/ml). By ANCOVA co-varying for pre-test, the difference between the two groups after 4 months tended towards significance [$F(1, 23) = 3.37$, $p = .08$; Fig. 5]. For the SEC group alone, there was a significant decrease in baseline testosterone over the 4 months [$t(11) = 3.89$, $p = .002$].

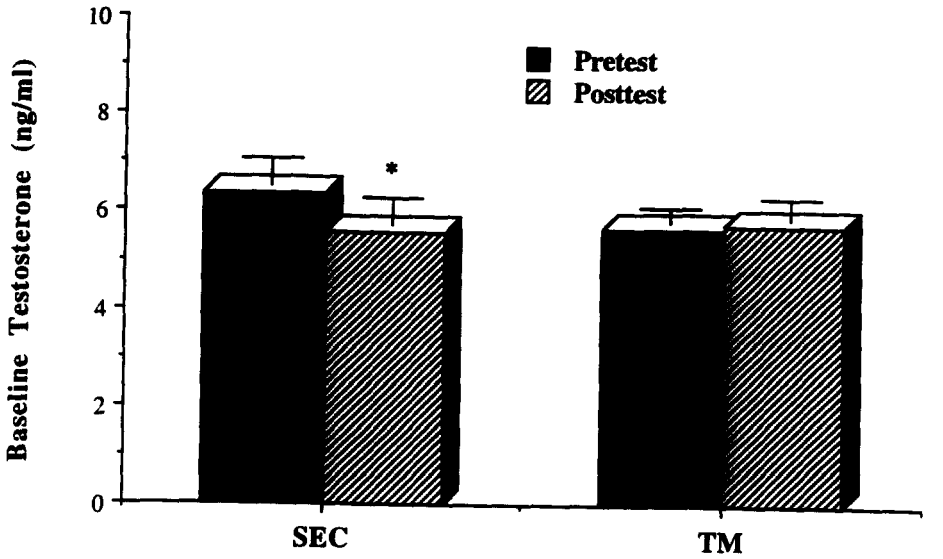

Fig. 5. Changes in baseline testosterone from pre- to post-test. The difference in changes between the two groups for testosterone at the baseline trended to significance by ANCOVA [$F(1, 23) = 3.37$, $p = .08$]. Testosterone baseline for the SEC group decreased significantly [$t(11) = 3.89$, $p = .002$], but for the TM group it was unchanged; *$p = .002$.

During the pre-test in all subjects for whom there were complete data ($n = 26$), testosterone increased insignificantly (4.5%) in response to stressors, going from a baseline of 5.98 ± 0.29 to 6.25 ± 0.36 ng/ml at the end of the session. At the post-test, however, a 9.2% increase across the stress session in the TM group approached significance, going from 5.74 ± 0.41 at baseline to 6.27 ± 0.35 ng/ml at the end [$t(14) = 2.08$, $p = .06$], while the response in the SEC group remained the same as in the pre-test (4.8%), going from 5.57 ± 0.55 to 5.84 ± 0.66 ng/ml [$t(12) = 1.20$, $p = .25$]. This apparent difference between the two groups was not significant by ANCOVA.

DISCUSSION

The primary findings of this randomized controlled study, i.e. those meeting the most stringent standards of significance (ANCOVA co-varying for pre-test) involved the opposite direction of changes in the two treatment groups. Specifically, the area-under-the-curve variable for the cortisol response, the TSH change across the stress session, and the GH change across the stress session all appeared to be affected in opposite directions over the course of the treatments. Secondary findings were the significant decreases (by paired t-test) in baseline cortisol and average of cortisol across the stress session in the TM group from pre- to post-test, the trend towards a decrease in baseline testosterone in the SEC group compared to the TM group, going from pre- to post-test, and the significant (by t-test) decrease of baseline testosterone in the SEC group from pre- to post-test. Taken together, these data suggest that 4 months' practice of the TM technique had a different effect on

subjects than 4 months of the stress education procedure, in agreement with prior studies. However, because attrition from the study was substantial and self-selected, other possible interpretations cannot be excluded, as detailed below.

The present results appear in general to support other findings (e.g. Bevan et al., 1976; Jevning et al., 1978, 1987, 1992; Werner et al., 1986; Walton et al., 1995), suggesting that hormonal changes occurring during the practice of the TM technique are relevant to changes in regulation that persist outside the practice, especially in the cases of cortisol and TSH. Reports of an acute decrease in cortisol during the TM technique have come from several laboratories. These studies have either compared a practice period of the technique with a period of eyes-closed rest, or contrasted long-term or advanced practitioners with short-term practitioners (less than 1 year of practice) or with non-practitioner controls (Bevan et al., 1976; Jevning et al., 1978, 1992; Walton et al., 1995). In one study combining cross-sectional and longitudinal approaches, a significant, 27% decline of cortisol was found during a 30 min session of the technique in long-term practitioners, compared to no change in non-TM controls during eyes-closed rest (Jevning et al., 1978). When the same controls were re-tested after learning and practicing the technique for 3–4 months, the cortisol decline observed during the practice was intermediate between those found for the long-term group and the non-TM controls (Jevning et al., 1978). Another study found 24 h urinary cortisol excretion in long-term (mean = 8.5 years) TM practitioners to be less than 50% of that for age-matched controls (Walton et al., 1995). Data from the latter study also found this cortisol difference to be correlated with other physiological parameters, particularly sodium excretion and the ratio of sodium to potassium excretion, which are recognized risk factors for hypertension.

The decrease of baseline cortisol from pre- to post-test, found here in the TM group, is similar to the decrease of plasma cortisol observed in earlier longitudinal studies (Bevan et al., 1976; Jevning et al., 1978; Werner et al., 1986). Since chronic stress in animals appears to elevate baseline glucocorticoids (e.g. Akana et al., 1992), the significant reduction of baseline cortisol seen here may be consistent with a reversal of the effects of prior chronic stress. The increased cortisol response to stressors exhibited by the TM group after 4 months of practice may add further support to this conclusion, because the opposite profile is associated with chronic stress in studies of non-human primates and rodents (Sapolsky, 1990; Sapolsky et al., 1986, 1991; Brooke et al., 1994). The observed changes in testosterone also fit this interpretation (see below).

This combination (i.e. lower baseline cortisol but higher response to acute stress) appears to reflect a more adaptive, low-stress profile in the dominant male baboon in the wild compared to subordinate males (Sapolsky, 1990). Enhanced glucocorticoid negative feedback as an underlying contributor to this greater hormonal response also has considerable empirical support (see for review Sapolsky et al., 1986; Sapolsky, 1992). However, recent data on the cortisol profile of patients with post-traumatic stress disorder (PTSD) show some resemblance to the profile above, and these data also indicate that PTSD patients have extraordinarily efficient glucocorticoid feedback mechanisms (Yehuda et al., 1996). A question that may arise in the interpretation of the present results is whether the TM group is somehow becoming more like PTSD patients. The present data do not unequivocally answer this question. However, numerous other studies have found both short- and long-term effects of the TM program that are opposite to those characterizing PTSD. Moreover, a controlled trial using the TM program as treatment for PTSD found

significant improvements in eight out of nine dependent variables, compared to controls receiving psychotherapy (Brooks and Scarano, 1985).

While the meaning of the observed cortisol and testosterone changes may be fairly clear in relation to chronic stress, changes of TSH that might arise from chronic stress have been less well characterized. In the present study, an increase of TSH (11%, combining both groups) was observed during the pre-test stress session, consistent with published accounts of a TSH rise during acute stress (Rolandi et al., 1985; Mougey et al., 1991). As with cortisol, post-test TSH reactivity to stress differed significantly between the groups. However, in this case the altered direction of change appeared to be due as much to an increase of baseline as to a drop of the end-of-session response. TSH has been reported to decline acutely during individual practice sessions of the TM technique (Jevning et al., 1987) and longitudinally in long-term TM–Sidhi practitioners (Werner et al., 1986). Previous accounts of a reduction of TSH secretion after beginning the advanced (TM–Sidhi) program, with T_3 and T_4 remaining unchanged, were interpreted to suggest an altered 'set point' for feedback control of TSH (Werner et al., 1986). How the present results might relate to these earlier observations is unclear.

Earlier studies have not examined the effect of the TM technique on testosterone response to stress. The increased testosterone response to acute stressors in the TM group suggested by the present results is consistent with studies of successful male baboons in the wild, which showed a greater testosterone response to acute stress than did the more highly stressed, unsuccessful males (Sapolsky, 1982). However, because cortisol exerts direct inhibitory effects on the level of gonadotropin releasing hormone in the hypothalamus (Chandran et al., 1994), a lower testosterone baseline and response to acute stress may be a secondary result of chronically elevated cortisol. Cortisol levels were not higher in the SEC group than in the TM group, even at post-test. Nevertheless, because baseline testosterone is known to decrease with chronic stress (Sapolsky, 1982; Allen et al., 1985; Leedy and Wilson, 1985), the decrease of baseline testosterone in the SEC group may suggest chronic stress rose in this group from pre- to post-test, as is suggested also by the decline in cortisol response to stress in this group. The lack of change in baseline testosterone seen here in the TM group is consistent with an earlier report of unchanged baseline testosterone during acute practice of this technique (Jevning et al., 1978).

A tendency of GH to decrease, both during the TM technique and longitudinally with regular practice, has been reported previously (Bevan et al., 1976; Cooper et al., 1985; Werner et al., 1986). The (insignificant) longitudinal decrease found here in the TM group appears to agree with these earlier findings. Furthermore, the opposite relative changes in response to the stress session appear to parallel the opposite changes in cortisol response to stressors in the two groups. Parallel changes in GH and cortisol are common (Brown et al., 1978) and may well be mediated, at least in part, by effects of cortisol on somatostatin levels (Papachristou et al., 1994).

One potential weakness of the present study was the absence of a no-stress control group. At least in the case of cortisol, the actual increase due to the stress session was likely to have been bigger than the one observed because in the normal circadian rhythm of cortisol the level is declining throughout the hours involved in the present investigation (Rose and Hurst, 1975; McCann et al., 1993). In support of this, when no-stress control data from a closely similar experiment (McCann et al., 1993) were used to calculate the stress response in the present study at pre-test, a cortisol increase of 30% was obtained, comparing favorably with other tests of naturalistic stressors on plasma cortisol in humans at this time of day.

Overall, there were more changes in the TM group that were suggestive of a reduction of chronic stress than in the SEC group, which tended to change in the opposite direction. The reason for this may have been two-fold, namely, an ability of the TM technique to prevent or reverse effects attributed to chronic stress and a tendency of stress level to increase across the school year. The majority of the subjects were medical students, and the pre- and post-tests were non-uniformly spread across the year. The pre-tests were concentrated near the middle of the school year while the post-tests occurred nearer the end, approaching final exams. Thus, it is probable there was an overall tendency for the stress level to increase for both groups, and the different changes in the two groups therefore reflect differential effects of the two interventions.

Another possible interpretation of the data, however, derives from the self-selected attrition from the study, which left the TM group with a significantly higher baseline cortisol and a trend toward higher average cortisol than the SEC group. Based on findings in animal studies, this suggests these groups had experienced different levels of chronic stress at pre-test. If true, this would leave open the possibility that this initial difference might explain the tendency of the two groups to change in opposite directions over the 4 months of the study. However, as described in the Results section, the outcomes of two exploratory tests of this hypothesis provide little support for this interpretation. Moreover, in the more comprehensive area-under-the-curve variable for the acute response of cortisol to the stressors, where the groups did not differ at pre-test, the significantly different changes from pre- to post-test in the two groups were consistent with the original hypothesis. Furthermore, none of the other endocrine parameters differed significantly between the TM and SEC groups at pre-test.

Yet another possible interpretation of the observed results is that the stress education class had its own effects distinct from (and largely opposite to) any effects that may have derived from practice of the TM technique. Since prior studies have not found physiological effects for similar intellectually based didactic programs, this appears unlikely. Final answers to these questions, however, will require replication of the study with two additional control groups, one with no stressors and one with no treatment. Such a study also might benefit from larger monetary incentives to the subjects to minimize attrition, as well as from a longer time between stressors, and multiple blood samples for all hormones.

The significance of the current findings for health remains unproven. However, a large body of research suggests a robust cortisol response to acute stressors is beneficial in preventing stress-activated defense mechanisms from overshooting and damaging the organism (see for review Munck et al., 1984; Munck and Naray-Fejes-Toth, 1994). Chronically elevated baseline or average cortisol, on the other hand, appears to increase risk for a variety of diseases (e.g. Selye and Tuchweber, 1976; Sapolsky et al., 1986; Seeman and Robbins, 1994). Although the changes in adaptive mechanisms observed here, which may have been due to the TM technique, appear small, other results suggest such changes increase longitudinally with regular practice and that the contribution to health can be significant (e.g. Jevning et al., 1978; Werner et al., 1986; Walton et al., 1995; Alexander et al., 1996). Furthermore, additional physiologic changes which are relevant to the cardiovascular effects of the technique were found in other aspects of the present experiment. Specifically, the high regularity TM subgroup showed a significant pre- to post-test decrease of ambulatory diastolic blood pressure compared to the low regularity TM subgroup and to the high and low regularity SEC subgroups (Wenneberg et al., 1997). In addition, the urinary excretion of sodium and other cations, a recognized risk factor for

hypertension, decreased significantly in the TM group compared to the SEC group, and this pre-to-post change in cation excretion was highly correlated with the pre-to-post change in cortisol (Levitsky et al., 1995). Plasma and platelet serotonin also were measured. Plasma serotonin in the TM group appeared to decrease both at baseline and in response to acute stress, while in the SEC group, it appeared to increase (MacLean et al., 1992b). These results are consistent with the possibility that a decrease in plasma serotonin (Vanhoutte, 1991), along with decreases in cortisol, aldosterone, sodium intake, sodium/potassium ratio and catecholamines apparently resulting from practice of the technique (Walton et al., 1995), play a role in reducing hypertension and other cardiovascular diseases (Alexander et al., 1994, 1996; Schneider et al., 1995; Zamarra et al., 1996). In view of the present results, and of other studies which support a cumulative improvement in health (Orme-Johnson, 1987; Alexander et al., 1989; Herron et al., 1996), it would appear important to examine, in the same study, the long-term effects of the TM program on adaptive mechanisms and on comprehensive health status.

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